Clinical trial results:
A Phase IIb, Multicenter, Randomized, Double-blind, Placebo-controlled, Multidose, 24-week Study to Evaluate the Efficacy and Safety of Atacicept in Subjects with Systemic Lupus Erythematosus (SLE)

Summary

EudraCT number	2013-002773-21
Trial protocol	CZ DE BG GB ES IT
Global end of trial date	08 December 2016

Results information

Result version number	v1 (current)
This version publication date	22 November 2017
First version publication date	22 November 2017

Trial information

Trial identification

Sponsor protocol code	EMR700461-023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01972568
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Center Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.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	30 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of atacicept compared to placebo in reducing SLE disease activity in subjects treated with standard of care (SoC) therapy and to investigate the dose-response relationship

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Philippines: 21
Country: Number of subjects enrolled	Bulgaria: 27
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	South Africa: 12
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Argentina: 52
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Chile: 19
Country: Number of subjects enrolled	Mexico: 55
Country: Number of subjects enrolled	Peru: 7
Country: Number of subjects enrolled	United States: 63

Worldwide total number of subjects	306
EEA total number of subjects	51

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)	301
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at 136 sites in 18 countries in Asia, Europe, North America, Central America, and South America.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Atacicept 75 mg

Arm description:

Subjects received atacicept 75 milligram (mg) as once-weekly subcutaneous injection for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Atacicept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received atacicept 75 mg as once-weekly subcutaneous injection for 24 weeks.

Arm title	Atacicept 150 mg

Arm description:

Subjects received atacicept 150 mg as once-weekly subcutaneous injection for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Atacicept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received atacicept 150 mg as once-weekly subcutaneous injection for 24 weeks.

Arm title	Placebo

Arm description:

Subjects received placebo matched to atacicept as once-weekly subcutaneous injection for 24 weeks.

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

Dosage and administration details:
Subjects received placebo matched to atacicept as once-weekly subcutaneous injection for 24 weeks.

Number of subjects in period 1	Atacicept 75 mg	Atacicept 150 mg	Placebo
Started	102	104	100
Completed	86	92	84
Not completed	16	12	16
Consent withdrawn by subject	6	3	7
Adverse event, non-fatal	5	6	5
Lost to follow-up	1	-	-
Other events	3	-	-
Protocol deviation	1	2	2
Lack of efficacy	-	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Atacicept 75 mg
Reporting group description:	
Subjects received atacicept 75 milligram (mg) as once-weekly subcutaneous injection for 24 weeks.	
Reporting group title	Atacicept 150 mg
Reporting group description:	
Subjects received atacicept 150 mg as once-weekly subcutaneous injection for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to atacicept as once-weekly subcutaneous injection for 24 weeks.	

Reporting group values	Atacicept 75 mg	Atacicept 150 mg	Placebo
Number of subjects	102	104	100
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 37 ± 11.2	 39 ± 11.6	 40 ± 13.0
Gender, Male/Female Units: Subjects			
Female	93	97	90
Male	9	7	10

Reporting group values	Total		
Number of subjects	306		
Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 -		
Gender, Male/Female Units: Subjects			
Female	280		
Male	26		

End points

End points reporting groups

Reporting group title	Atacicept 75 mg
Reporting group description:	
Subjects received atacicept 75 milligram (mg) as once-weekly subcutaneous injection for 24 weeks.	
Reporting group title	Atacicept 150 mg
Reporting group description:	
Subjects received atacicept 150 mg as once-weekly subcutaneous injection for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to atacicept as once-weekly subcutaneous injection for 24 weeks.	

Primary: Percentage of Subjects With Systemic Lupus Erythematosus Responder Index (SRI) Response at Week 24 Using Screening Visit as Baseline

End point title	Percentage of Subjects With Systemic Lupus Erythematosus Responder Index (SRI) Response at Week 24 Using Screening Visit as Baseline
End point description:	
SRI response, a composite measure of reduced SLE disease activity, was defined as a reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) disease activity score of greater than or equal to (>=) 4 points; no significant worsening in Physician's Global Assessment (PGA) score (<10 % increase, defined as <0.3 point increase for statistical analyses); no new British Isles Lupus Assessment Group (BILAG) A organ domain scores and <=1 (defined as no more than one) new BILAG B organ domain score. Modified intent-to-treat (mITT) analysis set included all randomised subjects who had received at least 1 dose of IMP.	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	100	
Units: percentage of subjects				
number (not applicable)	57.8	53.8	44.0	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atacicept 150 mg v Placebo

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1208
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	1.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	2.72

Primary: Percentage of Subjects With Systemic Lupus Erythematosus (SLE) Responder Index (SRI) Response at Week 24 Using Day 1 as Baseline

End point title	Percentage of Subjects With Systemic Lupus Erythematosus (SLE) Responder Index (SRI) Response at Week 24 Using Day 1 as Baseline

End point description:

SRI response, a composite measure of reduced SLE disease activity, was defined as a reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) disease activity score of greater than or equal to (>=) 4 points; no significant worsening in Physician's Global Assessment (PGA) score (<10 % increase, defined as <0.3 point increase for statistical analyses); no new British Isles Lupus Assessment Group (BILAG) A organ domain scores and <=1 (defined as no more than one) new BILAG B organ domain score. mITT analysis set included all randomized subjects who had received at least 1 dose of IMP.

End point type	Primary

End point timeframe:

Week 24

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	100	
Units: percentage of subjects				
number (not applicable)	55.9	55.8	41.0	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atacicept 150 mg v Placebo

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0202
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	3.46

Secondary: Percentage of Subjects at Week 24 Whose Prednisone-Equivalent Corticosteroid (CS) Dose Reduced From Screening by >=25% and to a dose of =<7.5mg/day, and no British Isles Lupus Assessment Group(BILAG) A or 2B Flare in Disease Activity

End point title	Percentage of Subjects at Week 24 Whose Prednisone-Equivalent Corticosteroid (CS) Dose Reduced From Screening by >=25% and to a dose of =<7.5mg/day, and no British Isles Lupus Assessment Group(BILAG) A or 2B Flare in Disease Activity

End point description:

BILAG A or 2B flare defined by 1 new BILAG A organ domain score and/or 2 new BILAG B organ domain scores compared to the Screening Visit.The BILAG disease activity index evaluates systemic lupus erythematosus (SLE) activity in 8 organ systems,using a separate alphabetic score (A to E) assigned to each organ system defined as follows. BILAG A: Disease sufficiently active requiring disease-modifying treatment (prednisone >20 mg daily or immunosuppressants); BILAG B: moderate disease activity requiring treatment with systemic low-dose oral glucocorticoids,intramuscular or soft tissue CS injection,topical CS or immunosuppressants,or symptomatic therapy such as antimalarials or NSAIDs. BILAG C: mild disease; BILAG D: system previously affected but now inactive and BILAG E: system never involved. mITT analysis set included included all randomised subjects who had received at least 1 dose of IMP.Here "Number of Subjects Analysed" signifies those subjects whose CS dose >=10mg at Screening.

End point type	Secondary

End point timeframe:

Week 24

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	56	53	53	
Units: percentage of subjects				
number (not applicable)	17.9	11.3	18.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Patient Global Impression of Change (PGIC) Categories at Week 24

End point title	Percentage of Subjects With Patient Global Impression of Change (PGIC) Categories at Week 24

End point description:

The PGIC is self-rated scale that asks the subject to describe the change in activity limitations, symptoms, emotions, and overall Quality of life (QoL) related to the subject's painful condition on the following scale: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse) and 7 (very much worse). Percentage of subjects in the PGIC categories of very much or much improved (1 or 2), minimally improved or no change or minimally worse (3 or 4 or 5) and much or very much worse (6 or 7) at Week 24 were presented. mITT analysis set included all randomised subjects who had received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Week 24

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	100	
Units: percentage of subjects				
number (not applicable)				
Very much or much improved	57.8	53.8	46.0	
Minimally improved or no change or minimally worse	39.2	44.2	46.0	
Much or very much worse	2.0	1.0	6.0	
Missing	1.0	1.0	2.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Screening in Prednisolone-Equivalent Corticosteroid (CS) Daily Dose at Week 24

End point title	Change From Screening in Prednisolone-Equivalent Corticosteroid (CS) Daily Dose at Week 24

End point description:

Change From screening visit to Week 24 of prednisolone-equivalent CS daily dose was presented. mITT analysis set included all randomised subjects who had received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Screening and Week 24

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	100	
Units: mg per day				
arithmetic mean (standard deviation)	-2.64 (± 6.106)	-1.87 (± 4.653)	-1.89 (± 5.588)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Randomization to First SRI Response During Treatment Period

End point title	Time From Randomization to First SRI Response During Treatment Period

End point description:

SRI response, a composite measure of reduced SLE disease activity, was defined as a reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) disease activity score of greater than or equal to (>=) 4 points; no significant worsening in Physician's Global Assessment (PGA) score (<10 % increase, defined as <0.3 point increase for statistical analyses); no new British Isles Lupus Assessment Group (BILAG) A organ domain scores and <=1 (defined as no more than one) new BILAG B organ domain score. Time to randomization to first SRI response during treatment period was presented. mITT analysis set included all randomised subjects who had received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Baseline up to 24 Weeks

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	100	
Units: weeks				
median (confidence interval 95%)	12.4 (12.1 to 16.7)	16.1 (12.0 to 16.4)	16.1 (12.1 to 20.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With British Isles Lupus Assessment Group (BILAG)-Based Combined Lupus Assessment (BICLA) Response at Week 24

End point title	Percentage of Subjects With British Isles Lupus Assessment Group (BILAG)-Based Combined Lupus Assessment (BICLA) Response at Week 24

End point description:

The BICLA response is defined as BILAG-2004 improvement (all screening visit BILAG A improving to B/C/D, all screening visit BILAG B to C/D, and <=1 new BILAG B and no new BILAG A); no deterioration in SLEDAI total score'; PGA increase by <10% (defined as <0.3 point increase for the statistical

analyses) and no nonpermitted medication/treatment. mITT analysis set included all randomised subjects who had received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Week 24

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	100	93	
Units: percentage of subjects				
number (not applicable)	53.4	49.0	45.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug. A serious AE was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent are events between first dose of study drug and up to 48 weeks. TEAEs include both Serious TEAEs and non-serious TEAEs. Safety analysis set included all randomised subjects who received at least 1 dose of IMP.

End point type	Secondary

End point timeframe:

Baseline up to 24 weeks after last dose of study drug (assessed up to maximum of 48 weeks)

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	100	
Units: percentage of subjects				
number (not applicable)				
TEAEs	81.4	80.8	72.0	
Serious TEAEs	8.8	5.8	12.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Week 0 Day 1 in SF-36 Components at Week 24

End point title	Change From Week 0 Day 1 in SF-36 Components at Week 24

End point description:

The 36-Item Short-Form Health Survey (SF-36) is a standardized survey evaluating 8 aspects of functional health and well being: physical and social functioning, physical and emotional role limitations, bodily pain, general health, vitality, mental health. These 8 aspects can also be summarized as physical and mental component summary scores. Total of 10 variables were analyzed (8 aspects, 2 component summary scores). The score for each of the 8 aspects and 2 component summary scores was scaled from 0 to 100, where 0 = lowest level of functioning and 100 = highest level of functioning.

End point type	Secondary

End point timeframe:

Week 0 Day 1 and Week 24

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	104	100	
Units: units on a scale				
arithmetic mean (standard deviation)				
Physical Component Summary (n=101,100, 97)	4.7 (± 7.95)	3.4 (± 7.57)	3.5 (± 10.33)	
Mental Component Summary (n=101,100, 97)	1.9 (± 12.01)	1.8 (± 9.08)	0.7 (± 11.44)	
Physical Functioning (n=85, 89, 82)	3.5 (± 9.30)	3.8 (± 8.42)	3.3 (± 8.62)	
Role-Physical (n=85, 89, 82)	4.3 (± 10.26)	2.3 (± 8.64)	3.9 (± 9.51)	
Bodily Pain (n=85, 89, 82)	6.0 (± 10.22)	4.4 (± 9.30)	5.6 (± 10.72)	
General Health (n=84, 89, 82)	2.9 (± 8.43)	3.0 (± 7.72)	4.4 (± 8.00)	
Vitality (n=84, 89, 82)	3.9 (± 9.86)	3.7 (± 9.76)	3.5 (± 9.57)	
Social Functioning (n=85, 89, 82)	3.8 (± 11.45)	2.2 (± 10.06)	4.3 (± 11.08)	

Statistical analyses

No statistical analyses for this end point

Post-hoc: High Disease Activity Subpopulation (SLEDAI-2K >=10 at Screening): Logistic Regression of Percentage of Subjects With SRI-6 Response at Week 24

End point title	High Disease Activity Subpopulation (SLEDAI-2K >=10 at Screening): Logistic Regression of Percentage of Subjects With SRI-6 Response at Week 24

End point description:

SRI-6 response, a composite measure of reduced SLE disease activity, was defined as a reduction in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) disease activity score of greater than or equal to (>=) 6 points; no significant worsening in Physician's Global Assessment (PGA) score (<10 % increase, defined as <0.3 point increase for statistical analyses); no new British Isles Lupus Assessment Group (BILAG) A organ domain scores and <=1 (defined as no more than one) new BILAG B organ domain score. Logistic regression of number of subjects with SRI-6 response was analzed by using Logistic regression model. mITT_HDA analysis set included mITT population with high disease activity (HDA) defined as screening SLE Disease Activity Index (SLEDAI) >=10.

End point type	Post-hoc

End point timeframe:
Week 24

End point values	Atacicept 75 mg	Atacicept 150 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	55	51	52	
Units: percentage of subjects				
number (not applicable)	43.6	54.9	28.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Atacicept 150 mg v Placebo
Number of subjects included in analysis	103
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0048
Method	Logistic regression model
Parameter estimate	Odds ratio (OR)
Point estimate	3.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.44
upper limit	7.61

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 24 weeks after last dose of study drug (assessed up to maximum of 48 weeks)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Atacicept 75 mg
Reporting group description:	
Subjects received atacicept 75 milligram (mg) as once-weekly subcutaneous injection for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to atacicept as once-weekly subcutaneous injection for 24 weeks.	
Reporting group title	Atacicept 150 mg
Reporting group description:	
Subjects received atacicept 150 mg as once-weekly subcutaneous injection for 24 weeks.	

Serious adverse events	Atacicept 75 mg	Placebo	Atacicept 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 102 (8.82%)	12 / 100 (12.00%)	6 / 104 (5.77%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament injury			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve prolapse			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular dilatation			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			

subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal lobe epilepsy			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 102 (0.00%)	2 / 100 (2.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	1 / 102 (0.98%)	2 / 100 (2.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchitis			
subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac valve vegetation			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective aortitis			
subjects affected / exposed	0 / 102 (0.00%)	0 / 100 (0.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph node abscess			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasopharyngitis			

subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 102 (0.98%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis bacterial			

subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal sepsis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	1 / 104 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 102 (0.98%)	0 / 100 (0.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 102 (0.00%)	1 / 100 (1.00%)	0 / 104 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Atacicept 75 mg	Placebo	Atacicept 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 102 (81.37%)	72 / 100 (72.00%)	84 / 104 (80.77%)
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 102 (10.78%)	8 / 100 (8.00%)	15 / 104 (14.42%)
occurrences (all)	11	8	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 102 (5.88%)	2 / 100 (2.00%)	3 / 104 (2.88%)
occurrences (all)	6	2	3
Injection site pain			

subjects affected / exposed	12 / 102 (11.76%)	7 / 100 (7.00%)	14 / 104 (13.46%)
occurrences (all)	12	7	14
Injection site reaction			
subjects affected / exposed	42 / 102 (41.18%)	19 / 100 (19.00%)	43 / 104 (41.35%)
occurrences (all)	42	19	43
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	8 / 102 (7.84%)	5 / 100 (5.00%)	12 / 104 (11.54%)
occurrences (all)	8	5	12
Nausea			
subjects affected / exposed	9 / 102 (8.82%)	1 / 100 (1.00%)	5 / 104 (4.81%)
occurrences (all)	9	1	5
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 102 (3.92%)	7 / 100 (7.00%)	3 / 104 (2.88%)
occurrences (all)	4	7	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 102 (5.88%)	5 / 100 (5.00%)	7 / 104 (6.73%)
occurrences (all)	6	5	7
Upper respiratory tract infection			
subjects affected / exposed	10 / 102 (9.80%)	3 / 100 (3.00%)	13 / 104 (12.50%)
occurrences (all)	10	3	13
Urinary tract infection			
subjects affected / exposed	12 / 102 (11.76%)	17 / 100 (17.00%)	12 / 104 (11.54%)
occurrences (all)	12	17	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 June 2014	- Included additional detail and clarity in the secondary endpoints - Included additional detail and clarity in the study entry criteria - Included additional detail and clarity in the efficacy and safety assessments
25 March 2015	- Clarified hepatitis B and hepatitis C screening requirements - Clarified language regarding nonpermitted medications and provided further instruction regarding which will require IMP discontinuation and which will constitute a protocol violation - Clarified language regarding continuing with the trial visits if withdrawal of IMP - Clarified that other than TB testing, the Screening laboratory results could be re-assessed one time with the permission of the Medical Monitor - Clarified language regarding for flow cytometry of PD markers and deleted exploratory monocyte and neutrophils PD endpoints due to challenges encountered with developing a validated assay. Of note, the monocyte and neutrophil absolute numbers were continued to be measured by the cell blood count as the standard laboratory measurements - Clarified language regarding the vaccine recommendation for subjects with prior severe hypersensitivity reactions to the vaccines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported