Clinical trial results:
A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 16 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active ankylosing spondylitis

Summary

EudraCT number	2010-024529-18
Trial protocol	GB DE BE BG IT
Global end of trial date	18 December 2014

Results information

Result version number	v1 (current)
This version publication date	09 July 2016
First version publication date	09 July 2016

Trial information

Trial identification

Sponsor protocol code	CAIN457F2305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01358175
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111,

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	18 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that the efficacy of at least one dose of secukinumab at Week 16 is superior to placebo in patients with active AS based on the proportion of patients achieving an ASAS 20 (Assessment of Spondyloarthritis International Society) response.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Peru: 37
Country: Number of subjects enrolled	Russian Federation: 70
Country: Number of subjects enrolled	Taiwan: 57
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Bulgaria: 28
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Mexico: 40
Country: Number of subjects enrolled	Netherlands: 12
Worldwide total number of subjects	371
EEA total number of subjects	135

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)	354
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A screening (SCR) period running 4 weeks before randomization was used to assess eligibility, followed by a treatment period of 2 years.

Period 1

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

Blinding implementation details:

monitor/sponsor up to week 52

Arms

Are arms mutually exclusive?	Yes
Arm title	Secukinumab 10 mg/kg i.v. / 75 mg s.c.

Arm description:

Three i.v. infusions: at Baseline and Weeks 2 and 4, followed by one S.C. injection every four weeks until the end of the study.

Arm type	Experimental
Investigational medicinal product name	Secukinumab
Investigational medicinal product code	AIN457
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Secukinumab (75 mg)

Arm title	Secukinumab 10 mg/kg i.v. / 150 mg s.c.

Arm description:

Three i.v. infusions: at Baseline and Weeks 2 and 4, followed by one S.C. injection every four weeks until the end of the study.

Arm type	Experimental
Investigational medicinal product name	Secukinumab
Investigational medicinal product code	AIN457
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Secukinumab (150 mg)

Arm title	Placebo

Arm description:

Placebo iv at Baseline, Week 2 and Week 4, and then Placebo S.C. at Week 8 and Week 12

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Placebo

Number of subjects in period 1	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Started	124	125	122
Completed	103	97	90
Not completed	21	28	32
Adverse event, serious fatal	1	-	1
Consent withdrawn by subject	9	5	10
Physician decision	1	-	-
Adverse event, non-fatal	6	11	11
Pregnancy	-	1	-
Non Compliance with Study Treatment	-	1	1
Lost to follow-up	1	1	3
Technical issues	-	1	-
Lack of efficacy	3	8	6

Baseline characteristics

Reporting groups	
Reporting group title	Secukinumab 10 mg/kg i.v. / 75 mg s.c.
Reporting group description:	
Three i.v. infusions: at Baseline and Weeks 2 and 4, followed by one S.C. injection every four weeks until the end of the study.	
Reporting group title	Secukinumab 10 mg/kg i.v. / 150 mg s.c.
Reporting group description:	
Three i.v. infusions: at Baseline and Weeks 2 and 4, followed by one S.C. injection every four weeks until the end of the study.	
Reporting group title	Placebo
Reporting group description:	
Placebo iv at Baseline, Week 2 and Week 4, and then Placebo S.C. at Week 8 and Week 12	

Reporting group values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo
Number of subjects	124	125	122
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	117	122	115
>=65 years	7	3	7
Age continuous Units: years			
arithmetic mean	42.3	40.1	43.1
standard deviation	± 13.24	± 11.61	± 12.44
Gender, Male/Female Units: participants			
Female	36	41	37
Male	88	84	85

Reporting group values	Total		
Number of subjects	371		
Age Categorical Units: participants			
<=18 years	0		
Between 18 and 65 years	354		
>=65 years	17		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: participants			
Female	114		
Male	257		

End points

End points reporting groups

Reporting group title	Secukinumab 10 mg/kg i.v. / 75 mg s.c.
Reporting group description:	
Three i.v. infusions: at Baseline and Weeks 2 and 4, followed by one S.C. injection every four weeks until the end of the study.	
Reporting group title	Secukinumab 10 mg/kg i.v. / 150 mg s.c.
Reporting group description:	
Three i.v. infusions: at Baseline and Weeks 2 and 4, followed by one S.C. injection every four weeks until the end of the study.	
Reporting group title	Placebo
Reporting group description:	
Placebo iv at Baseline, Week 2 and Week 4, and then Placebo S.C. at Week 8 and Week 12	

Primary: Assessment of responders for the SpondyloArthritis International Society / ASAS 20 response

End point title	Assessment of responders for the SpondyloArthritis International Society / ASAS 20 response
End point description:	
ASAS 20 response is a validated composite assessment, reflecting the proportion of treated patients who achieve within a defined timeframe at least 20% improvement in score in at least 3 of a conventional set of 4 clinical domains relevent to AS and no worsening in the fourth domain. ASAS 20 is used to assess the efficacy of at least one dose of secukinumab against placebo.	
End point type	Primary
End point timeframe:	
16 weeks	

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: % responders				
number (not applicable)	59.7	60.8	28.7	

Statistical analyses

Statistical analysis title	Assessment of Responders
Comparison groups	Secukinumab 10 mg/kg i.v. / 75 mg s.c. v Placebo

Number of subjects included in analysis	246
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	6.42

Statistical analysis title	Assessment of Responders
Comparison groups	Secukinumab 10 mg/kg i.v. / 150 mg s.c. v Placebo
Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.28
upper limit	6.65

Secondary: Assessment of responders for the SpondyloArthritis International Society ASAS 40 response

End point title	Assessment of responders for the SpondyloArthritis International Society ASAS 40 response

End point description:

ASAS 40 response is a validated composite assessment, reflecting the proportion of treated patients who achieve within a defined timeframe at least 40% improvement in score in at least 3 of a conventional set of 4 clinical domains relevent to AS and no worsening in the fourth domain. ASAS 40 is used to assess the efficacy of at least one dose of secukinumab against placebo.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: % responders				
number (not applicable)	33.1	41.6	13.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Serum hsCRP

End point title	Change from baseline in Serum hsCRP

End point description:

The change from baseline in hsCRP is expressed as a ratio of post-baseline to baseline values. With the ratio normalized to 1.0 at baseline, ratios less than 1.0 represent decreased post-baseline values, whereas ratios greater than 1.0 represent increased post-baseline values.

End point type	Secondary

End point timeframe:

Week 16

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: ratio				
least squares mean (standard error)	0.45 (± 1.092)	0.4 (± 1.09)	0.97 (± 1.095)	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of responders for the SpondyloArthritis International Society ASAS 5/6 response

End point title	Assessment of responders for the SpondyloArthritis International Society ASAS 5/6 response

End point description:

ASAS 5/6 response is a validated composite assessment, reflecting the proportion of treated patients who achieve within a defined timeframe at least 20% improvement in score in at least 5 of a conventional set of 6 clinical domains relevent to AS and no worsening in the remaining domain. In this study, ASAS 5/6 is used to assess the efficacy of at least one dose of secukinumab against placebo.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: % change from baseline				
number (not applicable)	45.2	48.8	13.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bath Ankylosing Spondylitis Disease Activity Index / BASDAI

End point title	Change from Baseline in Bath Ankylosing Spondylitis Disease Activity Index / BASDAI

End point description:

BASDAI is a validated assessment tool using 0 through 10 scales (0 indicating "no problem" and 10 indicating " worst problem"), to characterize six clinical domains pertaining to five major symptoms of AS perceived by the patients. Computed composite scores of 4 or greater indicate suboptimal disease control. In this study, the BASDAI is used to assess the efficacy of at least one dose of secukinumab verus placebo.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: units on scale				
number (not applicable)	-2.34	-2.32	-0.59	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Physical function component of the short-form health survey / SF-36 PCS

End point title	Change from baseline in Physical function component of the short-form health survey / SF-36 PCS

End point description:

SF-36 is a 36 item questionnaire which measures Quality of Life across eight domains, which are both phyically and emotionally based. Two overall summary scores, the Phyical Component Summary (PCS) and Mental Component Summary (MCS) can be computed. In this study, SF-36 PCS is used to assess improvement from baseline of at least one dose of secukinumab versus placebo.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: units on a scale				
number (not applicable)	5.64	5.57	0.96	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Ankylosing Spondylitis Quality of Life questionnaire / ASQoL

End point title	Change from Baseline in Ankylosing Spondylitis Quality of Life questionnaire / ASQoL

End point description:

ASQoL is an 18 item questionnaire that assesses disease-specific quality of life (QoL), consisting of statements that are relevant to the physical and mental conditions for a participant with AS: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each statement is answered by the participant as a 'Yes' (scored as 1) or 'No' (scored as 0). All item scores are summed to give a total score. Total score can range from 0 (good QoL) to 18 (poor QoL). In this study, ASQoL is used to assess improvement from baseline of at least one dose of secukinumab versus placebo.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: units on a scale				
number (not applicable)	-3.61	-3.58	-1.04	

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of responders for ASAS partial remission

End point title	Assessment of responders for ASAS partial remission

End point description:

ASAS partial remission is a composite assessment, reflecting the proportion of treated patients who achieve within a defined time frame a value not above 2 units in each of the 4 ASAS domains on a scale of 10. In this study ASAS partial remission is used to assess the efficacy of at least one dose of secukinumab versus placebo.

End point type	Secondary

End point timeframe:

16 weeks

End point values	Secukinumab 10 mg/kg i.v. / 75 mg s.c.	Secukinumab 10 mg/kg i.v. / 150 mg s.c.	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	124	125	122	
Units: % responders				
number (not applicable)	16.1	15.2	3.3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	AIN457 75 mg

Reporting group description:

AIN457 75 mg

Reporting group title	AIN457 150 mg

Reporting group description:

AIN457 150 mg

Reporting group title	Any AIN457

Reporting group description:

Any AIN457

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	AIN457 75 mg	AIN457 150 mg	Any AIN457
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 179 (13.41%)	22 / 181 (12.15%)	46 / 360 (12.78%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	0 / 179 (0.00%)	0 / 181 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral venous disease			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 179 (0.00%)	0 / 181 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Application site pain			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			

subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Asthma			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal septum deviation			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Respiratory failure			

subjects affected / exposed	1 / 179 (0.56%)	1 / 181 (0.55%)	2 / 360 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 179 (0.00%)	0 / 181 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 179 (0.00%)	0 / 181 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Cartilage injury			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dislocation of vertebra			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Laceration			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative thrombosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 179 (0.00%)	2 / 181 (1.10%)	2 / 360 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Coronary artery stenosis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 179 (1.12%)	2 / 181 (1.10%)	4 / 360 (1.11%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			

subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paresis			
subjects affected / exposed	0 / 179 (0.00%)	0 / 181 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 179 (0.00%)	0 / 181 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	0 / 179 (0.00%)	0 / 181 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	1 / 179 (0.56%)	1 / 181 (0.55%)	2 / 360 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epigastric discomfort			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar hernia			

subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 179 (1.12%)	0 / 181 (0.00%)	2 / 360 (0.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatosplenomegaly			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Hyperparathyroidism			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	0 / 179 (0.00%)	3 / 181 (1.66%)	3 / 360 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 179 (0.56%)	0 / 181 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pyelonephritis acute			
subjects affected / exposed	0 / 179 (0.00%)	1 / 181 (0.55%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tonsillitis			
subjects affected / exposed	0 / 179 (0.00%)	2 / 181 (1.10%)	2 / 360 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 122 (4.10%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphoma			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral venous disease			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Varicose vein			

subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion incomplete			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Application site pain			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest discomfort			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthma			

subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal septum deviation				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary fibrosis				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Completed suicide				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Depression				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Injury, poisoning and procedural complications				

Cartilage injury				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Craniocerebral injury				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dislocation of vertebra				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laceration				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative thrombosis				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				

subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac failure				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				

Brain oedema			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Trigeminal neuralgia			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vocal cord paresis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Abdominal lymphadenopathy			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vertigo			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			

subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epigastric discomfort				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar hernia				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 122 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				

subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis toxic			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatosplenomegaly			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			

subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Helicobacter gastritis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tonsillitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	AIN457 75 mg	AIN457 150 mg	Any AIN457
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 179 (69.83%)	142 / 181 (78.45%)	267 / 360 (74.17%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 179 (4.47%)	6 / 181 (3.31%)	14 / 360 (3.89%)
occurrences (all)	9	6	15
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 179 (3.35%)	5 / 181 (2.76%)	11 / 360 (3.06%)
occurrences (all)	7	6	13
Non-cardiac chest pain			
subjects affected / exposed	0 / 179 (0.00%)	4 / 181 (2.21%)	4 / 360 (1.11%)
occurrences (all)	0	6	6
Pyrexia			
subjects affected / exposed	0 / 179 (0.00%)	5 / 181 (2.76%)	5 / 360 (1.39%)
occurrences (all)	0	8	8
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 179 (5.03%)	10 / 181 (5.52%)	19 / 360 (5.28%)
occurrences (all)	11	13	24
Dyspnoea			
subjects affected / exposed	4 / 179 (2.23%)	1 / 181 (0.55%)	5 / 360 (1.39%)
occurrences (all)	4	4	8
Nasal congestion			
subjects affected / exposed	4 / 179 (2.23%)	2 / 181 (1.10%)	6 / 360 (1.67%)
occurrences (all)	4	2	6
Rhinorrhoea			
subjects affected / exposed	4 / 179 (2.23%)	3 / 181 (1.66%)	7 / 360 (1.94%)
occurrences (all)	4	3	7
Oropharyngeal pain			
subjects affected / exposed	13 / 179 (7.26%)	16 / 181 (8.84%)	29 / 360 (8.06%)
occurrences (all)	23	23	46
Psychiatric disorders			

Anxiety			
subjects affected / exposed	5 / 179 (2.79%)	0 / 181 (0.00%)	5 / 360 (1.39%)
occurrences (all)	5	0	5
Insomnia			
subjects affected / exposed	4 / 179 (2.23%)	6 / 181 (3.31%)	10 / 360 (2.78%)
occurrences (all)	7	7	14
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 179 (1.68%)	6 / 181 (3.31%)	9 / 360 (2.50%)
occurrences (all)	3	6	9
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 179 (0.56%)	4 / 181 (2.21%)	5 / 360 (1.39%)
occurrences (all)	1	4	5
Low density lipoprotein increased			
subjects affected / exposed	1 / 179 (0.56%)	5 / 181 (2.76%)	6 / 360 (1.67%)
occurrences (all)	1	6	7
Osteoprotegerin decreased			
subjects affected / exposed	2 / 179 (1.12%)	6 / 181 (3.31%)	8 / 360 (2.22%)
occurrences (all)	2	6	8
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 179 (2.79%)	4 / 181 (2.21%)	9 / 360 (2.50%)
occurrences (all)	5	4	9
Laceration			
subjects affected / exposed	4 / 179 (2.23%)	1 / 181 (0.55%)	5 / 360 (1.39%)
occurrences (all)	6	2	8
Wound			
subjects affected / exposed	4 / 179 (2.23%)	6 / 181 (3.31%)	10 / 360 (2.78%)
occurrences (all)	4	7	11
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 179 (3.35%)	8 / 181 (4.42%)	14 / 360 (3.89%)
occurrences (all)	8	8	16
Headache			
subjects affected / exposed	20 / 179 (11.17%)	22 / 181 (12.15%)	42 / 360 (11.67%)
occurrences (all)	25	40	65

Paraesthesia			
subjects affected / exposed	3 / 179 (1.68%)	7 / 181 (3.87%)	10 / 360 (2.78%)
occurrences (all)	4	7	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 179 (2.23%)	4 / 181 (2.21%)	8 / 360 (2.22%)
occurrences (all)	4	6	10
Leukopenia			
subjects affected / exposed	12 / 179 (6.70%)	8 / 181 (4.42%)	20 / 360 (5.56%)
occurrences (all)	15	10	25
Lymphadenopathy			
subjects affected / exposed	6 / 179 (3.35%)	3 / 181 (1.66%)	9 / 360 (2.50%)
occurrences (all)	6	4	10
Neutropenia			
subjects affected / exposed	5 / 179 (2.79%)	3 / 181 (1.66%)	8 / 360 (2.22%)
occurrences (all)	6	3	9
Eye disorders			
Uveitis			
subjects affected / exposed	4 / 179 (2.23%)	7 / 181 (3.87%)	11 / 360 (3.06%)
occurrences (all)	4	8	12
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 179 (1.68%)	9 / 181 (4.97%)	12 / 360 (3.33%)
occurrences (all)	3	9	12
Abdominal pain upper			
subjects affected / exposed	9 / 179 (5.03%)	8 / 181 (4.42%)	17 / 360 (4.72%)
occurrences (all)	9	8	17
Constipation			
subjects affected / exposed	4 / 179 (2.23%)	4 / 181 (2.21%)	8 / 360 (2.22%)
occurrences (all)	5	5	10
Diarrhoea			
subjects affected / exposed	22 / 179 (12.29%)	25 / 181 (13.81%)	47 / 360 (13.06%)
occurrences (all)	29	34	63
Crohn's disease			
subjects affected / exposed	4 / 179 (2.23%)	1 / 181 (0.55%)	5 / 360 (1.39%)
occurrences (all)	6	1	7
Mouth ulceration			

subjects affected / exposed	9 / 179 (5.03%)	7 / 181 (3.87%)	16 / 360 (4.44%)
occurrences (all)	14	11	25
Nausea			
subjects affected / exposed	9 / 179 (5.03%)	10 / 181 (5.52%)	19 / 360 (5.28%)
occurrences (all)	11	12	23
Tongue ulceration			
subjects affected / exposed	1 / 179 (0.56%)	4 / 181 (2.21%)	5 / 360 (1.39%)
occurrences (all)	1	6	7
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 179 (0.00%)	6 / 181 (3.31%)	6 / 360 (1.67%)
occurrences (all)	0	7	7
Pruritus			
subjects affected / exposed	3 / 179 (1.68%)	7 / 181 (3.87%)	10 / 360 (2.78%)
occurrences (all)	3	8	11
Rash			
subjects affected / exposed	2 / 179 (1.12%)	7 / 181 (3.87%)	9 / 360 (2.50%)
occurrences (all)	2	7	9
Urticaria			
subjects affected / exposed	1 / 179 (0.56%)	4 / 181 (2.21%)	5 / 360 (1.39%)
occurrences (all)	1	4	5
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	4 / 179 (2.23%)	7 / 181 (3.87%)	11 / 360 (3.06%)
occurrences (all)	4	9	13
Arthralgia			
subjects affected / exposed	11 / 179 (6.15%)	13 / 181 (7.18%)	24 / 360 (6.67%)
occurrences (all)	18	15	33
Back pain			
subjects affected / exposed	7 / 179 (3.91%)	12 / 181 (6.63%)	19 / 360 (5.28%)
occurrences (all)	8	13	21
Muscle contracture			
subjects affected / exposed	1 / 179 (0.56%)	4 / 181 (2.21%)	5 / 360 (1.39%)
occurrences (all)	3	4	7
Muscle spasms			

subjects affected / exposed	3 / 179 (1.68%)	4 / 181 (2.21%)	7 / 360 (1.94%)
occurrences (all)	3	4	7
Musculoskeletal pain			
subjects affected / exposed	4 / 179 (2.23%)	3 / 181 (1.66%)	7 / 360 (1.94%)
occurrences (all)	4	4	8
Neck pain			
subjects affected / exposed	5 / 179 (2.79%)	3 / 181 (1.66%)	8 / 360 (2.22%)
occurrences (all)	5	3	8
Osteoporosis			
subjects affected / exposed	2 / 179 (1.12%)	6 / 181 (3.31%)	8 / 360 (2.22%)
occurrences (all)	2	6	8
Rotator cuff syndrome			
subjects affected / exposed	4 / 179 (2.23%)	1 / 181 (0.55%)	5 / 360 (1.39%)
occurrences (all)	5	1	6
Pain in extremity			
subjects affected / exposed	6 / 179 (3.35%)	5 / 181 (2.76%)	11 / 360 (3.06%)
occurrences (all)	9	5	14
Tendonitis			
subjects affected / exposed	5 / 179 (2.79%)	3 / 181 (1.66%)	8 / 360 (2.22%)
occurrences (all)	6	3	9
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	5 / 179 (2.79%)	3 / 181 (1.66%)	8 / 360 (2.22%)
occurrences (all)	5	3	8
Gastroenteritis			
subjects affected / exposed	7 / 179 (3.91%)	7 / 181 (3.87%)	14 / 360 (3.89%)
occurrences (all)	8	7	15
Bronchitis			
subjects affected / exposed	2 / 179 (1.12%)	10 / 181 (5.52%)	12 / 360 (3.33%)
occurrences (all)	2	10	12
Infection parasitic			
subjects affected / exposed	4 / 179 (2.23%)	1 / 181 (0.55%)	5 / 360 (1.39%)
occurrences (all)	4	1	5
Influenza			
subjects affected / exposed	13 / 179 (7.26%)	17 / 181 (9.39%)	30 / 360 (8.33%)
occurrences (all)	17	22	39

Nasopharyngitis			
subjects affected / exposed	35 / 179 (19.55%)	44 / 181 (24.31%)	79 / 360 (21.94%)
occurrences (all)	59	77	136
Pharyngitis			
subjects affected / exposed	12 / 179 (6.70%)	21 / 181 (11.60%)	33 / 360 (9.17%)
occurrences (all)	16	25	41
Oral herpes			
subjects affected / exposed	2 / 179 (1.12%)	8 / 181 (4.42%)	10 / 360 (2.78%)
occurrences (all)	3	13	16
Rhinitis			
subjects affected / exposed	5 / 179 (2.79%)	12 / 181 (6.63%)	17 / 360 (4.72%)
occurrences (all)	7	16	23
Sinusitis			
subjects affected / exposed	4 / 179 (2.23%)	7 / 181 (3.87%)	11 / 360 (3.06%)
occurrences (all)	4	8	12
Tonsillitis			
subjects affected / exposed	0 / 179 (0.00%)	5 / 181 (2.76%)	5 / 360 (1.39%)
occurrences (all)	0	6	6
Upper respiratory tract infection			
subjects affected / exposed	21 / 179 (11.73%)	17 / 181 (9.39%)	38 / 360 (10.56%)
occurrences (all)	35	24	59
Urinary tract infection			
subjects affected / exposed	3 / 179 (1.68%)	9 / 181 (4.97%)	12 / 360 (3.33%)
occurrences (all)	4	13	17
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	16 / 179 (8.94%)	14 / 181 (7.73%)	30 / 360 (8.33%)
occurrences (all)	16	14	30
Hypercholesterolaemia			
subjects affected / exposed	3 / 179 (1.68%)	5 / 181 (2.76%)	8 / 360 (2.22%)
occurrences (all)	3	7	10
Hyperglycaemia			
subjects affected / exposed	0 / 179 (0.00%)	4 / 181 (2.21%)	4 / 360 (1.11%)
occurrences (all)	0	6	6
Hyperlipidaemia			

subjects affected / exposed	3 / 179 (1.68%)	2 / 181 (1.10%)	5 / 360 (1.39%)
occurrences (all)	3	2	5

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 122 (45.90%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Non-cardiac chest pain			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Rhinorrhoea			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	6 / 122 (4.92%)		
occurrences (all)	6		

Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 0 / 122 (0.00%) 0 2 / 122 (1.64%) 2		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Low density lipoprotein increased subjects affected / exposed occurrences (all) Osteoprotegerin decreased subjects affected / exposed occurrences (all)	 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 2 / 122 (1.64%) 2		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Laceration subjects affected / exposed occurrences (all) Wound subjects affected / exposed occurrences (all)	 0 / 122 (0.00%) 0 1 / 122 (0.82%) 1 0 / 122 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache	 4 / 122 (3.28%) 4 		

subjects affected / exposed	7 / 122 (5.74%)		
occurrences (all)	12		
Paraesthesia			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Leukopenia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Lymphadenopathy			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Eye disorders			
Uveitis			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	7 / 122 (5.74%)		
occurrences (all)	7		
Crohn's disease			

subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Tongue ulceration			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Ankylosing spondylitis			
subjects affected / exposed	4 / 122 (3.28%)		
occurrences (all)	5		
Arthralgia			
subjects affected / exposed	4 / 122 (3.28%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Muscle contracture			

subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Osteoporosis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Rotator cuff syndrome			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Tendonitis			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Infection parasitic			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		

Influenza			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	9 / 122 (7.38%)		
occurrences (all)	9		
Pharyngitis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Rhinitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences (all)	3		
Tonsillitis			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	0 / 122 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	6 / 122 (4.92%)		
occurrences (all)	6		
Hypercholesterolaemia			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences (all)	2		
Hyperglycaemia			

subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Hyperlipidaemia			
subjects affected / exposed	3 / 122 (2.46%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2011	This protocol amendment is issued to clarify discrepancies in the protocol. However, none of the changes has an impact on the conduct of the trial or the patient's treatment. A discrepancy between the population and the inclusion criteria was clarified. Wording on the subject number for re-screened subject was removed. Subject will be tracked using a unique subject identifier, that will be applied within the database but not visible for the investigator and therefore the sentence was misleading. A serum biomarker sample log was added in the appendix.
10 December 2012	This protocol amendment is issued to update sections of the data analysis plan, specifically to update how missing values are handled. The guidance language for study treatment interruptions and discontinuation has been clarified. The notable laboratory values and guidance for subject observation post study treatment administration have been aligned with the wording used in all current secukinumab arthritis studies. None of the changes made are due to safety concerns and none of the changes have impact on the conduct of the trial or alter in any way the treatment of study subjects.
22 November 2013	This protocol amendment is primarily issued for the following reasons: To expand the statistical hierarchy (primary plus ranked secondary variables) to include more endpoints which are relevant to determining the overall therapeutic value of a therapy for Ankylosing Spondylitis. These endpoints include but are not limited to ASQoL, BASDAI and SF-36. In addition, the analysis was changed to include all patients in the FAS, rather than focusing only on the subset of patients who are TNFα inhibitor naïve, as the FAS would be more representative of the general population of AS patients.To align the primary and secondary assessments with the ASAS Handbook (Sieper 2009) As the primary endpoint is at Week 16, there is no longer a need for the sponsor to be blinded past this endpoint. The conduct of the interim analysis was revised. However, sites and patients will remain blinded until all patients reach Week 52 to ensure an unbiased assessment of the secukinumab doses. None of the changes made are due to safety concerns and none of the changes have an impact on the conduct of the trial or alter in any way the treatment of study subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported