Clinical trial results:
A Single-Arm, Open-Label Study To Assess The Immunogenicity, Safety, And Efficacy Of Etanercept Manufactured Using The High Capacity Process Administered To Subjects With Rheumatoid Arthritis

Summary

EudraCT number	2013-004569-16
Trial protocol	HU SK DE BG GR HR
Global end of trial date	18 June 2016

Results information

Result version number	v1 (current)
This version publication date	05 April 2017
First version publication date	05 April 2017

Trial information

Trial identification

Sponsor protocol code	B1801359

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02378506
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800--718--1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800--718--1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the immunogenicity of Etanercept manufactured using the high capacity process administered weekly in subjects with rheumatoid arthritis over 24 weeks.

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 Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 19
Country: Number of subjects enrolled	Croatia: 19
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Poland: 24
Country: Number of subjects enrolled	Serbia: 8
Country: Number of subjects enrolled	Slovakia: 39
Country: Number of subjects enrolled	South Africa: 32
Worldwide total number of subjects	187
EEA total number of subjects	147

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)	142
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

188 subjects were randomized, however only 187 were treated.

Period 1

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

Arms

Arm title	Etanercept

Arm description:

Subjects with moderate to severe rheumatoid arthritis (RA), received subcutaneous Etanercept 50 milligram (mg) once weekly up to Week 24 and were followed up to Week 28.

Arm type	Experimental
Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received subcutaneous Etanercept 50 mg once weekly up to Week 24.

Number of subjects in period 1	Etanercept
Started	187
Completed	163
Not completed	24
Consent withdrawn by subject	4
Adverse Event	14
Death	1
Protocol deviation	2
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Etanercept
Reporting group description:	
Subjects with moderate to severe rheumatoid arthritis (RA), received subcutaneous Etanercept 50 milligram (mg) once weekly up to Week 24 and were followed up to Week 28.	

Reporting group values	Etanercept	Total	
Number of subjects	187	187	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	142	142	
From 65-84 years	45	45	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	54.2		
standard deviation	± 12.89	-	
Gender Categorical Units: Subjects			
Female	159	159	
Male	28	28	

End points

End points reporting groups

Reporting group title	Etanercept

Reporting group description:

Subjects with moderate to severe rheumatoid arthritis (RA), received subcutaneous Etanercept 50 milligram (mg) once weekly up to Week 24 and were followed up to Week 28.

Primary: Percentage of Subjects With Positive Etanercept Anti-Drug Antibody (ADA) Status at Week 12

End point title	Percentage of Subjects With Positive Etanercept Anti-Drug Antibody (ADA) Status at Week 12[1]

End point description:

Subjects who developed anti-drug antibodies after treatment with Etanercept were evaluated. Percentage of subjects with positive anti-drug antibodies were summarized. Analysis set included all subjects who had taken at least 1 dose of study medication and had at least 1 Etanercept anti-drug antibody evaluation. Here, 'Number of Subjects Analyzed' (N) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Week 12

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 data was planned to be analyzed in this endpoint

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: percentage of subjects				
number (confidence interval 95%)	1.9 (0.5 to 5)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Positive Etanercept Anti-Drug Antibody (ADA) Status at Week 24

End point title	Percentage of Subjects With Positive Etanercept Anti-Drug Antibody (ADA) Status at Week 24[2]

End point description:

Subjects who developed anti-drug antibodies after treatment with Etanercept were evaluated. Percentage of subjects with positive anti-drug antibodies were summarized. Analysis set included all subjects who had taken at least 1 dose of study medication and had at least 1 Etanercept anti-drug antibody evaluation. Here, 'N' signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Week 24

Notes:

[2] - 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 data was planned to be analyzed in this endpoint

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	175			
Units: percentage of subjects				
number (confidence interval 95%)	2.9 (1.1 to 6.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Positive Etanercept Anti-Drug Antibody (ADA) Status: Throughout Study Treatment

End point title	Percentage of Subjects With Positive Etanercept Anti-Drug Antibody (ADA) Status: Throughout Study Treatment[3]

End point description:

Subjects who developed anti-drug antibodies after treatment with Etanercept were evaluated. Percentage of subjects with positive anti-drug antibodies were summarized. Analysis set included all subjects who had taken at least 1 dose of study medication and had at least 1 Etanercept anti-drug antibody evaluation.

End point type	Primary

End point timeframe:

Baseline up to Week 24

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 data was planned to be analyzed in this endpoint

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	176			
Units: percentage of subjects				
number (confidence interval 95%)	4.5 (2.2 to 8.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Positive Etanercept Neutralizing Anti-drug Antibody Status: Throughout Study Treatment

End point title	Percentage of Subjects With Positive Etanercept Neutralizing Anti-drug Antibody Status: Throughout Study Treatment

End point description:

Percentage of subjects with positive Etanercept neutralizing anti-drug antibodies were summarized. Analysis set included all subjects who had taken at least 1 dose of study medication and had at least 1

Etanercept anti-drug antibody evaluation.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 24

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	176			
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 1.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious adverse events. Safety population included all subjects who had taken at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 28 (Follow-up)

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: subjects				
number (not applicable)				
AEs	90			
SAEs	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Investigator-Identified Serious Infections

End point title	Number of Subjects With Investigator-Identified Serious Infections

End point description:

Infection was considered as serious by investigator for any of the following outcomes: death; life-threatening; required initial or prolonged inpatient hospitalization; persistent or significant disability/incapacity or congenital anomaly/birth defect. Safety population included all subjects who had taken at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 28 (Follow-up)

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: subjects				
number (not applicable)	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Injection Site Reactions

End point title	Number of Subjects With Injection Site Reactions

End point description:

Injection site reactions included injection site erythema, swelling, pain, and warmth. Safety population included all subjects who had taken at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 28 (Follow-up)

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: subjects				
number (not applicable)	27			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 and 4 Clinical Laboratory Abnormalities

End point title	Number of Subjects With Grade 3 and 4 Clinical Laboratory Abnormalities

End point description:

Laboratory abnormalities (national cancer institute toxicity criteria version 4.0), Grade 3: neutrophil (>=0.5, <1.0 10^9/L), lymphocyte (<0.5 10^9/L), hemoglobin (Hb) (<80, >=65 gram per liter [g/L]), platelet (<50.0, >=25.0 10^9/L), white blood count (WBC) (<2.0, >=1.0 10^9/L); alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) (>5.0*upper range [UR], <=20.0*UR unit per liter [U/L]); bilirubin (>1.5*UR, <=3.0*UR micromole per liter [mcmol/L]); creatinine (>3.0*UR, <=6.0* UR mcmol/L); albumin (<20.0 g/L), urea (>3.0* UR, <=4.0* UR g/L); potassium (K)-high, low (>6.0, <=7.0 or <3.0, >=2.5 mcmol/L); sodium (Na)-high, low (>155, <=160 or <130, >=120 mcmol/L) and Grade 4: neutrophil(<0.5 10^9/L), Hb(<65 g/L); platelet(<25.0 10^9/L); WBC(<1.0 10^9/L); AP, AST, ALT(>20.0*UR U/L); bilirubin(>3.0* UR mcmol/L); creatinine(>6.0* UR mcmol/L); urea(>4.0* UR g/L); K-high, low(>7.0 or <2.5 mcmol/L); Na-high, low(>160 or <120 mcmol/L). Safety population.

End point type	Secondary

End point timeframe:

Baseline (Day 1) up to Week 28 (Follow-up)

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: subjects				
number (not applicable)	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 20% (ACR20) Response

End point description:

ACR20 responder: subjects with 20% improvement in tender, swollen 28-joint counts, 20% improvement in at least 3 of 5 measures: subject global assessment of arthritis (subject assessed overall arthritis, score: 0 [no arthritis] to 10 [extreme arthritis], higher score=more arthritis); physician global assessment of arthritis (physician judged subject's overall arthritis, score: 0 [no arthritis] to 10 [extreme arthritis], higher score=more arthritis); subject pain visual analogue scale (VAS) (subject assessed arthritis pain by 100 millimeter (mm) VAS, score: 0 mm [no pain] to 100 mm [extreme pain], higher score=more pain); health assessment questionnaire-disability index (functional disability evaluation, score: 0 [no difficulty] to 3 [extreme difficulty], higher score=more disability); C-reactive protein. Percentage of subjects with ACR20 response were reported. mITT. n = number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Week 4, 12, 24

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 4 (n =186)	55.9 (48.7 to 62.9)			
Week 12 (n =179)	76.5 (69.9 to 82.3)			
Week 24 (n =161)	82 (75.5 to 87.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 50% (ACR50) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 50% (ACR50) Response

End point description:

ACR50 responder: subjects with 50% improvement in tender, swollen 28-joint counts, 50% improvement in at least 3 of 5 measures: subject global assessment of arthritis (subject assessed overall arthritis, score: 0 [no arthritis] to 10 [extreme arthritis], higher score=more arthritis); physician global assessment of arthritis (physician judged subject's overall arthritis, score: 0 [no arthritis] to 10 [extreme arthritis], higher score=more arthritis); subject pain visual analogue scale (VAS) (subject assessed arthritis pain by 100 millimeter (mm) VAS, score: 0 mm [no pain] to 100 mm [extreme pain], higher score=more pain); health assessment questionnaire-disability index (functional disability evaluation, score: 0 [no difficulty] to 3 [extreme difficulty], higher score=more disability); C-reactive protein. Percentage of subjects with ACR50 response were reported. mITT. n = number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Week 4, 12, 24

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 4 (n =186)	16.1 (11.4 to 21.9)			
Week 12 (n =179)	36.3 (29.5 to 43.5)			
Week 24 (n =161)	57.8 (50.1 to 65.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Achieving American College of Rheumatology 70% (ACR70) Response

End point title	Percentage of Subjects Achieving American College of Rheumatology 70% (ACR70) Response

End point description:

ACR70 responder: subjects with 70% improvement in tender, swollen 28-joint counts, 70% improvement in at least 3 of 5 measures: subject global assessment of arthritis (subject assessed overall arthritis, score: 0 [no arthritis] to 10 [extreme arthritis], higher score=more arthritis); physician global assessment of arthritis (physician judged subject's overall arthritis, score: 0 [no arthritis] to 10 [extreme arthritis], higher score=more arthritis); subject pain visual analogue scale (VAS) (subject assessed arthritis pain by 100 millimeter (mm) VAS, score: 0 mm [no pain] to 100 mm [extreme pain], higher score=more pain); health assessment questionnaire-disability index (functional disability evaluation, score: 0 [no difficulty] to 3 [extreme difficulty], higher score=more disability); C-reactive protein. Percentage of subjects with ACR70 response were reported. mITT. n = number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Week 4, 12, 24

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: percentage of subjects				
number (confidence interval 95%)				
Week 4 (n =186) Week 12 (n =179) Week 24 (n =161)	3.2 (1.4 to 6.5) 13.4 (9 to 19) 26.7 (20.3 to 33.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Scale Based on 28 Joint Count Erythrocyte Sedimentation Rate (4 Variables) (DAS28-4 [ESR]) at Week 4, 12 and 24

End point title	Change From Baseline in Disease Activity Scale Based on 28 Joint Count Erythrocyte Sedimentation Rate (4 Variables) (DAS28-4 [ESR]) at Week 4, 12 and 24

End point description:

DAS28: measure of disease activity in subjects with rheumatoid arthritis. DAS28¬4 (ESR) was calculated from number of swollen joints (SJC) and tender joints (TJC) using the 28 joints count, erythrocyte sedimentation rate (millimeter per hour [mm/hour]) and subject's general health visual analog scale assessment (scores: 0 mm [very well] to 100 mm [extremely bad], higher scores indicate worse health condition). Total DAS28¬4 (ESR) score: 0 (none) to 10 (extreme disease activity), higher scores indicate more disease activity. DAS28-4 (ESR) less than (<) 2.6= remission, <3.2= low disease activity, greater than or equal to (>=) 3.2 to 5.1= moderate disease activity and >5.1= high disease activity. Modified intent-to-treat (mITT) population included all subjects who had taken at least 1 dose of study medication. Here, "n" signifies number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 24

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =187)	6.2 (± 0.93)			
Change at Week 4 (n =186)	-1.5 (± 1.04)			
Change at Week 12 (n =180)	-2.3 (± 1.19)			
Change at Week 24 (n =162)	-2.8 (± 1.27)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Disease Activity Scale Based on 28 Joint Count C-Reactive Protein (4 Variables) (DAS28-4 [CRP]) at Week 4, 12 and 24

End point title	Change From Baseline in Disease Activity Scale Based on 28 Joint Count C-Reactive Protein (4 Variables) (DAS28-4 [CRP]) at Week 4, 12 and 24

End point description:

DAS28 is a measure of disease activity in subjects with rheumatoid arthritis. DAS28-4 (CRP) was calculated from the number of swollen joints and tender joints using the 28 joints count, C-Reactive protein (milligram per liter [mg/L]) and subject's general health visual analog scale assessment (scores ranging 0 mm [very well] to 100 mm [extremely bad], higher scores indicate worse health condition). Total DAS28-4 (CRP) score range: 0 (none) to 10 (extreme disease activity), higher scores indicate more disease activity. DAS28-4 (CRP) less than (<) 2.6= remission, <3.2= low disease activity, greater than or equal to (≥) 3.2 to 5.1= moderate disease activity and >5.1= high disease activity. mITT population included all subjects who had taken at least 1 dose of study medication. Here, "n" signifies number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 24

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =187)	5.4 (± 0.91)			
Change at Week 4 (n =187)	-1.5 (± 1.02)			
Change at Week 12 (n =179)	-2.2 (± 1.09)			
Change at Week 24 (n =162)	-2.5 (± 1.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 4, 12 and 24

End point title	Change From Baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 4, 12 and 24

End point description:

HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and other activities. Each item scored on 4-point scale from 0 to 3: 0= no difficulty; 1= some difficulty; 2= much difficulty; 3= unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0 (least difficulty) and 3 (extreme difficulty), where higher scores indicate more difficulty while performing daily living activities. mITT population included all subjects who had taken at least 1 dose of study medication. Here, "n" signifies number of subjects evaluable at specified time points.

End point type	Secondary

End point timeframe:

Baseline, Week 4, 12, 24

End point values	Etanercept			
Subject group type	Reporting group			
Number of subjects analysed	187			
Units: units on a scale				
arithmetic mean (standard deviation)				
Baseline (n =186)	1.3 (± 0.58)			
Change at Week 4 (n =186)	-0.3 (± 0.39)			
Change at Week 12 (n =179)	-0.4 (± 0.48)			
Change at Week 24 (n =161)	-0.5 (± 0.56)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) up to Week 28 (follow-up)

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non serious in another subject, or one subject may have experienced both a serious and non serious event during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Etanercept

Reporting group description:

Subjects with moderate to severe rheumatoid arthritis (RA), received subcutaneous Etanercept 50 milligram (mg) once weekly up to Week 24 and were followed up to Week 28.

Serious adverse events	Etanercept		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 187 (4.81%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Urticaria			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus ureteric			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Metatarsalgia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			

subjects affected / exposed	1 / 187 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Etanercept		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 187 (45.45%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	4 / 187 (2.14%)		
occurrences (all)	4		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 187 (2.67%)		
occurrences (all)	5		
Influenza like illness			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	20 / 187 (10.70%)		
occurrences (all)	46		
Injection site nodule			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	5		
Injection site pruritus			
subjects affected / exposed	7 / 187 (3.74%)		
occurrences (all)	7		

Injection site rash subjects affected / exposed occurrences (all)	2 / 187 (1.07%) 5		
Injection site reaction subjects affected / exposed occurrences (all)	5 / 187 (2.67%) 5		
Injection site swelling subjects affected / exposed occurrences (all)	3 / 187 (1.60%) 9		
Injection site urticaria subjects affected / exposed occurrences (all)	1 / 187 (0.53%) 1		
Injection site vesicles subjects affected / exposed occurrences (all)	1 / 187 (0.53%) 1		
Malaise subjects affected / exposed occurrences (all)	1 / 187 (0.53%) 1		
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 187 (0.53%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	1 / 187 (0.53%) 1		
Reproductive system and breast disorders Amenorrhoea subjects affected / exposed[1] occurrences (all)	Additional description: This event was gender specific. 1 / 159 (0.63%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	2 / 187 (1.07%) 2		
Cough subjects affected / exposed occurrences (all)	2 / 187 (1.07%) 2		

Upper-airway cough syndrome			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Impulsive behaviour			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 187 (1.07%)		
occurrences (all)	2		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Blood pressure diastolic abnormal			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Lymphocyte count decreased			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Neutrophil count decreased			
subjects affected / exposed	2 / 187 (1.07%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Vitamin D decreased			

subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	3 / 187 (1.60%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	2		
Fall			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Nervous system disorders			
Cerebrovascular disorder			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Headache			

subjects affected / exposed	5 / 187 (2.67%)		
occurrences (all)	5		
Migraine			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 187 (1.60%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Hepatobiliary disorders			

Hepatic cyst			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Hepatic steatosis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	4 / 187 (2.14%)		
occurrences (all)	4		
Pruritus			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Psoriasis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Rash macular			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 187 (1.60%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 187 (1.07%)		
occurrences (all)	2		
Joint instability			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Rheumatoid arthritis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	3 / 187 (1.60%)		
occurrences (all)	3		
Fungal skin infection			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	2 / 187 (1.07%)		
occurrences (all)	2		
Genitourinary tract infection			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Gingivitis			

subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 187 (1.07%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	13 / 187 (6.95%)		
occurrences (all)	16		
Otitis media acute			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	2 / 187 (1.07%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	13 / 187 (6.95%)		
occurrences (all)	14		
Urinary tract infection			
subjects affected / exposed	4 / 187 (2.14%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		
Iron deficiency			
subjects affected / exposed	1 / 187 (0.53%)		
occurrences (all)	1		

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: This event was gender specific

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported