Clinical trial results:
A Phase IIIB Multicenter, Randomized, Double-Blind, Double-Dummy Study to Compare the Efficacy and Safety of Abatacept Administered Subcutaneously and Intravenously in Subjects with Rheumatoid Arthritis, Receiving Background Methotrexate, and Experiencing an Inadequate Response to Methotrexate.

Summary

EudraCT number	2007-005434-37
Trial protocol	FR IE HU GB BE DE NL IT AT GR
Global end of trial date	12 September 2014

Results information

Result version number	v1 (current)
This version publication date	18 May 2016
First version publication date	18 May 2016

Trial information

Trial identification

Sponsor protocol code	IM101-174

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00559585
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	12 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study is to demonstrate that subcutaneous (SC) injections of abatacept are non-inferior to intravenous (IV) infusions of abatacept in ACR 20 responses after 6 months of treatment in subjects who have active RA, are receiving methotrexate and experiencing an inadequate response to methotrexate. The main objective of the long-term (LT) period was to assess the safety and long-term tolerability of SC injections of abatacept as well as the maintenance of efficacy responses in subjects who completed the initial 6-month short-term (ST) period.

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: -

Actual start date of recruitment	17 January 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 290
Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Brazil: 163
Country: Number of subjects enrolled	Canada: 60
Country: Number of subjects enrolled	Chile: 79
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	India: 75
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Korea, Republic of: 76
Country: Number of subjects enrolled	Mexico: 433

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Peru: 201
Country: Number of subjects enrolled	Poland: 200
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	South Africa: 122
Country: Number of subjects enrolled	Taiwan: 51
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	United States: 468
Worldwide total number of subjects	2493
EEA total number of subjects	360

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)	2163
From 65 to 84 years	329
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 222 centers in 24 countries.

Pre-assignment

Screening details:

2493 subjects were enrolled in the study: Enrolled for Double blind short term period - 2473; randomised - 1464; randomised and treated - 1457. 20 enrolled in Anti-TNF sub-study: randomized in substudy - 18.

Period 1

Period 1 title	Short Term Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Both subject and investigator were blinded in the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Subcutaneous (SC) Abatacept

Arm description:

Subjects received weekly injections of 125 mg SC abatacept for 6 months (with a loading dose of IV abatacept on Day 1, based on weight). A double-dummy design was used to protect the blind, thus, Subjects also received IV injections of placebo (IV placebo) with the exception that on Day 1, a loading dose of IV abatacept replaced the IV placebo treatment.

Arm type	Experimental
Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS-188667
Other name	Orencia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125-mg/mL was administered as subcutaneous injection once weekly.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept was administered as intravenous infusion on day 1 based on weight of the subject: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg.

Investigational medicinal product name	Abatacept matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept matching placebo was administered as intravenous infusion on Day 15, Day 29, and every 28 days thereafter through day 141.

Arm title	Intravenous (IV) Abatacept

Arm description:

Subjects received IV abatacept infusions on Days 1, 15, and 29 and every 28 days thereafter. A double-dummy design was used to protect the blind, thus, Subjects also received subcutaneous injections of placebo (subcutaneous placebo).

Arm type	Active comparator
Investigational medicinal product name	Abatacept matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept matching placebo was administered as subcutaneous injection on Day 8 and weekly thereafter.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS-188667
Other name	Orencia
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept was administered as intravenous infusion based on the weight of the subject: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg.

Arm title	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)

Arm description:

Subjects who had failed one anti-TNF therapy received abatacept 125 mg subcutaneous injections once weekly for 6 months (with an IV abatacept loading dose on Day 1, based on weight: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg). A double-dummy design was used to protect the blind, thus, subjects also received IV injections of placebo (IV Placebo) with the exception that on Day 1 a loading dose of IV abatacept replaced the IV Placebo treatment.

Arm type	Experimental
Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS-188667
Other name	Orencia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125-mg/mL was administered as subcutaneous injection once weekly.

Investigational medicinal product name	Abatacept matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept matching placebo was administered as intravenous infusion on Day 15, Day 29, and every 28 days thereafter through day 141.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept was administered as intravenous infusion on day 1 based on weight of the subject: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg.

Arm title	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)

Arm description:

Subjects who had failed one anti-TNF therapy received IV abatacept infusions on Days 1, 15, 29, and every 28 days, thereafter for 6 months. A double-dummy design was used to protect the blind, thus, subjects also received SC injections of placebo (SC Placebo).

Arm type	Active comparator
Investigational medicinal product name	Abatacept matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept matching placebo was administered as subcutaneous injection on Day 8 and weekly thereafter.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS-188667
Other name	Orencia
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept was administered as intravenous infusion based on the weight of the subject: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg.

Number of subjects in period 1[1]	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)
Started	736	721	8
Completed	693	676	7
Not completed	43	45	1
Physician decision	-	1	-
Missed doses	-	1	-
Subject no longer meets study criteria	2	1	-
Suspended drug due to surgery	-	1	-
Subject Withdrew-Recurrent Infection	-	1	-
Consent withdrawn by subject	11	5	-
Subject gain weight	1	-	-
Adverse event, non-fatal	17	25	-
Death	1	1	-
Poor compliance/noncompliance	3	-	-
Ongoing Infection Risk	1	-	-
Incomplete breast exam	-	1	-
Lost to follow-up	-	6	-
Early discontinuation	-	1	-
Lack of efficacy	6	1	1
Administrative reason by sponsor	1	-	-

Number of subjects in period 1[1]	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)
Started	10
Completed	9
Not completed	1
Physician decision	-
Missed doses	-
Subject no longer meets study criteria	-
Suspended drug due to surgery	-
Subject Withdrew-Recurrent Infection	-
Consent withdrawn by subject	-
Subject gain weight	-
Adverse event, non-fatal	-
Death	-
Poor compliance/noncompliance	-
Ongoing Infection Risk	-
Incomplete breast exam	-
Lost to follow-up	-
Early discontinuation	-
Lack of efficacy	1
Administrative reason by sponsor	-

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: 2493 subjects were enrolled in the study: 2473 were enrolled for Double blind short term period; 1464 were randomised; 1457 were randomised and treated. Reasons for enrolled but not randomised were: withdrew consent - 61, lost to follow-up - 7, subject no longer meet study criteria - 918, other reasons - 23. 20 enrolled in Anti-TNF sub-study; 2 not randomised as no longer met criteria; 18 randomized in substudy.

Period 2

Period 2 title	Open Label LT Period Main + Sub-Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Subcutaneous (SC) Abatacept

Arm description:

Subjects could either continue with or switch to 125 mg weekly SC abatacept injections until the SC formulation became commercially available on a country basis or the Sponsor terminated the study. The Anti-TNF Sub-study terminated due to low recruitment and Subjects were permitted to roll into the LT Open Label Period.

Arm type	Experimental

Investigational medicinal product name	Abatacept
Investigational medicinal product code	BMS-188667
Other name	Orencia
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Abatacept 125-mg/mL was administered as subcutaneous injection once weekly.

Investigational medicinal product name	Abatacept matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept matching placebo was administered as intravenous infusion on Day 15, Day 29, and every 28 days thereafter through day 141.

Investigational medicinal product name	Abatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Abatacept was administered as intravenous infusion on day 1 based on weight of the subject: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg.

Number of subjects in period 2[2]	Subcutaneous (SC) Abatacept
Started	1373
Completed	945
Not completed	428
Consent withdrawn by subject	81
Adverse event, non-fatal	100
Death	20
Poor compliance/noncompliance	8
no end of study status page	1
Pregnancy	16
non-specified	71
Lost to follow-up	32
No longer met criteria	1
Administrative reason by sponsor	9
Lack of efficacy	89

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 1385 subjects who completed the short term double blind period, 1373 entered into

long term period.

Baseline characteristics

Reporting groups	
Reporting group title	Subcutaneous (SC) Abatacept
Reporting group description:	
Subjects received weekly injections of 125 mg SC abatacept for 6 months (with a loading dose of IV abatacept on Day 1, based on weight). A double-dummy design was used to protect the blind, thus, Subjects also received IV injections of placebo (IV placebo) with the exception that on Day 1, a loading dose of IV abatacept replaced the IV placebo treatment.	
Reporting group title	Intravenous (IV) Abatacept
Reporting group description:	
Subjects received IV abatacept infusions on Days 1, 15, and 29 and every 28 days thereafter. A double-dummy design was used to protect the blind, thus, Subjects also received subcutaneous injections of placebo (subcutaneous placebo).	
Reporting group title	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)
Reporting group description:	
Subjects who had failed one anti-TNF therapy received abatacept 125 mg subcutaneous injections once weekly for 6 months (with an IV abatacept loading dose on Day 1, based on weight: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg). A double-dummy design was used to protect the blind, thus, subjects also received IV injections of placebo (IV Placebo) with the exception that on Day 1 a loading dose of IV abatacept replaced the IV Placebo treatment.	
Reporting group title	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)
Reporting group description:	
Subjects who had failed one anti-TNF therapy received IV abatacept infusions on Days 1, 15, 29, and every 28 days, thereafter for 6 months. A double-dummy design was used to protect the blind, thus, subjects also received SC injections of placebo (SC Placebo).	

Reporting group values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)
Number of subjects	736	721	8
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	49.9	50.1	43
standard deviation	± 13.2	± 12.6	± 16.6
Gender categorical Units: Subjects			
Female	621	580	8
Male	115	141	0
Weight category Units: Subjects			
<60 kg	186	179	2
60-100 kg	492	489	5
>100 kg	58	53	1
Race Units: Subjects			
White	550	537	7
Black/African American	29	27	1
American Indian/Alaska Native	5	1	0

Asian	64	73	0
Native Hawaiian/other Pacific Islander	0	0	0
Other	88	83	0
Region Units: Subjects			
North America	142	128	7
South America	359	349	0
Europe	127	128	1
Rest of World	108	116	0
Duration of disease category Units: Subjects			
<= 2 years	240	221	5
2 - <= 5 years	155	150	2
5- <= 10 years	142	164	0
> 10 years	199	186	1
Rheumatoid Factor Status			
Rheumatoid factor (RF or RhF) is an autoantibody (antibody directed against an organism's own tissues) most relevant in rheumatoid arthritis. It is an antibody against the Fc portion of Immunoglobulin (Ig)G, which is itself an antibody. RF and IgG join to form immune complexes which contribute to the disease process. A positive value for RF was >20 IU/mL; a negative value for RF was ≤ 20 IU/mL.			
Units: Subjects			
Negative	110	100	4
Positive	614	611	4
Unknown	12	10	0
Weight Units: kilogram(s)			
arithmetic mean	72	71.8	72.9
standard deviation	± 18	± 17.6	± 21.5
Duration of disease Units: year			
arithmetic mean	7.6	7.7	4.6
standard deviation	± 8.1	± 7.8	± 7.5
Number of Tender Joints Units: tender joints			
arithmetic mean	30.1	29.1	29.4
standard deviation	± 14.1	± 13.3	± 15.2
Number of Swollen Joints Units: swollen joints			
arithmetic mean	20.4	19.4	20.4
standard deviation	± 9.6	± 8.6	± 11.8
Subject Pain Assessment			
The subject self-reported pain assessment is a core component of the ACR scoring system where increasing score indicates increasing level of severity as indicated on a 100 mm Visual Analog Scale (VAS) with 0 mm representing no pain and 100 mm representing the most pain possible. For each post-baseline visit in the DB, time-matched baseline Subject Pain Assessment values were presented and represent the mean baseline value for only that cohort of subjects with assessments available at that visit.			
Units: units on a scale			
arithmetic mean	67.8	66.8	76
standard deviation	± 20.1	± 20.5	± 18.2
Physical Function (Health Assessment Questionnaire Disability Index [HAQ-DI])			
The disability section of the full HAQ includes 20 questions to assess physical The HAQ-DI includes 20			

questions to assess physical function in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. The domain questions are evaluated on a 4-point scale: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do. HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. HAQ-DI overall score ranges from a minimum of 0 to a maximum of 3.0.			
Units: units on a scale			
arithmetic mean	1.72	1.67	1.97
standard deviation	± 0.68	± 0.67	± 0.44
Subject Global Assessment			
Subjects used a horizontal VAS of 100 mm for overall assessment of rheumatoid arthritis. Scale ranged from 0 (very well) to 100 (very poor). Subjects were instructed to draw a vertical through a horizontal line to indicate state of rheumatoid arthritis. Distance from the "very well" end of the horizontal line to the vertical line drawn by the subject was the global disease assessment score on a scale of 1-10, where 1=controlled or equivocal rheumatoid arthritis activity, 1.1-4=mild activity, 4-8=moderate activity, and 8.1-10=high activity.			
Units: units on a scale			
arithmetic mean	66.8	64.9	70.9
standard deviation	± 20.4	± 20	± 23.6
Physician Global Assessment			
Physician global rheumatoid arthritis assessment core component of the ACR scoring system where increasing score indicates increasing level of severity as indicated on a 100 mm Visual Analog Scale, with 0 mm representing no pain and 100 mm representing the most pain possible.			
Units: units on a scale			
arithmetic mean	64.3	63.1	66.5
standard deviation	± 16.5	± 16.6	± 17.3
High Sensitivity C-Reactive Protein (hsCRP) Level			
Hs-CRP is an acute phase reactant protein that is a clinical marker for Rheumatoid Arthritis (RA). Levels of hs-CRP can be used to determine Disease Activity Score (DAS28).			
Units: mg/dL			
arithmetic mean	2.62	2.71	2.98
standard deviation	± 2.9	± 2.94	± 3.14
Disease Activity Score (CRP)			
The DAS28 (CRP) is a continuous disease measure which is a composite of 4 variables: the 28 tender joint count, the 28 swollen joint count, CRP levels, and subject assessment of disease activity measure on a visual analogue scale. The DAS28 has numeric thresholds that define high disease activity (>5.1), low disease activity (<3.2) and remission (<2.6). A clinically significant response= decrease in DAS28 score of >1.2 from baseline.			
Units: units on a scale			
arithmetic mean	6.23	6.2	6.31
standard deviation	± 0.85	± 0.84	± 0.81
Baseline Methotrexate (MTX) Dose			
Units: mg/wk			
arithmetic mean	16.3	16.5	14.4
standard deviation	± 3.6	± 3.8	± 3.5

Reporting group values	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)	Total	
Number of subjects	10	1475	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	47.4		
standard deviation	± 11.9	-	

Gender categorical Units: Subjects			
Female	9	1218	
Male	1	257	
Weight category Units: Subjects			
<60 kg	2	369	
60-100 kg	6	992	
>100 kg	2	114	
Race Units: Subjects			
White	9	1103	
Black/African American	0	57	
American Indian/Alaska Native	0	6	
Asian	1	138	
Native Hawaiian/other Pacific Islander	0	0	
Other	0	171	
Region Units: Subjects			
North America	7	284	
South America	0	708	
Europe	3	259	
Rest of World	0	224	
Duration of disease category Units: Subjects			
<= 2 years	4	470	
2 - <= 5 years	0	307	
5- <= 10 years	2	308	
> 10 years	4	390	
Rheumatoid Factor Status			
Rheumatoid factor (RF or RhF) is an autoantibody (antibody directed against an organism's own tissues) most relevant in rheumatoid arthritis. It is an antibody against the Fc portion of Immunoglobulin (Ig)G, which is itself an antibody. RF and IgG join to form immune complexes which contribute to the disease process. A positive value for RF was >20 IU/mL; a negative value for RF was ≤ 20 IU/mL.			
Units: Subjects			
Negative	4	218	
Positive	6	1235	
Unknown	0	22	
Weight Units: kilogram(s)			
arithmetic mean	85.8		
standard deviation	± 18.9	-	
Duration of disease Units: year			
arithmetic mean	12.4		
standard deviation	± 13.3	-	
Number of Tender Joints Units: tender joints			
arithmetic mean	24.4		
standard deviation	± 16.3	-	
Number of Swollen Joints			

Units: swollen joints			
arithmetic mean	17.7		
standard deviation	± 15.1	-	
Subject Pain Assessment			
The subject self-reported pain assessment is a core component of the ACR scoring system where increasing score indicates increasing level of severity as indicated on a 100 mm Visual Analog Scale (VAS) with 0 mm representing no pain and 100 mm representing the most pain possible. For each post-baseline visit in the DB, time-matched baseline Subject Pain Assessment values were presented and represent the mean baseline value for only that cohort of subjects with assessments available at that visit.			
Units: units on a scale			
arithmetic mean	57.5		
standard deviation	± 23.9	-	
Physical Function (Health Assessment Questionnaire Disability Index [HAQ-DI])			
The disability section of the full HAQ includes 20 questions to assess physical The HAQ-DI includes 20 questions to assess physical function in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. The domain questions are evaluated on a 4-point scale: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do. HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. HAQ-DI overall score ranges from a minimum of 0 to a maximum of 3.0.			
Units: units on a scale			
arithmetic mean	1.64		
standard deviation	± 0.62	-	
Subject Global Assessment			
Subjects used a horizontal VAS of 100 mm for overall assessment of rheumatoid arthritis. Scale ranged from 0 (very well) to 100 (very poor). Subjects were instructed to draw a vertical through a horizontal line to indicate state of rheumatoid arthritis. Distance from the "very well" end of the horizontal line to the vertical line drawn by the subject was the global disease assessment score on a scale of 1-10, where 1=controlled or equivocal rheumatoid arthritis activity, 1.1-4=mild activity, 4-8=moderate activity, and 8.1-10=high activity.			
Units: units on a scale			
arithmetic mean	60.7		
standard deviation	± 19.4	-	
Physician Global Assessment			
Physician global rheumatoid arthritis assessment core component of the ACR scoring system where increasing score indicates increasing level of severity as indicated on a 100 mm Visual Analog Scale, with 0 mm representing no pain and 100 mm representing the most pain possible.			
Units: units on a scale			
arithmetic mean	55.4		
standard deviation	± 20	-	
High Sensitivity C-Reactive Protein (hsCRP) Level			
Hs-CRP is an acute phase reactant protein that is a clinical marker for Rheumatoid Arthritis (RA). Levels of hs-CRP can be used to determine Disease Activity Score (DAS28).			
Units: mg/dL			
arithmetic mean	4.77		
standard deviation	± 5.18	-	
Disease Activity Score (CRP)			
The DAS28 (CRP) is a continuous disease measure which is a composite of 4 variables: the 28 tender joint count, the 28 swollen joint count, CRP levels, and subject assessment of disease activity measure on a visual analogue scale. The DAS28 has numeric thresholds that define high disease activity (>5.1), low disease activity (<3.2) and remission (<2.6). A clinically significant response= decrease in DAS28 score of >1.2 from baseline.			
Units: units on a scale			
arithmetic mean	5.76		
standard deviation	± 1.2	-	
Baseline Methotrexate (MTX) Dose			

Units: mg/wk			
arithmetic mean	15.3		
standard deviation	± 4.3	-	

End points

End points reporting groups

Reporting group title	Subcutaneous (SC) Abatacept

Reporting group description:

Subjects received weekly injections of 125 mg SC abatacept for 6 months (with a loading dose of IV abatacept on Day 1, based on weight). A double-dummy design was used to protect the blind, thus, Subjects also received IV injections of placebo (IV placebo) with the exception that on Day 1, a loading dose of IV abatacept replaced the IV placebo treatment.

Reporting group title	Intravenous (IV) Abatacept

Reporting group description:

Subjects received IV abatacept infusions on Days 1, 15, and 29 and every 28 days thereafter. A double-dummy design was used to protect the blind, thus, Subjects also received subcutaneous injections of placebo (subcutaneous placebo).

Reporting group title	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)

Reporting group description:

Subjects who had failed one anti-TNF therapy received abatacept 125 mg subcutaneous injections once weekly for 6 months (with an IV abatacept loading dose on Day 1, based on weight: 500 mg for subjects <60 kg, 750 mg for subjects in between 60 to 100 kg, and 1 gram for subjects >100 kg). A double-dummy design was used to protect the blind, thus, subjects also received IV injections of placebo (IV Placebo) with the exception that on Day 1 a loading dose of IV abatacept replaced the IV Placebo treatment.

Reporting group title	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)

Reporting group description:

Subjects who had failed one anti-TNF therapy received IV abatacept infusions on Days 1, 15, 29, and every 28 days, thereafter for 6 months. A double-dummy design was used to protect the blind, thus, subjects also received SC injections of placebo (SC Placebo).

Reporting group title	Subcutaneous (SC) Abatacept

Reporting group description:

Subjects could either continue with or switch to 125 mg weekly SC abatacept injections until the SC formulation became commercially available on a country basis or the Sponsor terminated the study. The Anti-TNF Sub-study terminated due to low recruitment and Subjects were permitted to roll into the LT Open Label Period.

Primary: Double-blind Period: Number of Subjects Achieving American College of Rheumatology (ACR) 20 Response

End point title	Double-blind Period: Number of Subjects Achieving American College of Rheumatology (ACR) 20 Response[1][2]

End point description:

The ACR 20 definition of improvement is a 20% improvement from baseline in the number of tender and swollen joints, and a 20% improvement from baseline in 3 of the remaining 5 core set measures: subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and acute phase reactant value (C-reactive protein). The analysis was performed in Per protocol (PP) population, defined as subjects who are compliant with the study criteria.

End point type	Primary

End point timeframe:

Day 169

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

[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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	678		
Units: Subjects	527	514		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-TNF Failure Sub-study Double-blind Period: Number of Subjects With Positive Anti-abatacept or Anti-Cytotoxic T Lymphocyte Antigen 4-T Cell (CTLA4-T) Response in Anti-TNF Failure Population

End point title	Anti-TNF Failure Sub-study Double-blind Period: Number of Subjects With Positive Anti-abatacept or Anti-Cytotoxic T Lymphocyte Antigen 4-T Cell (CTLA4-T) Response in Anti-TNF Failure Population[3][4]

End point description:

Serum samples from all treated adult subjects with active rheumatoid arthritis who were from the Anti-TNF failure population (Subjects who had failed one anti-TNF therapy) were screened for the presence of drug-specific antibodies using Enzyme Linked Immunoabsorbant Assay (ELISA). The analysis was performed in all randomised subjects in the Anti-TNF Failure Sub-study who received at least 1 dose of study medication. n=Number of subjects with at least 1 assessment available.

End point type	Primary

End point timeframe:

Days 1, 85, and 169 and postvisits on Days 28, 56, and 85

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

[4] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: Subjects				
Day 85 Anti-abatacept (n=8,10)	0	0		
Day 85 Anti-CTLA4-T (n=8,10)	0	0		
Day 169 Anti-abatacept (n=6,9)	0	0		
Day 169 Anti-CTLA4-T(n=6,9)	1	0		
Overall Treatment Anti-abatacept (n=8,10)	0	0		
Overall on Treatment Anti-CTLA4-T(n=8,10)	1	0		
28 days post Anti-abatacept (n=1,1)	0	0		
28 days post Anti-CTLA4-T (n=1,1)	0	0		
56 days post Anti-abatacept (n=0,1)	0	0		
56 days post Anti-CTLA4-T (n=0,1)	0	0		
85 days post Anti-abatacept (n=0,1)	0	0		

85 days post Anti-CTLA4-T (n=0,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Anti-TNF Failure Sub-study Double-blind Period: Number of Subjects Achieving American College of Rheumatology (ACR) 20 Response

End point title	Anti-TNF Failure Sub-study Double-blind Period: Number of Subjects Achieving American College of Rheumatology (ACR) 20 Response[5][6]

End point description:

The ACR 20 definition of improvement is a 20% improvement from baseline in the number of tender and swollen joints, and a 20% improvement from baseline in 3 of the remaining 5 core set measures: subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and acute phase reactant value (C-reactive protein). Subjects who had failed one anti-TNF therapy were included in the sub-studyThe analysis was performed in all randomised subjects in the Anti-TNF Failure Sub-study who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Day 169

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

[6] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: Subjects	5	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects Achieving ACR 50 and ACR 70 Responses

End point title	Double-blind Period: Number of Subjects Achieving ACR 50 and ACR 70 Responses[7]

End point description:

The ACR 50 definition of improvement is a 50% improvement from baseline in the number of tender and swollen joint counts, and a 50% improvement from baseline in 3 of the remaining 5 core set measures: Subject global assessment of pain, Subject global assessment of disease activity, physician global

assessment of disease activity, Subject assessment of physical function and acute phase reactant value (C-reactive protein). ACR 70 is defined similarly with 70% improvements from baseline for tender and swollen joint counts and 3 out of 5 core measures. Analysis was performed in Per-Protocol population, defined as subjects who are compliant with the study criteria.

End point type	Secondary

End point timeframe:

Day 169

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	678		
Units: Subjects				
ACR 50	357	341		
ACR 70	183	170		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Mean Baseline Health Assessment Questionnaire Disability Index (HAQ-DI) for Subjects With Assessments

End point title	Double-blind Period: Mean Baseline Health Assessment Questionnaire Disability Index (HAQ-DI) for Subjects With Assessments[8]

End point description:

The disability section of the full HAQ-DI includes 20 questions to assess physical functions in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip and common activities. The questions are evaluated on a 4-point scale: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, and 3=unable to do. Higher scores=greater dysfunction. A disability index was calculated by summing the worst scores in each domain and dividing by the number of domains answered. Analysis was performed on all subjects who received at least 1 dose of study medication at any time and had HAD-QI scores available.

End point type	Secondary

End point timeframe:

Day 169

Notes:

[8] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	729	711		
Units: Units on a scale				
arithmetic mean (standard deviation)	1.72 (± 0.68)	1.67 (± 0.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Adjusted Mean Change From Baseline to Day 169 in HAQ-DI

End point title	Double-blind Period: Adjusted Mean Change From Baseline to Day 169 in HAQ-DI[9]

End point description:

The HAQ-DI includes 20 questions to assess physical function in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. The domain questions are evaluated on a 4-point scale: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do. HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. HAQ-DI ranges from 0 to a maximum overall score of 3.0. Analysis was performed on all subjects who received at least 1 dose of study medication at any time and had HAD-QI scores available.

End point type	Secondary

End point timeframe:

Baseline to Day 169

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	729	711		
Units: Units on a scale				
arithmetic mean (standard error)	-0.69 (± 0.02)	-0.7 (± 0.02)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects Achieving Clinically Meaningful HAQ-DI Response at Day 169

End point title	Double-blind Period: Number of Subjects Achieving Clinically Meaningful HAQ-DI Response at Day 169[10]

End point description:

The disability section of the full HAQ-DI includes 20 questions to assess physical functions in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip and common activities. The questions are evaluated on a 4-point scale: 0=without any difficulty, 1= with some difficulty, 2= with much difficulty, and 3=unable to do. Higher scores=greater dysfunction. A disability index was calculated by summing the worst scores in each domain and dividing by the number of domains answered. Clinically meaningful HAQ-DI response=an improvement of at least 0.3 units from baseline in HAQ-DI. Analysis was performed in all the subjects who received at least 1 dose of study medication at any time and had HAD-QI scores available.

End point type	Secondary

End point timeframe:

Day 169

Notes:

[10] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	729	711		
Units: Subjects	483	442		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With Death As Outcome, Serious Adverse Events (SAEs), Treatment- related SAEs, SAEs Leading to Discontinuation, Adverse Events (AEs), Treatment-related AEs, or AEs Leading to Discontinuation

End point title	Double-blind Period: Number of Subjects With Death As Outcome, Serious Adverse Events (SAEs), Treatment- related SAEs, SAEs Leading to Discontinuation, Adverse Events (AEs), Treatment-related AEs, or AEs Leading to Discontinuation[11]

End point description:

AE=any new untoward medical event or worsening of a preexisting medical condition that does not necessarily have a causal relationship with this treatment. SAE=any untoward medical occurrence that at any dose: results in death, is life- threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, results in development of drug dependency or drug abuse, is an important medical event. Treatment-related SAE=possibly, probably, or certainly related to study drug. All randomised subjects who received at least 1 dose of study medication were analysed.

End point type	Secondary

End point timeframe:

Day 1 to 56 days after last dose in short-term or first dose in the long-term, whichever occurs first.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
Deaths	2	5		
SAEs	31	35		
Treatment-related SAEs	5	12		
SAEs Leading to Discontinuation	8	14		
AEs	493	470		
Treatment-related AEs	204	210		

AEs Leading to Discontinuation	15	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-TNF Failure Sub-study Double-blind Period: Number of Subjects With SAEs, AEs Leading to Discontinuation or Who Died

End point title	Anti-TNF Failure Sub-study Double-blind Period: Number of Subjects With SAEs, AEs Leading to Discontinuation or Who Died[12]

End point description:

AE=any new untoward medical event or worsening of a preexisting medical condition that does not necessarily have a causal relationship with this treatment. SAE=any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, results in development of drug dependency or drug abuse, is an important medical event. Subjects who had failed one anti-TNF therapy were included in the sub-study. All randomised subjects who received at least 1 dose of study medication were analysed.

End point type	Secondary

End point timeframe:

Day 1 to 56 days after last dose in short-term or first dose in the long-term, whichever occurs first.

Notes:

[12] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: Subjects				
Deaths	0	0		
SAEs	0	0		
AEs Leading to Discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With AEs of Special Interest

End point title	Double-blind Period: Number of Subjects With AEs of Special Interest[13]

End point description:

AE=any new untoward medical occurrence or worsening of a preexisting medical condition that does not necessarily have a causal relationship with this treatment. AEs of special interest are those AEs that may

be associated with the use of immunomodulatory drugs: all infections,serious infections,and opportunistic infections; autoimmune disorders; malignancies; acute infusional AEs (prespecified AEs occurring within 1 hr of start of infusion), peri-infusional AEs (prespecified AEs occurring within 24 hrs of the start of infusion), system injection reactions, and local injection site reactions. All randomised subjects who received at least 1 dose of study medication were analysed.

End point type	Secondary

End point timeframe:

Day 1 up to 56 days post last dose in short- term period or first dose in the long -term period, whichever occurs first.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
Infections	234	221		
Malignancies	3	5		
Autoimmune Disorders	7	6		
Acute Infusional AEs	20	16		
Peri-infusional AEs	59	59		
Local Injection Site Reactions	19	18		
Systemic Injection Reactions	56	56		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With Clinically Significant Abnormalities in Vital Sign Measurements

End point title	Double-blind Period: Number of Subjects With Clinically Significant Abnormalities in Vital Sign Measurements[14]

End point description:

Vital sign measurements were performed for subjects before and after infusion/subcutaneous injection of study medication at each visit and included seated systolic blood pressure, seated diastolic blood pressure, temperature, and heart rate. Abnormalities were determined to be clinically significant by the investigator. All randomised subjects who received at least 1 dose of study medication were analysed.

End point type	Secondary

End point timeframe:

Day 1 through end of short-term period (Day 169)

Notes:

[14] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With Hematology Laboratory Test Results Meeting the Criteria for Marked Abnormality

End point title	Double-blind Period: Number of Subjects With Hematology Laboratory Test Results Meeting the Criteria for Marked Abnormality[15]

End point description:

ULN=upper limit of normal; LLN=lower limit of normal; BL= baseline. Marked abnormality criteria: Hemoglobin: >3 g/dL decrease from BL; hematocrit: <0.75*BL; erythrocytes: <0.75*BL; platelets: <0.67*LLN/>1.5*ULN, or if BL<LLN, use <0.5*BL and <100,000 mm^3; leukocytes: <0.75*LLN/>1.25*ULN, or if BL<LLN use <0.8*BL or >ULN, or if BL>ULN, use >1.2*BL or <LLN; neutrophils+bands: <1.0*10^3 c/uL; eosinophils: >0.750*10^3 c/uL; basophils: >400 mm^3; monocytes: >2000 mm^3; lymphocytes: <0.750*10^3 c/uL/>7.50*10^3 c/uL. The analysis was performed in all the randomised subjects who received at least 1 dose of study medication. Here "n" = Number of subjects with assessments available.

End point type	Secondary

End point timeframe:

Day 1 through end of short-term period (Day 169)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
Low hemoglobin (LLN=11.5 g/dL); n=729, 713	2	5		
Low hematocrit (LLN=34%); n=726, 713	2	4		
Low erythrocytes(LLN=3.8 x10*6c/uL);n=729, 713	2	3		
Low platelets (LLN=140*10^9 c/L); n=725, 709	1	0		
High platelets (ULN=450*10^9 c/L); n=725, 709	0	0		
Low leukocytes (LLN= 3.8*10^3 c/uL); n=729, 713	6	2		
High eosinophils (ULN= 7*10^3 c/uL); n=730, 712	22	16		
High basophils (ULN= 0.2*10^3 c/uL); n=730, 712	0	0		
High monocytes (ULN=1*10^3 c/uL); n=730, 712	0	1		

Low lymphocytes (LLN= 0.7*10^3 c/uL);n=730,712	40	42		
Low neutrophils+bands(LLN=1.8*10^3 c/uL);n=730,713	0	0		
High leukocytes (ULN = 10.6*10^3 c/uL);n=729, 713	25	18		
High lymphocytes (ULN=4.5*10^3 c/uL); n=730,712	40	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With Liver Function Laboratory Test Results Meeting the Criteria for Marked Abnormality

End point title	Double-blind Period: Number of Subjects With Liver Function Laboratory Test Results Meeting the Criteria for Marked Abnormality[16]

End point description:

Marked abnormality criteria: Alkaline phosphatase (ALP): >2*ULN, or if BL>ULN, use >3*BL; aspartate aminotransferase (AST): >3*ULN, or if BL>ULN, use >4*BL; alanine aminotransferase (ALT): >3*ULN, or if BL>ULN, use >4*BL; G-glutamyl transferase (GGT): >2* ULN, or if BL>ULN, use >3*BL; bilirubin: >2* ULN, or if BL>ULN, use >4*BL; blood urea nitrogen: >2* BL; creatinine: >1.5*BL. The analysis was performed in all the randomised subjects who received at least 1 dose of study medication. Here "n" = Number of subjects with assessments available.

End point type	Secondary

End point timeframe:

Day 1 through end of short-term period (Day 169)

Notes:

[16] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
High ALP (ULN=400 U/L); n=730, 713	1	3		
High AST (ULN=44 U/L); n=729, 713	5	5		
High ALT (ULN=55 U/L);n=729, 713	12	16		
High GGT (ULN=65 U/L); n=730, 713	8	14		
High bilirubin (ULN=1.2 mg/dL); n=730, 713	1	0		
High blood urea nitrogen (26 mg/dL); n=730, 713	21	27		
High creatinine (ULN=1.5 mg/dL); n=730, 713	19	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With Electrolyte Laboratory Test Results Meeting the Criteria for Marked Abnormality

End point title	Double-blind Period: Number of Subjects With Electrolyte Laboratory Test Results Meeting the Criteria for Marked Abnormality[17]

End point description:

Marked abnormality criteria: Sodium: <0.95*LLN/>1.05*ULN, or if BL<LLN, use <0.95* BL or >ULN, or if BL>ULN, use>1.05* BL or <LLN; potassium: <0.9* LLN/>1.1*ULN, or if BL<LLN then use <0.9* BL or >ULN, or if BL>ULN, use>1.1* BL or <LLN; chlorine: <0.9*LLN/>1.1* ULN, or if BL<LLN, use <0.9*BL or >ULN, or if BL>ULN, use>1.1*BL or <LLN; calcium: <0.8* LLN/>1.2* ULN, or if BL<LLN, use <0.75*BL or >ULN, or if BL>ULN, use>1.25* BL or <LLN; phosphorous: <0.75* LLN/>1.25*ULN, or if BL<LLN, use 0.67*BL or >ULN, or if BL>ULN, use>1.33* BL or <LLN. The analysis was performed in all the randomised subjects who received at least 1 dose of study medication. Here "N" = number of subjects with assessments available.

End point type	Secondary

End point timeframe:

Day 1 through end of short-term period (Day 169)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
Low sodium (LLN=135 mEq/L)	2	0		
High sodium (ULN=148 mEq/L)	0	0		
Low potassium (LLN=3.5 mEq/L)	9	9		
High potassium (ULN=5.5 mEq/L)	1	0		
Low chlorine (LLN= 96 mEq/L)	0	0		
High chlorine (ULN=109 mEq/L)	0	0		
Low calcium (LLN=8.4 mg/dL)	1	0		
High calcium (ULN=10.6 mg/dL)	1	0		
Low phosphorous (LLN=0.8 mg/dL)	1	2		
High phosphorous (ULN=5.6 mg/dL)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Minimum Observed Serum Concentration of Abatacept

End point title	Double-blind Period: Minimum Observed Serum Concentration of Abatacept[18]

End point description:

A sensitive, validated immunoassay method will be used to measure concentrations of abatacept in serum. Subjects who received at least 1 dose of study medication and from whom at least 1 pharmacokinetic (PK) sample was collected and reported (N). Only subjects with adequate PK profiles were included in the summary statistics and statistical analysis (n). PK values were not sampled for IV

abatacept group on Day 120, 127, 134. Here, '99999' represents not estimable data for specified categories in respective arms.

End point type	Secondary

End point timeframe:

Days 57, 85, 113, 120, 127, 134, 141, and 169

Notes:

[18] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: µg/mL				
geometric mean (standard deviation)				
Day 57 (n=25, n=16)	31.6 (± 21.483)	23.14 (± 14.008)		
Day 85 (n=630, n=649)	28.3 (± 21.692)	20 (± 13.441)		
Day 113 (n=44, n=29)	26.49 (± 16.569)	18.76 (± 16.322)		
Day 120 (n=27)	25.1 (± 14.933)	99999 (± 99999)		
Day 127 (n=28)	29.16 (± 14.78)	99999 (± 99999)		
Day 134 (n=27)	25.1 (± 15.753)	99999 (± 99999)		
Day 141 (n=26, n=26)	25.79 (± 14.264)	18.1 (± 17.717)		
Day 169 (n=530, n=521)	24.91 (± 14.989)	18.1 (± 17.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-TNF Failure Sub-study Double-blind Period: Minimum Observed Serum Concentration (Cmin) of Abatacept

End point title	Anti-TNF Failure Sub-study Double-blind Period: Minimum Observed Serum Concentration (Cmin) of Abatacept[19]

End point description:

Serum concentrations of abatacept were analyzed using a validated ELISA. Steady-state trough observed concentration in serum (Cminss) was measured in µg/mL. Samples were obtained on Days 57, 85, 113, 120, 127, 134, 141, and 169. Subjects who had failed one anti-TNF therapy were included in the sub-study. Subjects who received at least 1 dose of study medication and who had adequate PK profiles were analyzed. n= number of subjects available at each specific time point. PK values were not sampled for IV abatacept group on Day 120, 127, 134. Here, '99999' represents not estimable data for specified categories in respective arms.

End point type	Secondary

End point timeframe:

Days 57, 85, 113, 120, 127, 134, 141, and 169 (ST Period)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	10		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Day 57 (n=3, 4)	25.53 (± 16)	15.51 (± 25)		
Day 85 (n=6, 9)	21.51 (± 26)	12.5 (± 48)		
Day 113 (n=6, 6)	23.14 (± 27)	11.1 (± 31)		
Day 120 (n=4, 0)	25.75 (± 17)	99999 (± 99999)		
Day 127 (n=3, 0)	25.42 (± 9)	99999 (± 99999)		
Day 134 (n=3, 0)	25.55 (± 13)	99999 (± 99999)		
Day 141 (n=4, 6)	20.85 (± 24)	8.34 (± 44)		
Day 169 (n=5, 7)	19.66 (± 25)	9 (± 53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Maximum Observed Serum Concentration of Abatacept

End point title	Double-blind Period: Maximum Observed Serum Concentration of Abatacept[20]

End point description:

Subjects who received at least 1 dose of study medication and who had adequate PK profiles for analysis were evaluated for this outcome measure. Here, 'Number of Subjects Analysed' signifies the subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

End of infusion on Days 1 and 113 for IV infusion and in the dosing interval of Days 113 to 120 for subcutaneous

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	30		
Units: µg/mL				
geometric mean (standard deviation)	40.39 (± 30.148)	222.35 (± 71.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-TNF Failure Substudy Double Blind Period: Geometric Mean Maximum Observed Serum Concentration of Abatacept

End point title	Anti-TNF Failure Substudy Double Blind Period: Geometric Mean Maximum Observed Serum Concentration of Abatacept[21]

End point description:

Serum concentrations of abatacept were analyzed using a validated enzyme-linked immunosorbent assay. Samples were obtained on Days 57, 85, 113, 120, 127, 134, 141, and 169. Cmax was measured in micrograms per milliliter (µg/mL). Subjects who had failed one anti-TNF therapy were included in the sub-study. Subjects in the Sub-study who received at least 1 dose of study medication and who had adequate pharmacokinetic profiles were analysed. Here, 'Number of Subjects Analysed' signifies the subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

End of infusion on Days 1 and 113 for IV infusion and in the dosing interval of Days 113 to 120 for subcutaneous

Notes:

[21] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: µg/mL				
geometric mean (geometric coefficient of variation)	35.84 (± 24)	229.88 (± 26)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Area Under The Curve In A Dose Interval (AUC TAU) of Abatacept

End point title	Double-blind Period: Area Under The Curve In A Dose Interval (AUC TAU) of Abatacept[22]

End point description:

A sensitive, validated immunoassay method was used to measure concentrations of abatacept in serum. The analysis was performed in all the subjects who received at least 1 dose of study medication and who had adequate PK profiles for analysis. Here, 'Number of Subjects Analysed' signifies the subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Dosing interval between Days 113 and 141 (TAU=28 days)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	33		
Units: µg*h/mL				
geometric mean (standard deviation)	5182.37 (± 2854.136)	39587.08 (± 15444.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-TNF Failure Sub-study Double Blind Period: Area Under The Curve In A Dose Interval (AUC TAU) of Abatacept

End point title	Anti-TNF Failure Sub-study Double Blind Period: Area Under The Curve In A Dose Interval (AUC TAU) of Abatacept[23]

End point description:

Serum concentrations of abatacept were analyzed using a validated ELISA. AUC(TAU) was measured as µg*h/mL. Samples were obtained on Days 113, 120, 127, 134, 141, and 169. Subjects who had failed one anti-TNF therapy were included in the sub-study. The analysis was performed in all subjects in the sub-study who received at least 1 dose of study medication and who had adequate PK profiles for analysis. Here, 'Number of Subjects Analysed' signifies the subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Dosing Interval between Days 113 and 141 (TAU=28 days)

Notes:

[23] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept (Anti-TNF Sub-Study)	Intravenous (IV) Abatacept (Anti-TNF Sub-Study)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	6		
Units: µg*h/mL				
geometric mean (geometric coefficient of variation)	4384.3 (± 17)	34260.55 (± 35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With Positive Anti-abatacept or Anti-Cytotoxic T Lymphocyte Antigen 4-T Cell (CTLA4-T) Responses Over Time by Enzyme Linked Immunoabsorbant Assay (ELISA)

End point title	Double-blind Period: Number of Subjects With Positive Anti-abatacept or Anti-Cytotoxic T Lymphocyte Antigen 4-T Cell (CTLA4-T) Responses Over Time by Enzyme Linked Immunoabsorbant Assay (ELISA)[24]

End point description:

Serum samples from all treated adult subjects with active rheumatoid arthritis were screened for the presence of drug-specific antibodies using ELISA. Immunogenicity was defined as the presence of a positive anti-abatacept (anti-ABA) or anti-CTLA4 antibody (anti-CTLA4). The analysis was performed in all the randomised subjects who received at least 1 dose of study medication. Here "n" = Number of subjects with at least 1 assessment available.

End point type	Secondary

End point timeframe:

Days 1, 85, and 169 and post-visits on Days 28, 56, and 85

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
Day 85 anti-ABA (n=700, n=682)	0	2		
Day 85 anti-CTLA4 (n=705, n=689)	0	0		
Day 85 total (n=706, n=689)	0	2		
Day 169 anti-ABA (n=671, n=648)	3	4		
Day 169 anti-CTLA4 (n=681, n=658)	2	4		
Day 169 total (n=681, n=658)	5	8		
Overall on-treatment visits anti-ABA (n=707, 691)	3	5		
Overall on-treatment visits anti-CTLA4 (n=716,702)	2	4		
Overall on-treatment visits total (n=716, 702)	5	9		
28 days post last dose anti-ABA (n=18, n=25)	0	0		
28 days post last dose anti-CTLA4 (n=20, n=27)	0	2		
28 days post last dose total (n=20, n=27)	0	2		
56 days post last dose anti-ABA (n=19, n=22)	0	0		

56 days post last dose anti-CTLA4 (n=19, n=23)	1	1		
56 days post last dose total (n=19, n=23)	1	1		
85 days post last dose anti-ABA (n=12, n=15)	0	0		
85 days post last dose anti-CTLA4 (n=13, n=15)	2	5		
85 days post last dose total (n=13, n=15)	2	5		
Overall post visits anti-ABA (n=26, n=29)	0	0		
Overall post visits anti-CTLA4 (n=28, n=31)	3	7		
Overall post visits total (n=28, n=31)	3	7		
Overall anti-ABA (n=714, n=698)	3	5		
Overall anti-CTLA4 (n=725, n=710)	5	11		
Overall total (n=725, n=710)	8	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Time-matched Median Percent Change From Baseline in Levels of Serum C-reactive Protein Over the Short-term Period

End point title	Double-blind Period: Time-matched Median Percent Change From Baseline in Levels of Serum C-reactive Protein Over the Short-term Period[25]

End point description:

C-reactive protein is an acute phase reactant protein that is a clinical marker for rheumatoid arthritis. Time-matched median percent change from baseline= (time-matched baseline value - Post-baseline value)/time-matched baseline value*100, where the time-matched baseline value represents the median baseline value for only that cohort of subjects with measurements available at that visit. The analysis was performed in all the randomised subjects who received at least 1 dose of study medication. Here "n" = Number of subjects with at least 1 assessment available.

End point type	Secondary

End point timeframe:

Baseline to Days 15, 29, 57, 85, 113, 141, and 169

Notes:

[25] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Percentage change				
median (inter-quartile range (Q1-Q3))				
Day 15 (n=720, n=703)	34.16 (-11.11 to 58.8)	33.74 (-6.24 to 58.41)		
Day 29 (n=727, n=711)	39.74 (3.83 to 66.99)	42.52 (0.42 to 68.66)		
Day 57 (n=727, n=711)	47.88 (6.84 to 73.53)	51.42 (7.53 to 74.95)		

Day 85 (n=727, n=711)	52.9 (8.7 to 78.25)	53.65 (11.05 to 79.42)		
Day 113 (n=727, n=711)	53.33 (7.09 to 80.29)	58.12 (11.21 to 81.26)		
Day 141 (n=727, n=711)	56.12 (5.28 to 83.24)	58.39 (16.14 to 81.52)		
Day 169 (n=727, n=711)	57.18 (11.18 to 83.28)	56.81 (17.92 to 82.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects With Positive Anti-abatacept Responses Over Time by Electrochemiluminescence Immunoassay

End point title	Double-blind Period: Number of Subjects With Positive Anti-abatacept Responses Over Time by Electrochemiluminescence Immunoassay[26]

End point description:

An electro-chemiluminescence immunoassay screened sera for drug-specific antibodies, immuno-competition was used to identify specific anti-abatacept reactivity. CTLA4 and Possibly Ig category=reactivity against extracellular domain of human CTLA4, constant regions of human IgG1, or both (CTLA4Ig; abatacept molecule). Ig and/or Junction (JNCT) category=reactivity against constant regions and/or hinge region of human IgG1. Drug-induced seropositivity was defined as a post-baseline titer higher than Baseline, or any post-baseline positivity if baseline value was missing. Trt=treatment. The analysis was performed in all the subjects who received at least 1 dose of abatacept and had at least 1 immunogenicity result reported during the short-term period.

End point type	Secondary

End point timeframe:

Days 85, and 169 and post-visits on Days 28, 56, and 85

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoint was planned to evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
Day 85 CTLA4 + possibly Ig (n=78, n=67)	0	0		
Day 85 Ig +/- JNCT (n=78, n=67)	0	0		
Day 85 total (n=78, n=67)	0	0		
Day 169 CTLA4 + possibly Ig (n=75, n=67)	0	1		
Day 169 Ig +/- JNCT (n=75, n=67)	0	0		
Day 169 total (n=75, n=67)	0	1		
Overall on-TRT CTLA4 + possibly Ig (n=79, 70)	0	1		
Overall on-TRT Ig +/- JNCT (n=79, 70)	0	0		
Overall on-TRT total (n=79, 70)	0	1		
28 days post last dose CTLA4+possibly Ig (n=2,n=2)	0	0		

28 days post last dose Ig +/- JNCT (n=2, n=2)	0	0		
28 days post last dose Total (n=2, n=2)	0	0		
56 days post last dose CTLA4+possibly Ig (n=2,n=2)	0	0		
56 days post last dose Ig +/- JNCT (n=2, n=2)	0	0		
56 days post last dose total (n=2, n=2)	0	0		
85 days post last dose CTLA4+possibly Ig (n=1,n=1)	0	0		
85 days post last dose Ig +/- JNCT (n=1, n=1)	0	0		
85 days post last dose total (n=1, n=1)	0	0		
Overall post visits CTLA4+possibly Ig (n=3, n=2)	0	0		
Overall post visits Ig +/- JNCT (n=3, n=2)	0	0		
Overall post visits total (n=3, n=2)	0	0		
Overall CTLA4+possibly Ig (n=82, n=71)	0	1		
Overall Ig +/- JNCT (n=82, n=71)	0	0		
Overall total (n=82, n=71)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Double-blind Period: Number of Subjects Seroconverting by Day 169 According to Status (Negative or Positive) at Baseline

End point title	Double-blind Period: Number of Subjects Seroconverting by Day 169 According to Status (Negative or Positive) at Baseline[27]

End point description:

Rheumatoid factor (RF) is an autoantibody (antibody directed against an organism's own tissues) most relevant in rheumatoid arthritis. It is an antibody against the Fc portion of Immunoglobulin (Ig)G, which is itself an antibody. RF and IgG join to form immune complexes which contribute to the disease process. The analysis was performed in all the randomised subjects who received at least 1 dose of study medication. Here "n" = Number of subjectsts with at least 1 assessment available.

End point type	Secondary

End point timeframe:

Baseline to Day 169

Notes:

[27] - 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 evaluate for the specified arm only.

End point values	Subcutaneous (SC) Abatacept	Intravenous (IV) Abatacept		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	736	721		
Units: Subjects				
Baseline RF negative	106	93		
Baseline RF negative; Day 169 RF positive	2	3		

Baseline RF positive	586	582		
Baseline RF positive ; Day 169 RF negative	33	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects Achieving ACR 20 Response at Days 169, 729, 1261, and 1821

End point title	Open-Label LT Period: Number of Subjects Achieving ACR 20 Response at Days 169, 729, 1261, and 1821

End point description:

The ACR 20 definition of improvement is a 20% improvement from baseline in the number of tender and swollen joints, and a 20% improvement from baseline in 3 of the remaining 5 core set measures: subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and acute phase reactant value (C-reactive protein). The analysis was performed in all the subjects who entered the LT period and received at least 1 dose of study drug during the LT period.

End point type	Secondary

End point timeframe:

Days 169, 729, 1261, 1821

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1365			
Units: Subjects				
Day 169 (n=1357)	1087			
Day 729 (n=1187)	973			
Day 1261 (n=1068)	904			
Day 1821 (n=421)	356			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects Achieving ACR 50 and ACR 70 Responses at Days 169, 729, 1261, 1821

End point title	Open-Label LT Period: Number of Subjects Achieving ACR 50 and ACR 70 Responses at Days 169, 729, 1261, 1821

End point description:

The ACR 50 definition of improvement is a 50% improvement from baseline in the number of tender and swollen joint counts, and a 50% improvement from baseline in 3 of the remaining 5 core set measures: subject global assessment of pain, subject global assessment of disease activity, physician global assessment of disease activity, subject assessment of physical function and acute phase reactant value (C-reactive protein). ACR 70 is defined similarly with 70% improvements from baseline for tender and swollen joint counts and 3 out of 5 core measures. All subjects who entered the LT period and received

at least 1 dose of study drug during the LT period were summarized.

End point type	Secondary

End point timeframe:

Days 169, 729, 1261, 1821

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1365			
Units: Subjects				
Day 169 ACR 50 (n=1362)	724			
Day 729 ACR 50 (n=1185)	720			
Day 1261 ACR 50(n=1069)	672			
Day 1821 ACR 50 (n=423)	277			
Day 169 ACR 70 (n=1362)	371			
Day 729 ACR 70 (n=1186)	443			
Day 1261 ACR 70 (n=1070)	438			
Day 1821 ACR 70 (n=425)	191			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Mean Change From Baseline in Disease Activity Score in 28 Joints (DAS28) Using C-reactive Protein (CRP) at Days 169, 729, 1261, 1821

End point title	Open-Label LT Period: Mean Change From Baseline in Disease Activity Score in 28 Joints (DAS28) Using C-reactive Protein (CRP) at Days 169, 729, 1261, 1821

End point description:

The DAS28 index measures disease activity in rheumatoid arthritis and is a composite derived from the number of swollen/tender joints, laboratory tests of inflammation (C-reactive protein measured in mg/L), and subject assessment of global health (by marking a visual analog scale 100 mm line from "very good" to "very bad"). A higher DAS28 score indicates worse control of disease. High disease activity is > 5.1, low disease activity is < 3.2 and remission is < 2.6. A clinically significant response= decrease in DAS28 score of >1.2 from baseline. All subjects who entered the LT period and received at least 1 dose of study drug during the LT period were summarized.

End point type	Secondary

End point timeframe:

Days 169, 729, 1261, 1821

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1365			
Units: units on a scale				
arithmetic mean (confidence interval 95%)				
Day 169 (n=1353)	-2.65 (-2.71 to -2.58)			
Day 729 (n=1181)	-2.94 (-3.01 to -2.86)			
Day 1261 (n=1063)	-3.09 (-3.17 to -3)			
Day 1821 (n=413)	-3.24 (-3.38 to -3.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects Achieving DAS 28 Remission at Days 169, 729, 1261, 1821

End point title	Open-Label LT Period: Number of Subjects Achieving DAS 28 Remission at Days 169, 729, 1261, 1821

End point description:

The DAS28 index measures disease activity in rheumatoid arthritis and is a composite derived from the number of swollen/tender joints, laboratory tests of inflammation (C-reactive protein measured in mg/L), and subject assessment of global health (by marking a visual analog scale 100 mm line from "very good" to "very bad"). A higher DAS28 score indicates worse control of disease. High disease activity is > 5.1, low disease activity is < 3.2 and remission is < 2.6. All subjects who entered the LT period and received at least 1 dose of study drug during the LT period were summarised.

End point type	Secondary

End point timeframe:

Days 169, 729, 1261, 1821

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1365			
Units: Subjects				
Day 169 (n=1355)	334			
Day 729 (n=1183)	411			
Day 1261 (n=1064)	425			
Day 1821 (n=413)	169			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects Achieving DAS 28 Low Disease Activity (LDA) at Days 169, 729, 1261, 1821

End point title	Open-Label LT Period: Number of Subjects Achieving DAS 28 Low Disease Activity (LDA) at Days 169, 729, 1261, 1821

End point description:

The DAS28 index measures disease activity in rheumatoid arthritis and is a composite derived from the number of swollen/tender joints, laboratory tests of inflammation (C-reactive protein measured in mg/L), and subject assessment of global health (by marking a visual analog scale 100 mm line from "very good" to "very bad"). A higher DAS28 score indicates worse control of disease. High disease activity is > 5.1, low disease activity is < 3.2 and remission is < 2.6. All Subjects who entered the LT period and received at least 1 dose of study drug during the LT period were summarised.

End point type	Secondary

End point timeframe:

Days 169, 729, 1261, 1821

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1365			
Units: Subjects				
Day 169 (n=1355)	553			
Day 729 (n=1183)	600			
Day 1261 (n=1064)	585			
Day 1821 (n=413)	238			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects With HAQ-DI Response at Days 169, 729, 1261, 1821

End point title	Open-Label LT Period: Number of Subjects With HAQ-DI Response at Days 169, 729, 1261, 1821

End point description:

The disability section of the full HAQ includes 20 questions to assess physical function in 8 domains: dressing, arising, eating, walking, hygiene, reach, grip, and common activities. The domain questions are evaluated on a 4-point scale: 0=without any difficulty, 1=with some difficulty, 2=with much difficulty, 3=unable to do. HAQ-DI=sum of worst scores in each domain divided by the number of domains answered. HAQ-DI overall score ranges from a minimum of 0 to a maximum of 3.0. HAQ response was defined as an improvement (reduction) from baseline (Day 1) of at least 0.3 units in the HAQ score. All subjects who entered the LT period, received at least 1 dose of study drug during the LT period, and had HAD-QI scores at baseline and at specified days were summarised.

End point type	Secondary

End point timeframe:

Days 169, 729, 1261, 1821

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1365			
Units: Subjects				
Day 169 (n=1364)	962			
Day 729 (n=1190)	853			
Day 1261 (n=1068)	780			
Day 1821 (n=427)	315			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects With Death As Outcome, Serious Adverse Events (SAEs), Treatment-related SAEs, SAEs Leading to Discontinuation, Adverse Events (AEs), Treatment-related AEs, or AEs Leading to Discontinuation

End point title	Open-Label LT Period: Number of Subjects With Death As Outcome, Serious Adverse Events (SAEs), Treatment-related SAEs, SAEs Leading to Discontinuation, Adverse Events (AEs), Treatment-related AEs, or AEs Leading to Discontinuation

End point description:

AE=any new untoward medical event or worsening of a preexisting medical condition that does not necessarily have a causal relationship with this treatment. SAE=any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, results in development of drug dependency or drug abuse, is an important medical event. Treatment-related SAE=possibly, probably, or certainly related to study drug. The analysis was performed in all the subjects who entered the LT Period and received at least 1 dose of study drug during the LT Period.

End point type	Secondary

End point timeframe:

End of ST Period (Day 169) to last dose plus 85 days, up to 5 years (September 2014)

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1373			
Units: Subjects				
Death	41			
SAE	353			
Treatment-related SAE	88			
SAEs leading to Discontinuation	73			
Treatment-related AEs	632			
AEs leading to Discontinuation	97			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects With Adverse Events (AEs) of Special Interest

End point title	Open-Label LT Period: Number of Subjects With Adverse Events (AEs) of Special Interest

End point description:

AE=any new untoward medical occurrence or worsening of a preexisting medical condition that does not necessarily have a causal relationship with this treatment. AEs of special interest are those AEs that may be associated with the use of immunomodulatory drugs: all infections, serious infections, and opportunistic infections; autoimmune disorders; malignancies; system injection reactions, and local injection site reactions. The analysis was performed in all the subjects who entered the LT Period and received at least 1 dose of study drug during the LT Period.

End point type	Secondary

End point timeframe:

End of ST Period (Day 169) to last dose plus 85 days, up to 5 years (September 2014)

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1373			
Units: Subjects				
All Infections	962			
Serious Infections	85			
Infections leading to Discontinuation	25			
Serious Infections leading to Discontinuation	16			
Malignancies	56			
Autoimmune Disorders	67			
Local Injection Site Reactions	33			
Systemic Injection Reactions	161			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects With Clinically Significant Abnormalities in Vital Sign Measurements

End point title	Open-Label LT Period: Number of Subjects With Clinically Significant Abnormalities in Vital Sign Measurements

End point description:

Vital sign assessments were performed in the LT period at 12-week intervals and at a yearly visit (at 16-week intervals) and, for subjects who withdrew from the study prematurely, 7 days after the last dose of SC abatacept. Vital signs included seated systolic blood pressure, seated diastolic blood pressure, temperature, and heart rate. Abnormalities were determined to be clinically significant by the investigator. The analysis was performed in all the subjects who entered the LT Period and received at least 1 dose of study drug during the LT Period.

End point type	Secondary

End point timeframe:

End of ST Period (Day 169) to last dose plus 7 days, up to 5 years (September 2014)

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1373			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Open-Label LT Period: Number of Subjects With Clinically Significant Laboratory Abnormalities

End point title	Open-Label LT Period: Number of Subjects With Clinically Significant Laboratory Abnormalities

End point description:

Laboratory assessments were performed in the LT period at 12-week intervals and at a yearly visit and, for subjects who withdrew from the study prematurely, 7 days after the last dose of SC abatacept. Abnormalities were determined to be clinically significant by the investigator. The analysis was performed in all the subjects who entered the LT Period and received at least 1 dose of study drug during the LT Period.

End point type	Secondary

End point timeframe:

End of ST Period (Day 169) to last dose plus 7 days, up to 5 years (September 2014)

End point values	Subcutaneous (SC) Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	1373			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose (Day 1) in ST period to last dose in LT period plus 85 days, up to 5 years (September 2014)

Adverse event reporting additional description:

Population includes both Main Study and Anti-TNF Failure Sub-study. Sub-study was terminated early and subjects could enter LT Period of Main study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	IV Abatacept

Reporting group description:

During the Main study Double Blind ST Period, subjects received IV abatacept infusions on Days 1, 15, 29, and every 28 days, thereafter for 6 months. A double-dummy design was used to protect the blind, thus, subjects also received SC injections of placebo (SC Placebo). An Anti-TNF Failure Sub-study was initiated (recruited separately from Main study) using the same treatment as the Main study in order to assess the immunogenicity and safety in the Anti-TNF Failure population. The Sub-study terminated due to low recruitment and subjects were permitted to roll into the LT Open Label Period. During the Open Label LT Period, subjects in both the Main Study and the Anti-TNF Failure Sub-study could switch to SC abatacept until the SC formulation became commercially available on a country basis or the Sponsor terminated the study.

Reporting group title	SC Abatacept

Reporting group description:

During the Main Study Double Blind ST Period, subjects received 125 mg weekly SC abatacept injections for 6 months (with an IV abatacept loading dose on Day 1, based on weight). A double-dummy design was used to protect the blind, thus, subjects also received IV injections of placebo (IV Placebo) with the exception that on Day 1 a loading dose of IV abatacept replaced the IV Placebo treatment. An Anti-TNF Failure Sub-study was initiated (recruited separately from Main study) using the same treatment as the Main study in order to assess the immunogenicity and safety in the Anti-TNF Failure population. The Sub-study terminated due to low recruitment and subjects were permitted to roll into the LT Open Label Period. During the Open Label LT Period, subjects in both the Main Study and the Anti-TNF Failure Sub-study could continue SC abatacept until the SC formulation became commercially available on a country basis or the Sponsor terminated the study.

Serious adverse events	IV Abatacept	SC Abatacept	
Total subjects affected by serious adverse events			
subjects affected / exposed	206 / 731 (28.18%)	199 / 744 (26.75%)	
number of deaths (all causes)	22	19	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ovarian epithelial cancer			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal cancer			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			

subjects affected / exposed	1 / 731 (0.14%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrous histiocytoma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	7 / 731 (0.96%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroadenoma of breast			
subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucoepidermoid carcinoma of salivary gland			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	2 / 731 (0.27%)	4 / 744 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary cancer metastatic			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic myelomonocytic leukaemia			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenosquamous cell lung cancer			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroma			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder cancer metastatic			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Papillary thyroid cancer			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiopathy			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 731 (0.14%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Mammoplasty			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	6 / 731 (0.82%)	4 / 744 (0.54%)	
occurrences causally related to treatment / all	1 / 7	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adhesion			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embedded device			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pyrexia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pacemaker generated arrhythmia			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Pelvic haematoma			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenomyosis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectocele			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian mass			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	2 / 731 (0.27%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystocele			
subjects affected / exposed	2 / 731 (0.27%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary toxicity			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary bulla			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Haemoptysis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aspiration			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	2 / 731 (0.27%)	6 / 744 (0.81%)	
occurrences causally related to treatment / all	1 / 2	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung disorder			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Tracheal stenosis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Enterococcus test positive			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Contusion			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dislocation of vertebra			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Median nerve injury			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	3 / 731 (0.41%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Multiple injuries			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	3 / 731 (0.41%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac function disturbance postoperative			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Metatarsus primus varus			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial septal defect			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 731 (0.14%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiopulmonary failure			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 731 (0.14%)	5 / 744 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial infarction			
subjects affected / exposed	5 / 731 (0.68%)	11 / 744 (1.48%)	
occurrences causally related to treatment / all	0 / 6	0 / 12	
deaths causally related to treatment / all	0 / 2	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 731 (0.14%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem stroke			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 731 (0.27%)	4 / 744 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basilar migraine			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral artery embolism			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriparesis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery aneurysm			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 731 (0.41%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 731 (0.27%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis lumbosacral			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyotrophic lateral sclerosis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical cord compression			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Hypersplenism			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenomegaly			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 731 (0.27%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	2 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising granulomatous lymphadenitis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniere's disease			

subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Keratitis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular fibrosis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal infarction			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 731 (0.27%)	4 / 744 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ischaemia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia haemorrhagic			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 731 (0.00%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphthous stomatitis			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocele			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Jaundice hepatocellular			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	3 / 731 (0.41%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 731 (0.14%)	4 / 744 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	4 / 731 (0.55%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 731 (0.27%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin wrinkling			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	3 / 731 (0.41%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	3 / 731 (0.41%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Stress urinary incontinence			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder prolapse			

subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Facet joint syndrome			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament disorder			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint contracture			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	2 / 731 (0.27%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costochondritis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			

subjects affected / exposed	3 / 731 (0.41%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	12 / 731 (1.64%)	16 / 744 (2.15%)	
occurrences causally related to treatment / all	0 / 15	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 731 (0.14%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	2 / 731 (0.27%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	12 / 731 (1.64%)	14 / 744 (1.88%)	
occurrences causally related to treatment / all	0 / 12	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective tenosynovitis			

subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingitis			
subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urosepsis			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Encephalitis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal tuberculosis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	3 / 731 (0.41%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	3 / 731 (0.41%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 influenza			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Abscess oral			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atypical pneumonia			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			

subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ludwig angina			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral hepatitis carrier			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 731 (1.64%)	8 / 744 (1.08%)	
occurrences causally related to treatment / all	9 / 13	4 / 8	
deaths causally related to treatment / all	1 / 3	2 / 3	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 731 (0.00%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 731 (0.27%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	3 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Herpes zoster			
subjects affected / exposed	2 / 731 (0.27%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	7 / 731 (0.96%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	7 / 9	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 731 (0.00%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			
subjects affected / exposed	1 / 731 (0.14%)	3 / 744 (0.40%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 731 (0.27%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tetanus			

subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 731 (0.14%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	2 / 731 (0.27%)	0 / 744 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 731 (0.14%)	2 / 744 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	0 / 731 (0.00%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diabetes mellitus			
subjects affected / exposed	1 / 731 (0.14%)	1 / 744 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	IV Abatacept	SC Abatacept	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	544 / 731 (74.42%)	567 / 744 (76.21%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	85 / 731 (11.63%)	96 / 744 (12.90%)	
occurrences (all)	103	114	
Nervous system disorders			
Dizziness			
subjects affected / exposed	40 / 731 (5.47%)	37 / 744 (4.97%)	
occurrences (all)	52	43	
Headache			
subjects affected / exposed	88 / 731 (12.04%)	86 / 744 (11.56%)	
occurrences (all)	156	120	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	26 / 731 (3.56%)	55 / 744 (7.39%)	
occurrences (all)	65	32	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	27 / 731 (3.69%)	39 / 744 (5.24%)	
occurrences (all)	37	46	
Abdominal pain upper			
subjects affected / exposed	47 / 731 (6.43%)	43 / 744 (5.78%)	
occurrences (all)	53	45	
Diarrhoea			

subjects affected / exposed	89 / 731 (12.18%)	96 / 744 (12.90%)	
occurrences (all)	128	129	
Gastritis			
subjects affected / exposed	30 / 731 (4.10%)	40 / 744 (5.38%)	
occurrences (all)	36	43	
Nausea			
subjects affected / exposed	53 / 731 (7.25%)	79 / 744 (10.62%)	
occurrences (all)	74	96	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	74 / 731 (10.12%)	72 / 744 (9.68%)	
occurrences (all)	108	91	
Psychiatric disorders			
Depression			
subjects affected / exposed	40 / 731 (5.47%)	37 / 744 (4.97%)	
occurrences (all)	42	40	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	76 / 731 (10.40%)	76 / 744 (10.22%)	
occurrences (all)	99	95	
Infections and infestations			
Bronchitis			
subjects affected / exposed	120 / 731 (16.42%)	109 / 744 (14.65%)	
occurrences (all)	182	183	
Gastroenteritis			
subjects affected / exposed	48 / 731 (6.57%)	60 / 744 (8.06%)	
occurrences (all)	57	72	
Influenza			
subjects affected / exposed	55 / 731 (7.52%)	51 / 744 (6.85%)	
occurrences (all)	82	74	
Nasopharyngitis			
subjects affected / exposed	143 / 731 (19.56%)	149 / 744 (20.03%)	
occurrences (all)	250	248	
Pharyngitis			
subjects affected / exposed	80 / 731 (10.94%)	74 / 744 (9.95%)	
occurrences (all)	127	109	

Sinusitis			
subjects affected / exposed	50 / 731 (6.84%)	69 / 744 (9.27%)	
occurrences (all)	77	122	
Upper respiratory tract infection			
subjects affected / exposed	131 / 731 (17.92%)	130 / 744 (17.47%)	
occurrences (all)	205	228	
Urinary tract infection			
subjects affected / exposed	133 / 731 (18.19%)	150 / 744 (20.16%)	
occurrences (all)	210	243	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2007	The target percentage for subcutaneous abatacept was increased to preserve the intravenous abatacept benefit over placebo to 70%. In accordance, the following revisions were made: • non-inferiority margin reduced to -7.5 • total sample size increased to 1440 • randomization ratio changed to 1:1.
25 April 2008	The purpose of this amendment was further clarification on target population to be methotrexate inadequate responders, introducing a limit of subjects with prior exposure to anti-TNF therapy to 10% of the study population, implementing stratification by weight and shifting the collection interval for Pharmacokinetic (PK) samples of the Full PK Profile.
25 September 2008	Incorporates changes in the main protocol that result from the implementation of the anti-TNF failure substudy at selected sites, like the increase of the total sample size. In addition, some minor clarifications and updates on the protocol document were added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported