Clinical trial results:
A Phase 3b, Randomized, Active Controlled Trial to Evaluate the Efficacy and Safety of Abatacept SC in Combination with Methotrexate in Inducing Clinical Remission Compared to Methotrexate Monotherapy in Adults with Very Early RA

Summary

EudraCT number	2010-018674-20
Trial protocol	FR DE BE SE FI DK IT
Global end of trial date	27 October 2014

Results information

Result version number	v1 (current)
This version publication date	01 April 2016
First version publication date	01 April 2016

Trial information

Trial identification

Sponsor protocol code	IM101-226

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01142726
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium,
Public contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.com
Scientific contact	Bristol Myers Squibb Study Director, Bristol Myers Squibb, clinical.trials@bms.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	27 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the study were to compare the clinical efficacy of abatacept in combination with methotrexate (MTX) to MTX alone on the following:
• The proportion of randomized and treated subjects with Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) <2.6 at Month 12
• The proportion of randomized and treated subjects with DAS28-CRP <2.6 at both Month 12 and Month 18.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator:

MTX is a standard of care for early treatment of Rheumatoid arthritis. Hence MTX was selected as the active comparator and Based on the results of study NCT00989235, it was hypothesized that the addition of abatacept to MTX will be superior to MTX in inducing DAS28 clinical remission after a year of treatment in subjects who have serologically positive early RA and are MTX naive. MTX was supplied as 2.5 mg tablets for weekly oral administration during the Treatment Period, and was titrated over a period of 6 to 8 weeks based on tolerability.

Actual start date of recruitment	10 December 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 42
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	Germany: 46
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 40
Country: Number of subjects enrolled	Mexico: 102
Country: Number of subjects enrolled	Poland: 53
Country: Number of subjects enrolled	South Africa: 66
Country: Number of subjects enrolled	Sweden: 23
Country: Number of subjects enrolled	United States: 73

Country: Number of subjects enrolled	France: 18
Worldwide total number of subjects	511
EEA total number of subjects	182

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	458
From 65 to 84 years	53
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 73 sites in 14 countries.

Pre-assignment

Screening details:

A total of 511 subjects were enrolled in the study, and 351 were randomized. Reasons that 160 enrolled subjects were not randomized were failure to meet study criteria (130/160), withdrawal of consent (20/160), poor/non-compliance (3/160), administrative reason by sponsor (2/160), lost to follow-up (1/160), and other reasons (4/160).

Period 1

Period 1 title	Treatment Phase: Day 1 Through Month 12
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Arm description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS 188667
Other name	Orencia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125 mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Arm title	Abatacept, 125 mg, Plus Methotrexate Placebo

Arm description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal

Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Arm type	Experimental
Investigational medicinal product name	Methotrexate placebo
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate matching placebo 2.5 mg tablet was administered orally once weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS 188667
Other name	Orencia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125 mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Arm title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Arm description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept matching placebo 125-mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Number of subjects in period 1[1]	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo
Started	119	116	116
Completed	103	91	96
Not completed	16	25	20
Consent withdrawn by subject	4	9	3
Adverse event, non-fatal	5	8	5
Poor compliance/noncompliance	1	-	-
Lost to follow-up	1	2	1
Lack of efficacy	5	6	11

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects reported in the baseline period are different from the worldwide number enrolled in the trial, as 160 enrolled subjects were not randomized. Reasons were failure to meet study criteria (130/160), withdrawal of consent (20/160), poor/non-compliance (3/160), administrative reason by sponsor (2/160), lost to follow-up (1/160), and other reasons (4/160).

Period 2

Period 2 title	Withdrawal Phase: Month 12 up to 24
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Arm description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS 188667
Other name	Orencia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125 mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Arm title	Abatacept, 125 mg, Plus Methotrexate Placebo

Arm description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Arm type	Experimental
Investigational medicinal product name	Methotrexate placebo
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate matching placebo 2.5 mg tablet was administered orally once weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS 188667
Other name	Orencia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125 mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Arm title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Arm description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Arm type	Active comparator
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept Placebo
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept matching placebo 125-mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Number of subjects in period 2[2]	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo
Started	84	66	75
Completed	14	10	17
Not completed	70	56	58
No longer met study criteria	1	-	-
Consent withdrawn by subject	1	1	2
Non-specified	-	1	1
Adverse event, non-fatal	-	-	1
Pregnancy	1	-	1
Lost to follow-up	2	-	-
Lack of efficacy	65	54	53

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Out of all subjects who completed treatment period 67 subjects did not enter the withdrawal period. 2 subjects in the MTX monotherapy arm entered the Withdrawal Period after the data cutoff date for the first analysis.

Period 3

Period 3 title	Re-Exposure Phase: Months 24 up to 30
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Arm description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Arm type	Experimental

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS 188667
Other name	Orencia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125 mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Arm title	Abatacept, 125 mg, Plus Methotrexate Placebo

Arm description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Arm type	Experimental
Investigational medicinal product name	Methotrexate placebo
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Methotrexate matching placebo 2.5 mg tablet was administered orally once weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS 188667
Other name	Orencia
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125 mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Arm title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Arm description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Arm type	Active comparator

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	Rheumatrex
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly during the 12-month Treatment Period.

Investigational medicinal product name	Abatacept Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept matching placebo 125-mg was administered as subcutaneous injection once weekly during the 12-month Treatment Period.

Number of subjects in period 3	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo
Started	14	10	17
Completed	54	46	40
Not completed	1	2	3
Consent withdrawn by subject	1	1	1
Adverse event, non-fatal	-	-	1
Pregnancy	-	-	1
Lack of efficacy	-	1	-
Joined	41	38	26
Re-joined in Period 3	41	38	26

Baseline characteristics

Reporting groups	
Reporting group title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Reporting group title	Abatacept, 125 mg, Plus Methotrexate Placebo

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Reporting group description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo
Number of subjects	119	116	116
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 46.4 ± 13.2	 45.4 ± 11.92	 49.1 ± 12.36
Gender categorical Units: Subjects			
Female Male	95 24	89 27	89 27
Race/Ethnicity Units: Subjects			
White	100	95	102

Asian	14	13	9
Black/African American	2	4	2
American Indian/Alaska native	1	1	1
Other	2	3	2
Rheumatoid factor status Units: Subjects			
Positive	113	111	110
Negative	6	5	6
Duration of rheumatoid arthritis Units: Years			
arithmetic mean	0.58	0.59	0.5
standard deviation	± 0.5	± 0.522	± 0.488
Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) Units: Units on a scale			
arithmetic mean	5.528	5.463	5.315
standard deviation	± 1.2501	± 1.1493	± 1.333
Health Assessment Questionnaire Disability Index (HAQ-DI) score Units: Units on a scale			
arithmetic mean	1.452	1.419	1.383
standard deviation	± 0.6778	± 0.6587	± 0.6493
Tender joint count Units: Joints			
arithmetic mean	24.3	23.9	21.7
standard deviation	± 15.74	± 14.47	± 14
Swollen joint count Units: Joints			
arithmetic mean	16.5	17.2	15.7
standard deviation	± 12.43	± 12.88	± 11.78

Reporting group values	Total		
Number of subjects	351		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	273		
Male	78		
Race/Ethnicity Units: Subjects			
White	297		
Asian	36		
Black/African American	8		
American Indian/Alaska native	3		
Other	7		
Rheumatoid factor status			

Units: Subjects			
Positive	334		
Negative	17		
Duration of rheumatoid arthritis			
Units: Years			
arithmetic mean			
standard deviation	-		
Disease Activity Score 28 based on C-reactive protein (DAS28-CRP)			
Units: Units on a scale			
arithmetic mean			
standard deviation	-		
Health Assessment Questionnaire Disability Index (HAQ-DI) score			
Units: Units on a scale			
arithmetic mean			
standard deviation	-		
Tender joint count			
Units: Joints			
arithmetic mean			
standard deviation	-		
Swollen joint count			
Units: Joints			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Reporting group title	Abatacept, 125 mg, Plus Methotrexate Placebo

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Reporting group description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Reporting group title	Abatacept, 125 mg, Plus Methotrexate Placebo

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Reporting group description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly,

plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Reporting group title	Abatacept, 125 mg, Plus Methotrexate Placebo

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Reporting group description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Primary: Percentage of Subjects Who Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria at Month 12 and at Both Months 12 and 18

End point title	Percentage of Subjects Who Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria at Month 12 and at Both Months 12 and 18[1]

End point description:

DAS28-CRP remission defined as <2.6; TP=treatment phase; WP=withdrawal phase. The DAS 28-CRP is a measure of disease activity in rheumatoid arthritis (RA) that assesses the 28 joints RA commonly affects; the score includes the number of tender and swollen joints (out of 28), CRP level (a measure of inflammation in the blood), and the subject's global assessment of health (ranging from very good to very bad). These measures are then fed into a complex mathematical formula to produce the overall DAS (a score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission). Analysis was performed in all the randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period. Percentage calculated as a/b, where a=number of subjects who achieved remission at Month 12 and at both Months 12 and 18, and b=number of subjects in the analysis. n=number of evaluable subjects.

End point type	Primary

End point timeframe:

Randomization to Months 12 and 18

Notes:

[1] - 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 endpoint was planned to be assessed for these reporting arms only.

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Methotrexate, 2.5 mg, Plus Abatacept Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	116		
Units: Percentage of subjects				
number (confidence interval 95%)				
Month 12 (TP Day 365) (n=115, 115)	60.9 (51.95 to 69.79)	45.2 (36.12 to 54.31)		
Both Months 12 & 18 (WP Day 169) (n=115, 115)	14.8 (8.3 to 21.27)	7.8 (2.92 to 12.73)		

Statistical analyses

Statistical analysis title	DAS28-CRP Remission at Month 12

Statistical analysis description:

Power estimate assumed 2-sided alpha level of 5% and that 60% of ABA + MTX subjects would be in DAS28-CRP remission at Month 12 compared with 38% of MTX monotherapy subjects. Also assumed that 48% of abatacept monotherapy subjects would be in DAS28-CRP remission at Month 12, yielding an expected treatment difference from MX of 10% in favor of ABA monotherapy; 116 subjects randomized to ABA monotherapy would yield a half-length of the 95% CI around that 10% treatment difference of 13.5%.

Comparison groups	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg v Methotrexate, 2.5 mg, Plus Abatacept Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.18
upper limit	3.43
Variability estimate	Standard error of the mean
Dispersion value	0.55

Statistical analysis title	DAS28-CRP Remission at Both Month 12 and 18

Statistical analysis description:

Conditional on statistical significance of the 1st co-primary efficacy analysis (CEA), a sample of 116 subjects per arm would provide 98% power for the 2nd CEA comparison of the percentage of subjects in

DAS28-CRP remission at Months 12 and 18 between the abatacept (ABA)+methotrexate (MTX) arm and the MTX monotherapy arm for intent-to treat population. This sample size calculation assumed 30% remission in the ABA+MTX arm and 8% in the monotherapy arm at Month 18 and a 2-sided alpha level of 5%.

Comparison groups	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg v Methotrexate, 2.5 mg, Plus Abatacept Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.045
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	6.18
Variability estimate	Standard error of the mean
Dispersion value	1.15

Secondary: Percentage of Subjects Who Received Monotherapy and Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria at Month 12 and at Both Months 12 and 18

End point title	Percentage of Subjects Who Received Monotherapy and Achieved Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria at Month 12 and at Both Months 12 and 18[2]

End point description:

TP=treatment period; WP=withdrawal period. Remission defined as DAS28-CRP<2.6. The DAS 28-CRP is a measure of disease activity in rheumatoid arthritis (RA) that assesses the 28 joints RA commonly affects; the score includes the number of tender and swollen joints (out of 28), CRP level (a measure of inflammation in the blood), and the subject's global assessment of health (ranging from very good to very bad). DAS-CRP scores range from 0 to 10, with higher values indicating greater disease activity. Individual measures are fed into a complex mathematical formula to produce the overall DAS (a score >5.1 implies active disease; <3.2, well controlled disease; and <2.6, remission). All randomized subjects who received at least 1 dose of double-blind monotherapy in the Treatment Period. Percentage calculated as a/b, where a=number of subjects who achieved remission at Month 12 and at both Months 12 and 18, and b=number of subjects in the analysis. n=number of evaluable subjects.

End point type	Secondary

End point timeframe:

Randomization to Months 12 and 18

Notes:

[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 endpoint was planned to be assessed for these reporting arms only.

End point values	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	116		
Units: Percentage of subjects				
number (confidence interval 95%)				

At Month 12 (TP Day 365) (n=113, 115)	42.5 (33.36 to 51.59)	45.2 (36.12 to 54.31)		
At both Months 12 & 18 (WP Day 169) (n=113, 115)	12.4 (6.31 to 18.46)	7.8 (2.92 to 12.73)		

Statistical analyses

Statistical analysis title	DAS28-CRP Remission- Month 12 (Monotherapy)
Statistical analysis description:	
Odds ratio was based on an Adjusted Logistic Regression test, including treatment, baseline DAS28-CRP value as well as the stratification factor (corticosteroid use at baseline (yes/no))	
Comparison groups	Methotrexate, 2.5 mg, Plus Abatacept Placebo v Abatacept, 125 mg, Plus Methotrexate Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.57
Variability estimate	Standard error of the mean
Dispersion value	0.25

Statistical analysis title	DAS28-CRP Remission- Month 12 and 18 (Monotherapy)
Statistical analysis description:	
Odds ratio was based on an Adjusted Logistic Regression test, including treatment, baseline DAS28-CRP value as well as the stratification factor (corticosteroid use at baseline (yes/no))	
Comparison groups	Abatacept, 125 mg, Plus Methotrexate Placebo v Methotrexate, 2.5 mg, Plus Abatacept Placebo
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	5.14
Variability estimate	Standard error of the mean
Dispersion value	0.96

Secondary: Percentage of Subjects With Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria Over Time - Intent to Treat Population

End point title	Percentage of Subjects With Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria Over Time - Intent to Treat Population

End point description:

TP=treatment period; WP=withdrawal period. Remission defined as DAS28-CRP<2.6. The DAS 28-CRP is a measure of disease activity in rheumatoid arthritis (RA) and assesses the 28 joints RA commonly affects; the score includes the number of tender and swollen joints (out of 28), CRP level (a measure of inflammation in the blood), and the subject's global assessment of health (ranging from very good to very bad). DAS-CRP scores range from 0 to 10, with higher values indicating greater disease activity. Individual measures are fed into a complex mathematical formula to produce the overall DAS (a score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission). Analysis was performed in all the randomized subjects who received at least 1 dose of double-blind study medication in Treatment Period. Percentage calculated as a/b, where a=number of subjects who achieved remission, and b=number of subjects in analysis (intent to treat).

End point type	Secondary

End point timeframe:

Randomization to Month 24

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Percentage of subjects				
number (confidence interval 95%)				
TP Day 29	13.4 (7.32 to 19.57)	8.6 (3.51 to 13.73)	6 (1.7 to 10.37)	
TP Day 57	24.4 (16.66 to 32.08)	11.2 (5.47 to 16.95)	9.5 (4.15 to 14.81)	
TP Day 85	36.1 (27.5 to 44.77)	21.6 (14.07 to 29.03)	17.2 (10.37 to 24.12)	
TP Day 113	37.8 (29.1 to 46.53)	29.3 (21.03 to 37.59)	19 (11.83 to 26.1)	
TP Day 141	45.4 (36.43 to 54.32)	29.3 (21.03 to 37.59)	25 (17.12 to 32.88)	
TP Day 169	45.4 (36.43 to 54.32)	32.8 (24.22 to 41.3)	26.7 (18.67 to 34.78)	
TP Day 197	52.1 (43.13 to 61.08)	36.2 (27.46 to 44.95)	25.9 (17.89 to 33.83)	
TP Day 225	57.1 (48.25 to 66.03)	40.5 (31.58 to 49.95)	30.2 (21.82 to 38.53)	
TP Day 253	62.2 (53.47 to 70.9)	37.9 (29.1 to 46.76)	30.2 (21.82 to 38.53)	
TP Day 281	51.3 (42.28 to 60.24)	42.2 (33.25 to 51.23)	32.8 (24.22 to 41.3)	
TP Day 309	56.3 (47.39 to 65.21)	37.9 (29.1 to 46.76)	36.2 (27.46 to 44.95)	
TP Day 337	63 (54.35 to 71.7)	43.1 (34.09 to 52.12)	33.6 (25.02 to 42.22)	

TP Day 365	61.3 (52.6 to 70.09)	43.1 (34.09 to 52.12)	45.7 (36.62 to 54.75)	
WP Day 29	51.3 (42.28 to 60.24)	36.2 (27.46 to 44.95)	27.6 (19.45 to 35.72)	
WP Day 57	40.3 (31.52 to 49.15)	25 (17.12 to 32.88)	18.1 (11.1 to 25.11)	
WP Day 85	31.1 (22.78 to 39.41)	18.1 (11.1 to 25.11)	18.1 (11.1 to 25.11)	
WP Day 169	19.3 (12.23 to 26.42)	12.9 (6.82 to 19.04)	9.5 (4.15 to 14.81)	
WP Day 253	17.6 (10.8 to 24.5)	9.5 (4.15 to 14.81)	13.8 (7.52 to 20.07)	
WP Day 365	9.2 (4.04 to 14.45)	6 (1.7 to 10.37)	6 (1.7 to 10.37)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted Mean Change From Baseline in Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) at Months 6, 12, and 18

End point title	Adjusted Mean Change From Baseline in Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) at Months 6, 12, and 18

End point description:

TP=treatment period; WP=withdrawal period. The DAS 28-CRP is a measure of disease activity in rheumatoid arthritis (RA) that assesses the 28 joints RA commonly affects; the score includes the number of tender and swollen joints (out of 28), CRP level (a measure of inflammation in the blood), and the subject's global assessment of health (ranging from very good to very bad). DAS-CRP scores range from 0 to 10, with higher values indicating greater disease activity. Individual measures are fed into a complex mathematical formula to produce the overall DAS (a score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission). Analysis was performed in all the randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period. n=number of evaluable subjects.

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Units on scale				
arithmetic mean (standard error)				
Month 6 (TP Day 169) (n=102, 96, 101)	-2.72 (± 0.12)	-2.33 (± 0.12)	-1.93 (± 0.12)	
Month 12 (TP Day 365) (n=95, 84, 91)	-3.09 (± 0.13)	-2.75 (± 0.13)	-2.58 (± 0.13)	
Month 18 (WP Day 169) (n=41, 31, 32)	-1.54 (± 0.26)	-1.51 (± 0.29)	-1.06 (± 0.29)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI) at Months 12 and 18

End point title	Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI) at Months 12 and 18

End point description:

TP=treatment period; WP=withdrawal period. SDAI-defined remission= ≤3.3. The SDAI was the simple linear sum of 5 outcome parameters: tender joint count (TJC) and swollen joint count (SJC) (based on a 28-joint assessment); subject's and physician's global assessments of disease activity (assessed on 0-10 cm visual analog scale, on which higher scores=greater affection due to disease activity); and C-reactive protein level (mg/dL). SDAI total score=0-86. SDAI <=3.3 indicates disease remission, >3.4 to 11=low, >11 to 26=moderate, and >26=high disease activity. TJC was assessed at each visit as no swelling=0, swelling=1. TJC was assessed at each visit as no tenderness =0, tenderness = 1. Higher score indicates greater affection due to disease activity. Analysis was performed in all randomized subjects who received at least 1 dose of double-blind study medication in TP. Percentage calculated as a/b, where a=number of subjects who achieved remission, and b=number of subjects in analysis.

End point type	Secondary

End point timeframe:

Randomization to Month 18

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Percentage of subjects				
number (confidence interval 95%)				
Month 12 (TP Day 365)	40.2 (33.15 to 50.89)	29.3 (21.03 to 37.59)	25 (17.12 to 32.88)	
Month 18 (WP Day 169)	10.9 (5.32 to 16.53)	8.6 (3.51 to 13.73)	6.9 (2.29 to 11.51)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted Mean Change From Baseline in Scores on Simplified Disease Activity Index (SDAI) Over Time

End point title	Adjusted Mean Change From Baseline in Scores on Simplified Disease Activity Index (SDAI) Over Time

End point description:

TP=treatment period; WP=withdrawal period. SDAI-defined remission= ≤3.3. The SDAI is the simple linear sum of 5 outcome parameters: swollen joint count (SJC) and tender joint count (TJC) (based on a 28-joint assessment); subject's and physician's global assessments of disease activity (assessed on 0-10 cm visual analog scale, on which higher scores=greater affection due to disease activity); and C-reactive protein level (mg/dL). SDAI total score=0-86. SDAI score <=3.3 indicates disease remission, >3.4 to 11=low, >11 to 26=moderate, and >26=high disease activity. SJC is assessed with no swelling=0, swelling=1 (higher score indicates greater swelling). TJC is assessed through identification of painful joints under pressure or to passive motion, with no tenderness=0, tenderness=1 (higher score

indicates greater affection due to disease activity). The analysis was performed in Intent to Treat (ITT) population. n= number of subjects with both post baseline and baseline measurements.

End point type	Secondary
End point timeframe:	
Randomization to Month 18	

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: units on a scale				
arithmetic mean (standard error)				
TP Day 29 (n=109, 101, 107)	-13.11 (± 1.33)	-12.14 (± 1.37)	-10.12 (± 1.33)	
TP Day 57 (n=108, 101, 103)	-18.9 (± 1.25)	-15.83 (± 1.28)	-15.99 (± 1.26)	
TP Day 85 (n=108, 99, 103)	-24.13 (± 1.16)	-20.51 (± 1.2)	-19.55 (± 1.17)	
TP Day 113 (n=103, 98, 101)	-25.4 (± 1.12)	-23.56 (± 1.15)	-21.02 (± 1.13)	
TP Day 141 (n=104, 96, 104)	-27.15 (± 1.1)	-25.99 (± 1.13)	-22.14 (± 1.1)	
TP Day 169 (n=102, 96, 100)	-28.42 (± 1.08)	-26.2 (± 1.11)	-22.8 (± 1.09)	
TP Day 197 (n=103, 97, 96)	-29.66 (± 1.01)	-27.57 (± 1.03)	-24.37 (± 1.02)	
TP Day 225 (n=99, 94, 92)	-30.13 (± 1.04)	-28.39 (± 1.06)	-24.73 (± 1.06)	
TP Day 253 (n=98, 94, 91)	-31.14 (± 1.04)	-28.39 (± 1.06)	-25.8 (± 1.05)	
TP Day 281 (n=96, 93, 89)	-30.98 (± 1.1)	-28.16 (± 1.12)	-26.23 (± 1.12)	
TP Day 309 (n=91, 87, 92)	-30.82 (± 1.16)	-27.79 (± 1.18)	-26.36 (± 1.17)	
TP Day 337 (n=93, 84, 87)	-31.11 (± 1.15)	-29.34 (± 1.19)	-27.26 (± 1.17)	
TP Day 365 (n=95, 84, 91)	-31.24 (± 1.17)	-28.88 (± 1.21)	-28.34 (± 1.19)	
WP Day 29 (n=73, 59, 64)	-30.42 (± 1.32)	-28.05 (± 1.39)	-23.52 (± 1.36)	
WP Day 57 (n=69, 54, 59)	-27.68 (± 1.59)	-24.17 (± 1.74)	-17.94 (± 1.68)	
WP Day 85 (n=67, 47, 52)	-22 (± 2.18)	-21.55 (± 2.57)	-17.54 (± 2.44)	
WP Day 169 (n=41, 31, 32)	-17.43 (± 2.82)	-19.13 (± 3.25)	-13.64 (± 3.19)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving a Health Assessment Questionnaire (HAQ) Response Over Time

End point title	Percentage of Subjects Achieving a Health Assessment Questionnaire (HAQ) Response Over Time

End point description:

HAQ response defined as a reduction of at least 0.3 units from baseline in score on the Health Assessment Questionnaire Disability Index (HAQ-DI), which assesses subject's functional ability by rating their abilities over the previous week. The HAQ-DI includes at least 2 questions from each of 8 categories: dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities. Subjects rate difficulty performing specific tasks: 0=without difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The sum of the categories score (the highest scored item in the category) is divided by the number of categories answered, yielding a score from 0-3. Analysis was performed in all randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period. Percentage calculated as a/b, where a=number of subjects who achieved remission, and b=number of subjects in the analysis.

End point type	Secondary

End point timeframe:

Randomization to Month 24

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: percentage of subjects				
arithmetic mean (confidence interval 95%)				
TP Day 29	42 (33.15 to 50.89)	31 (22.62 to 39.45)	21.6 (14.07 to 29.03)	
TP Day 57	55.5 (46.53 to 64.39)	44 (34.93 to 53)	37.9 (29.1 to 46.76)	
TP Day 85	63 (54.35 to 71.7)	45.7 (36.62 to 54.75)	41.4 (32.42 to 50.34)	
TP Day 113	63 (54.35 to 71.7)	49.1 (40.04 to 58.24)	45.7 (36.62 to 54.75)	
TP Day 141	62.2 (53.47 to 70.9)	51.7 (42.63 to 60.82)	44 (34.93 to 53)	
TP Day 169	63.9 (55.23 to 72.5)	56 (47 to 65.07)	41.4 (32.42 to 50.34)	
TP Day 197	66.4 (57.9 to 74.87)	59.5 (50.55 to 68.42)	41.4 (32.42 to 41.4)	
TP Day 225	66.4 (57.9 to 74.87)	57.8 (48.77 to 66.75)	38.8 (29.93 to 47.66)	
TP Day 253	68.9 (60.59 to 77.22)	55.2 (46.12 to 64.22)	45.7 (36.62 to 54.75)	
TP Day 281	64.7 (56.12 to 73.29)	56.9 (47.88 to 65.91)	46.6 (37.47 to 55.63)	
TP Day 309	65.5 (57.01 to 74.08)	56.99 (47.88 to 65.91)	46.6 (37.47 to 55.63)	
TP Day 337	64.7 (56.12 to 73.29)	55.2 (46.12 to 64.22)	46.6 (37.47 to 55.63)	
TP Day 365	67.2 (58.79 to 75.66)	52.6 (43.5 to 61.67)	44 (34.93 to 53)	
WP Day 29	52.1 (43.13 to 61.08)	39.7 (30.75 to 48.56)	37.1 (28.28 to 45.86)	
WP Day 57	43.7 (34.79 to 52.61)	34.5 (25.83 to 43.13)	26.7 (18.67 to 34.78)	

WP Day 85	39.5 (30.71 to 48.28)	28.4 (20.24 to 36.66)	23.3 (15.59 to 30.97)	
WP Day 169	22.7 (15.16 to 30.21)	16.4 (9.64 to 23.11)	10.3 (4.8 to 15.89)	
WP Day 253	15.1 (8.69 to 21.56)	9.5 (4.15 to 14.81)	6.9 (2.29 to 11.51)	
WP Day 365	10.1 (4.67 to 15.49)	6.9 (2.29 to 11.51)	5.2 (1.14 to 9.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted Mean Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) Response Over Time

End point title	Adjusted Mean Change From Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) Response Over Time

End point description:

HAQ response defined as a reduction of at least 0.3 units from baseline in score on the Health Assessment Questionnaire Disability Index (HAQ-DI), which assesses subject's functional ability by rating their abilities over the previous week. The HAQ-DI includes at least 2 questions from each of 8 categories: dressing and grooming, hygiene, arising, reach, eating, grip, walking, and common daily activities. Subjects rate difficulty performing specific tasks: 0=without difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. The sum of the categories score (the highest scored item in the category) is divided by the number of categories answered, yielding a score from 0-3. Analysis was performed in all randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period. Percentage calculated as a/b, where a=number of subjects who achieved remission at Day x, and b=number of subjects in the analysis.

End point type	Secondary

End point timeframe:

Randomization to Month 24

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Units on a scale				
arithmetic mean (standard error)				
TP Day 29 (n=104, 103, 91)	-0.33 (± 0.05)	-0.21 (± 0.05)	-0.09 (± 0.05)	
TP Day 57 (n=102, 100, 93)	-0.48 (± 0.05)	-0.38 (± 0.05)	-0.32 (± 0.05)	
TP Day 85 (n=105, 97, 88)	-0.64 (± 0.05)	-0.45 (± 0.05)	-0.4 (± 0.05)	
TP Day 113 (n=105, 98, 90)	-0.67 (± 0.05)	-0.55 (± 0.05)	-0.5 (± 0.05)	
TP Day 141 (n=100, 98, 88)	-0.72 (± 0.05)	-0.53 (± 0.05)	-0.46 (± 0.06)	
TP Day 169 (n=95, 95, 85)	-0.74 (± 0.05)	-0.59 (± 0.05)	-0.52 (± 0.06)	
TP Day 197 (n=99, 96, 83)	-0.78 (± 0.05)	-0.62 (± 0.06)	-0.54 (± 0.06)	
TP Day 225 (n=98, 95, 83)	-0.79 (± 0.06)	-0.67 (± 0.06)	-0.56 (± 0.06)	
TP Day 253 (n=96, 91, 84)	-0.82 (± 0.05)	-0.65 (± 0.06)	-0.63 (± 0.06)	
TP Day 281 (n=90, 93, 81)	-0.82 (± 0.06)	-0.65 (± 0.06)	-0.62 (± 0.06)	
TP Day 309 (n=89, 88, 82)	-0.81 (± 0.06)	-0.67 (± 0.06)	-0.66 (± 0.06)	

TP Day 337 (n=88, 85, 80)	-0.84 (± 0.06)	-0.7 (± 0.06)	-0.7 (± 0.06)	
TP Day 365 (n=90, 82, 77)	-0.87 (± 0.06)	-0.73 (± 0.06)	-0.72 (± 0.06)	
WP Day 29 (n=70, 55, 55)	-0.84 (± 0.06)	-0.67 (± 0.07)	-0.63 (± 0.07)	
WP Day 57 (n=66, 53, 54)	-0.67 (± 0.07)	-0.58 (± 0.08)	-0.39 (± 0.08)	
WP Day 85 (n=65, 45, 46)	-0.54 (± 0.08)	-0.48 (± 0.09)	-0.37 (± 0.09)	
WP Day 169 (n=34, 28, 26)	-0.52 (± 0.1)	-0.49 (± 0.11)	-0.33 (± 0.12)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted Mean Change From Baseline at Months 6, 12, and 18 in Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores of Short Form-36 (SF-36)

End point title	Adjusted Mean Change From Baseline at Months 6, 12, and 18 in Physical Component Summary (PCS) and Mental Component Summary (MCS) Scores of Short Form-36 (SF-36)

End point description:

TP=treatment period; WP=withdrawal period. The SF-36 is a 36-item self-administered questionnaire developed to assess health-related quality of life (QOL) and comprises 8 domains, including 4 physical (physical health, bodily pain, physical functioning and physical role limitations) and 4 mental (mental health, vitality, social functioning, and emotional role limitation) subscales. Responses are used to derive physical and mental component summary scores, ranging from 0 to 100, with higher scores indicating better QOL (0=Poorest Health; 100=Best Health). Mean change from baseline=post baseline value-baseline value; a higher value signifies improvement. Analysis was performed in all randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period. n=number of subjects evaluable.

End point type	Secondary

End point timeframe:

Randomization to Months 6, 12, and 18

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Units on a scale				
arithmetic mean (standard error)				
PCS score TP Day 169 (n=106, 95, 96)	11.68 (± 0.82)	9.16 (± 0.86)	7.47 (± 0.85)	
PCS score TP Day 365 (n=94, 88, 91)	13.91 (± 0.93)	10.23 (± 0.97)	10.92 (± 0.95)	
PCS score WP Day 169 (n=48, 36, 37)	6.16 (± 1.45)	4.59 (± 1.65)	6.27 (± 1.63)	
MCS score TP Day 169 (n=106, 95, 96)	6.11 (± 0.92)	3.99 (± 0.97)	4.69 (± 0.95)	
MCS score TP Day 365 (n=94, 88, 91)	7.67 (± 1.04)	5.48 (± 1.08)	7.23 (± 1.06)	
MCS score WP Day 169 (n=48, 36, 37)	2.75 (± 1.44)	4.36 (± 1.64)	2.23 (± 1.63)	

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted Mean Change From Baseline Over Time in Findings on Magnetic Resonance Imaging (MRI)

End point title	Adjusted Mean Change From Baseline Over Time in Findings on Magnetic Resonance Imaging (MRI)

End point description:

TP=treatment period; WP=withdrawal period. MRI was used to assess joint damage progression at Months 6, 12, and 18. If >20% of joints with a missing score for a parameter (erosion, osteitis, and synovitis), the MRI score of each parameter was considered missing. If ≤20% of joints had a missing score for a parameter, the MRI score was carried forward from the previous MRI assessment, or carried backward from the next MRI assessment, if missing score occurred at baseline. MRI total score ranged from 0 (best outcome) to 4 (worst outcome). A gadolinium-enhanced MRI of the dominant hand-wrist was performed on all randomized subjects at 5 points. MRI examination was standardized to ensure sufficient image quality for the evaluation of radiographic progression of rheumatoid arthritis. Analysis was performed in all randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period. n=number of subjects with both baseline and post-baseline measurements.

End point type	Secondary

End point timeframe:

Randomization to Month 18

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Units on a scale				
arithmetic mean (standard error)				
Osteitis TP Day 169 (n=93, 94, 89)	-2.03 (± 0.47)	-1.13 (± 0.47)	-0.73 (± 0.48)	
Osteitis TP Day 365 (n=83, 74, 78)	-2.32 (± 0.46)	-1.3 (± 0.46)	-0.9 (± 0.46)	
Osteitis WP Day 169 (n=31, 30, 25)	-1.94 (± 0.88)	0.98 (± 0.89)	-0.33 (± 0.96)	
Erosion TP Day 169 (n=93, 94, 89)	0.26 (± 0.28)	1.15 (± 0.28)	1.15 (± 0.28)	
Erosion TP Day 365 (n=83, 74, 78)	0.34 (± 0.35)	1.57 (± 0.28)	1.56 (± 0.36)	
Erosion WP Day 169 (n=31, 30, 25)	0.2 (± 0.47)	2.16 (± 0.48)	1.89 (± 0.5)	
Synovitis TP Day 169 (n=93, 94, 89)	-1.82 (± 0.21)	-0.93 (± 0.21)	-0.78 (± 0.21)	
Synovitis TP Day 365 (n=83, 74, 78)	-2.38 (± 0.29)	-1.36 (± 0.3)	-0.77 (± 0.3)	
Synovitis WP Day 169 (n=31, 30, 25)	-1.71 (± 0.45)	-0.95 (± 0.45)	-0.71 (± 0.49)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Death as Outcome, Serious Adverse Events (SAEs), Related SAEs, Discontinuations Due to SAEs, Related Adverse Events (AEs), and Discontinuations Due to AEs During the Treatment Period

End point title	Number of Subjects With Death as Outcome, Serious Adverse Events (SAEs), Related SAEs, Discontinuations Due to SAEs, Related Adverse Events (AEs), and Discontinuations Due to AEs During the Treatment Period

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Related=having certain, probable, possible, or unknown relationship to study drug. Analysis was performed in all the randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period.

End point type	Secondary

End point timeframe:

Day 1 to up to 56 days following the last dosing day (Day 365); all deaths during study period, including those that occurred >56 days after last dose in Treatment Period

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Subjects				
Deaths	0	0	2	
SAEs	8	14	9	
Related SAEs	3	3	1	
Discontinuations due to SAEs	2	5	3	
Related AEs	53	48	51	
Discontinuations due to AEs	4	8	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs) of Interest During the Treatment Period

End point title	Number of Subjects With Adverse Events (AEs) of Interest During the Treatment Period

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Related=having certain, probable, possible, or unknown relationship to study drug. AEs of special interest are events potentially associated with the drug or disease under study. Analysis was performed in all the randomized subjects who received at least 1 dose of double-blind study medication in the Treatment Period.

End point type	Secondary

End point timeframe:

Day 1 to 56 days following last dosing day (Day 365)

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Subjects				
Infections	68	64	63	
Malignancy	1	2	1	
Autoimmune disorders (pre-specified)	1	2	3	
Local injection site reactions (pre-specified)	2	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Results on Hematology and Clinical Laboratory Tests Meeting the Criteria for Marked Abnormality During Treatment Period

End point title	Number of Subjects With Results on Hematology and Clinical Laboratory Tests Meeting the Criteria for Marked Abnormality During Treatment Period

End point description:

Lower limit of normal (LLN); Upper limit of normal (ULN); Pretreatment (preRX). Criteria for marked abnormality: Platelet count (*10^9 c/µL) >1.5*ULN; potassium, serum (mEq) <0.9*LLN, or if preRX <LLN, use <0.9*preRX; blood urea nitrogen (mg/dL) >2*preRX; creatinine (mg/dL) >1.5*preRX; ALT (U/L) >3*ULN, or if preRX>ULN, use >4*preRX; AST (U/L) >3*ULN, or if preRX>ULN, use >4*preRX; ALP (U/L) >2*ULN, or if preRX>ULN, use >3*preRX; GGT (U/L) >2*ULN, or if preRX>ULN, use >3*preRX; glucose, fasting (mg/dL) <0.8*LLN or >1.5*ULN, or if preRX<LLN use <0.8*preRX or >ULN if preRX >ULN, use >2.0*preRX or OR <LLN; glucose, serum (mg/dL) <65 or >220; uric acid (mg/dL)>1.5*ULN, or if preRX, use >2*preRX; albumin (g/dL) <0.9*LLN, or if preRX<LLN, use <0.75*preRX; hemoglobin (g/dL)>3 decrease from preRX; hematocrit (%) <0.75*preRX. Analysis was performed in all randomized subjects who received at least 1 dose in Treatment Period. n=number of

End point type	Secondary

End point timeframe:

Day 1 up to 56 days following the last dosing day in the Treatment Period (Day 365)

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Subjects				
Platelet count (high) (n=119, 116, 115)	2	0	0	
Potassium, serum (low)	1	1	1	
Blood urea nitrogen (high)	4	1	2	
Creatinine (high)	2	1	3	
Alanine aminotransferase (ALT)(high)	3	0	2	
Aspartate aminotransferase (AST)(high)	2	0	1	
G-glutamyl transferase (GGT) (high)	3	1	1	
Glucose, fasting (low) (n=78, 72, 75)	2	0	2	

Glucose, fasting (high) (n=78, 72, 75)	1	2	1	
Glucose, serum (low) (n=84, 78, 75)	5	6	2	
Glucose, serum (high) (n=84, 78, 75)	1	4	3	
Uric acid (high)	0	1	0	
Albumin (low)	1	1	4	
Hemoglobin (low) (n=119, 116, 115)	0	2	0	
Hematocrit (low) (n=119, 116, 115)	0	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria Over Time During Withdrawal Period- Treated subjects in Remission at Month 12

End point title	Percentage of Subjects With Remission by Disease Activity Score 28 Based on C-reactive Protein (DAS28-CRP) Criteria Over Time During Withdrawal Period- Treated subjects in Remission at Month 12

End point description:

WP=withdrawal period. Remission defined as DAS28-CRP<2.6. The DAS 28-CRP is a measure of disease activity in rheumatoid arthritis (RA) and assesses the 28 joints RA commonly affects; the score includes the number of tender and swollen joints (out of 28), CRP level (a measure of inflammation in the blood), and the subject's global assessment of health (ranging from very good to very bad). DAS-CRP scores range from 0 to 10, with higher values indicating greater disease activity. The overall DAS score greater than 5.1 implies active disease; less than 3.2, well controlled disease; and less than 2.6, remission. Percentage= number of subjects with remission divided by number of subjects who were analyzed (all treated subjects who were in remission at end of treatment period and entered the Withdrawal Period). Analysis was performed in all the treated subjects who were in remission at Month 12 (DAS28-CRP<2.6) and entered the Withdrawal Period. (N=number of subjects analyzed).

End point type	Secondary

End point timeframe:

End of Treatment Period (Month 12) to End of Withdrawal Period (Month 24)

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	73	50	53	
Units: percentage of subjects				
number (confidence interval 95%)				
WP Day 29	75.3 (65.46 to 85.23)	72 (59.55 to 84.45)	54.7 (41.32 to 68.12)	
WP Day 57	58.9 (47.62 to 70.19)	56 (42.24 to 69.76)	32.1 (19.51 to 44.64)	
WP Day 85	42.5 (31.13 to 53.8)	40 (26.42 to 53.58)	35.8 (22.94 to 48.76)	
WP Day 169	26 (15.96 to 36.09)	30 (17.3 to 42.7)	17 (6.87 to 27.09)	
WP Day 253	20.5 (11.28 to 29.82)	22 (10.52 to 33.48)	20.8 (9.84 to 31.67)	

WP Day 365	12.3 (4.79 to 19.87)	14 (4.38 to 23.62)	11.3 (2.79 to 19.85)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI) Over Time in Treatment Period (TP) and Withdrawal Period (WP)

End point title	Percentage of Subjects Who Achieved Remission by Criteria of the Simplified Disease Activity Index (SDAI) Over Time in Treatment Period (TP) and Withdrawal Period (WP)

End point description:

SDAI-defined remission as ≤3.3. The SDAI is simple linear sum of 5 outcome parameters: tender joint count (TJC); swollen joint count (SJC) (based on a 28-joint assessment); subject's and physician's global assessments of disease activity (assessed on 0-10 cm visual analog scale, higher score=greater affection due to disease activity); and C-reactive protein level (mg/dL). SDAI total score=0-86. SDAI <=3.3 indicates disease remission, >3.4 to 11=low, >11 to 26=moderate, and >26=high disease activity. TJC was assessed as no swelling=0, swelling=1. SJC is assessed through painful joints under pressure or to passive motion. TJC is assessed as no tenderness =0, tenderness = 1. Higher score=greater affection due to disease activity. Percent=number with remission/number evaluated. Analysis was performed in all randomized subjects who received at least 1 dose in TP. Subjects were grouped according to treatment regimen to which they were randomized. N= number of subject evaluated.

End point type	Secondary

End point timeframe:

Randomization to Month 24

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: percentage of subjects				
number (confidence interval 95%)				
TP Day 29	4.2 (1.38 to 9.53)	3.4 (0.95 to 8.59)	1.7 (0.21 to 6.09)	
TP Day 57	9.2 (4.71 to 15.94)	6 (2.46 to 12.04)	1.7 (0.21 to 6.09)	
TP Day 85	17.6 (10.8 to 24.5)	8.6 (3.51 to 13.73)	6 (1.7 to 10.37)	
TP Day 113	23.5 (15.91 to 31.15)	17.2 (10.37 to 24.12)	7.8 (2.89 to 12.63)	
TP Day 141	31.9 (23.56 to 40.31)	23.3 (15.59 to 30.97)	10.3 (4.8 to 15.89)	
TP Day 169	31.1 (22.78 to 39.41)	20.7 (13.32 to 28.06)	11.2 (5.47 to 16.95)	
TP Day 197	33.6 (25.13 to 42.1)	21.6 (14.07 to 29.03)	12.9 (6.82 to 19.04)	

TP Day 225	38.7 (29.91 to 47.4)	25.9 (17.89 to 33.83)	14.7 (8.22 to 21.09)	
TP Day 253	37.8 (29.1 to 46.53)	25 (17.12 to 32.88)	13.8 (7.52 to 20.07)	
TP Day 281	37.8 (29.1 to 46.53)	26.7 (18.67 to 34.78)	18.1 (11.1 to 25.11)	
TP Day 309	40.3 (31.52 to 49.15)	26.7 (18.67 to 34.78)	19 (11.83 to 26.1)	
TP Day 337	41.2 (32.33 to 50.02)	31 (22.62 to 39.45)	19 (11.83 to 26.1)	
TP Day 365	42 (33.15 to 50.89)	29.3 (21.03 to 37.59)	25 (17.12 to 32.88)	
WP Day 29	38.7 (29.91 to 47.4)	26.7 (18.67 to 34.78)	14.7 (8.22 to 21.09)	
WP Day 57	26.9 (18.92 to 34.86)	20.7 (13.32 to 28.06)	10.3 (4.8 to 15.89)	
WP Day 85	21 (13.69 to 28.33)	15.5 (8.93 to 22.11)	14.7 (8.22 to 21.09)	
WP Day 169	11.8 (5.98 to 17.55)	9.5 (4.15 to 14.81)	6.9 (2.29 to 11.51)	
WP Day 253	11.8 (5.98 to 17.55)	9.5 (4.15 to 14.81)	7.8 (2.89 to 12.63)	
WP Day 365	6.7 (2.22 to 11.22)	4.3 (0.61 to 8.01)	4.3 (0.61 to 8.01)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Death as Outcome, Serious Adverse Events (SAEs) and Discontinuations Due to AEs During the Full Study (All Periods)

End point title	Number of Subjects With Death as Outcome, Serious Adverse Events (SAEs) and Discontinuations Due to AEs During the Full Study (All Periods)

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Includes data up to last active dose date +56 days if the subjects discontinued the Treatment Period or did not enter the Withdrawal Period, up to the day of discontinuation in the Withdrawal Period for subjects discontinuing the Withdrawal Period without entering the Re-exposure Period (RP), up to Day 729 visit (Month 24) for subjects who complete the Withdrawal Period, and up to 56 days post last active dose in Re-exposure Period for subjects entering the Re-exposure Period. Analysis was performed in all the randomized subjects who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Day 1 to 56 days post last dose (TP: Day 365; WP: >56 days after last dose in TP, up to Month 24; RP: first dose to last dose + 56 days, up to Month 30

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	119	116	116	
Units: Subjects				
Death	0	0	2	
SAE	11	15	15	
Discontinued Due to AE	4	8	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events (AEs) of Interest During the Withdrawal Period AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that

End point title	Number of subjects with Adverse Events (AEs) of Interest During the Withdrawal Period AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. AEs of special interest are events potentially associated with the drug or disease under study. Includes events with an onset date on or after 57 days post last dosing day (active abatacept or active MTX whichever is the later) in the Treatment Period (TP) and up to end of Withdrawal Period. Treatment groups represent treatment received during the TP. Analysis was performed in all the randomized subjects who received at least 1 dose of double-blind study medication in the TP and entered the Withdrawal Period.

End point type	Secondary

End point timeframe:

Last dose in TP + 57 days, up to Month 24

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	66	75	
Units: Subjects				
Infections	8	6	10	
Malignancy	1	0	1	
Auto-immune disorders (pre-specified)	0	0	1	
Local injection site reactions (pre-specified)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Adverse Events (AEs) of Interest During the Re-exposure Period

End point title	Number of subjects with Adverse Events (AEs) of Interest During the Re-exposure Period

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. AEs of special interest are events potentially associated with the drug or disease under study. Includes data up to 56 days post the last dosing day (active abatacept or active MTX, whichever is the later) in the Re-exposure Period. Treatment groups represent Treatment received during Treatment Period.

End point type	Secondary

End point timeframe:

End of Withdrawal Period (up to Month 24) up to last dose of Re-exposure Period + 56 days

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	48	43	
Units: Subjects				
Infections	17	8	12	
Malignancy	0	0	0	
Auto-immune Disorders (pre-specified)	0	0	0	
Local Injection site reactions (pre-specified)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Results on Hematology and Clinical Laboratory Tests Meeting the Criteria for Marked Abnormality in Withdrawal Period

End point title	Number of Subjects With Results on Hematology and Clinical Laboratory Tests Meeting the Criteria for Marked Abnormality in Withdrawal Period

End point description:

LLN=lower limit of normal; ULN=upper limit of normal; preRX=pretreatment. Criteria for marked

abnormality on laboratory test results: creatinine (mg/dL) >1.5*preRX; ALT (U/L) >3*ULN, or if preRX>ULN, use >4*preRX; G-glutamyl transferase (GGT) (U/L) >2*ULN, or if preRX>ULN, use >3*preRX; glucose, fasting (mg/dL) <0.8*LLN or >1.5*ULN, or if preRX<LLN use <0.8*preRX or >ULN if preRX >ULN, use >2.0*preRX or OR <LLN; glucose, serum (mg/dL) <65 or >220; uric acid (mg/dL)>1.5*ULN, or if preRX, use >2*preRX; hemoglobin (g/dL)>3 decrease from preRX. Analysis was performed in all the randomized subjects who received at least 1 dose of study drug in the Treatment Period, entered the Withdrawal Period, and had values available. n=number of subjects evaluable.

End point type	Secondary

End point timeframe:

End of Withdrawal Period (up to Month 24) up to last dose of Re-exposure Period + 56 days

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84	66	75	
Units: Subjects				
Hemoglobin Low (n=60, 52, 48)	1	2	0	
Creatinine High (n=60, 52, 48)	1	2	2	
Alanine aminotransferase (ALT) High (n=60, 52, 48)	1	0	0	
GGT High (n=60, 52, 48)	1	0	0	
Fasting Glucose High (30, 28, 25)	0	2	1	
Glucose Low (n=36,31,27)	5	3	0	
Glucose High (n=36, 31, 27)	0	1	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Results on Hematology and Clinical Laboratory Tests Meeting the Criteria for Marked Abnormality in Re-exposure Period

End point title	Number of Subjects With Results on Hematology and Clinical Laboratory Tests Meeting the Criteria for Marked Abnormality in Re-exposure Period

End point description:

LLN=lower limit of normal; ULN=upper limit of normal; preRX=pretreatment. Criteria for marked abnormality on laboratory test results: creatinine (mg/dL) >1.5*preRX; ALT (U/L) >3*ULN, or if preRX>ULN, use >4*preRX; AST (U/L) >3*ULN, or if preRX>ULN, use >4*preRX; ALP (U/L) >2*ULN, or if preRX>ULN, use >3*preRX; G-glutamyl transferase U/L) >2*ULN, or if preRX>ULN, use >3*preRX; glucose, fasting (mg/dL) <0.8*LLN or >1.5*ULN, or if preRX<LLN use <0.8*preRX or >ULN if preRX >ULN, use >2.0*preRX or OR <LLN; glucose, serum (mg/dL) <65 or >220; hemoglobin (g/dL)>3 decrease from preRX; hematocrit (%) < 0.75*preRX. Analysis was performed in all all the treated subjects entering the Re-exposure Period and having measurements available were analyzed. n= number of subjects evaluable. Treatment groups represent Treatment received during Treatment Period.

End point type	Secondary

End point timeframe:

Start of re-exposure period to 56 days post last dose, up to Month 30

End point values	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	48	43	
Units: Subjects				
Hematocrit Low (n=55,47,43)	0	1	0	
Hemoglobin Low (n=55,48, 43)	0	2	0	
Creatinine High (n=55, 48, 43)	0	1	0	
ALT High (n=55, 48, 43)	2	0	2	
ALP High (n=55, 48, 43)	1	0	0	
AST High (n=55, 48, 43)	2	0	1	
GGT High (n=55, 48, 43)	2	0	1	
Fasting Glucose Low (n=33, 32, 28)	1	0	0	
Fasting Glucose High (n=33, 32, 28)	0	2	1	
Glucose Low (n=27,24,18)	0	2	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to last dose + 56 days, up to 30 Months

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate (MTX), 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept subcutaneous (SC) 125 mg/week and MTX.

Reporting group title	Abatacept, 125 mg, Plus Methotrexate Placebo

Reporting group description:

Subjects received abatacept, 125 mg subcutaneously, plus methotrexate placebo tablets orally, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of <3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Reporting group title	Methotrexate, 2.5 mg, Plus Abatacept Placebo

Reporting group description:

Subjects received methotrexate, 2.5 mg orally as tablets, with a target dose range of 10-20 mg weekly, plus abatacept placebo subcutaneously, once weekly during the 12-month Treatment Period. Subjects with a Low Disease Activity Score (LDAS) defined as DAS28-CRP score of < 3.2 at Month 12 (end of Treatment Period) entered the Withdrawal Period for up to 12 months, during which all study medication was withdrawn. Subjects with a DAS28-CRP score of >3.2 were discontinued from the study. All MTX and corticosteroids, if not already discontinued, were to be tapered off during the first month of the Withdrawal Period. Subjects who experienced a worsening of rheumatoid arthritis (RA) symptoms or a RA flare after at least 3 months in the Withdrawal Period were eligible to enroll into a 6-month Re-exposure Period, during which they received open-label treatment with abatacept SC (125 mg/week) and MTX.

Serious adverse events	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 119 (9.24%)	15 / 116 (12.93%)	15 / 116 (12.93%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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
Bowen's disease			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Carcinoid tumour pulmonary			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Colon adenoma			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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
Uterine cancer			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine neoplasm			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

General disorders and administration site conditions			
Strangulated hernia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Immune system disorders			
Myocardial infarction			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Reproductive system and breast disorders			
Endometrial disorder			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Respiratory, thoracic and mediastinal disorders			
Emphysema			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Respiratory failure			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Investigations			
Hepatic enzyme			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transaminases increased			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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
Injury, poisoning and procedural complications			
Hand fracture			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Overdose			
subjects affected / exposed	3 / 119 (2.52%)	1 / 116 (0.86%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	2 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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
Tendon rupture			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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			
Myocarditis post infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Sciatica			

subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Pancytopenia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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
Gastrointestinal disorders			
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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
Cholecystitis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 116 (0.00%)	0 / 116 (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
Rheumatoid arthritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
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			
Abscess limb			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Herpes zoster			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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
Pneumonia			

subjects affected / exposed	1 / 119 (0.84%)	1 / 116 (0.86%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 119 (0.00%)	0 / 116 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 119 (0.00%)	1 / 116 (0.86%)	0 / 116 (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

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

Non-serious adverse events	Abatacept, 125 mg, Plus Methotrexate, 2.5 mg	Abatacept, 125 mg, Plus Methotrexate Placebo	Methotrexate, 2.5 mg, Plus Abatacept Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 119 (68.07%)	64 / 116 (55.17%)	78 / 116 (67.24%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 119 (3.36%)	2 / 116 (1.72%)	6 / 116 (5.17%)
occurrences (all)	4	2	6
Pregnancy, puerperium and perinatal conditions			
Pharyngitis			
subjects affected / exposed	3 / 119 (2.52%)	6 / 116 (5.17%)	7 / 116 (6.03%)
occurrences (all)	5	6	8
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 119 (6.72%)	8 / 116 (6.90%)	7 / 116 (6.03%)
occurrences (all)	10	9	7
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	5 / 119 (4.20%)	6 / 116 (5.17%)	6 / 116 (5.17%)
occurrences (all)	5	6	10
Gastritis			
subjects affected / exposed	4 / 119 (3.36%)	1 / 116 (0.86%)	7 / 116 (6.03%)
occurrences (all)	4	1	7
Diarrhoea			
subjects affected / exposed	5 / 119 (4.20%)	8 / 116 (6.90%)	4 / 116 (3.45%)
occurrences (all)	6	8	4
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 119 (5.04%)	1 / 116 (0.86%)	1 / 116 (0.86%)
occurrences (all)	9	1	1
Mouth ulceration			
subjects affected / exposed	6 / 119 (5.04%)	5 / 116 (4.31%)	2 / 116 (1.72%)
occurrences (all)	10	5	2
Nausea			
subjects affected / exposed	18 / 119 (15.13%)	8 / 116 (6.90%)	16 / 116 (13.79%)
occurrences (all)	26	8	18
Vomiting			
subjects affected / exposed	6 / 119 (5.04%)	3 / 116 (2.59%)	1 / 116 (0.86%)
occurrences (all)	6	3	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 119 (3.36%)	9 / 116 (7.76%)	7 / 116 (6.03%)
occurrences (all)	4	12	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 119 (6.72%)	6 / 116 (5.17%)	10 / 116 (8.62%)
occurrences (all)	8	7	12
Gastroenteritis			
subjects affected / exposed	6 / 119 (5.04%)	3 / 116 (2.59%)	8 / 116 (6.90%)
occurrences (all)	6	3	11
Influenza			
subjects affected / exposed	5 / 119 (4.20%)	9 / 116 (7.76%)	6 / 116 (5.17%)
occurrences (all)	5	12	7
Nasopharyngitis			

subjects affected / exposed	28 / 119 (23.53%)	20 / 116 (17.24%)	22 / 116 (18.97%)
occurrences (all)	45	35	28
Sinusitis			
subjects affected / exposed	9 / 119 (7.56%)	4 / 116 (3.45%)	2 / 116 (1.72%)
occurrences (all)	11	4	3
Upper respiratory tract infection			
subjects affected / exposed	15 / 119 (12.61%)	15 / 116 (12.93%)	20 / 116 (17.24%)
occurrences (all)	21	24	25
Urinary tract infection			
subjects affected / exposed	14 / 119 (11.76%)	15 / 116 (12.93%)	15 / 116 (12.93%)
occurrences (all)	23	16	17

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2011	Incidences of Disease Activity Score was updated to Disease Activity Score 28 using C-reactive protein and time frame for stable oral corticosteroid use as well as routes of administration were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported