Clinical trial results:
A randomized, double-blind, placebo-controlled, multicenter study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the long term safety, tolerability and efficacy up to 2 years in patients with active psoriatic arthritis.

Summary

EudraCT number	2011-000276-34
Trial protocol	CZ SK GB DE BG PL BE IT
Global end of trial date	08 April 2015

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	CAIN457F2306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01392326
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 Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 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	08 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 April 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that the efficacy of secukinumab75 or 150 mg at Week 24 was superior to placebo in patients with active PsA based on the proportion of patients achieving an ACR20 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	08 September 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	Argentina: 27
Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 16
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Czech Republic: 44
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	Israel: 35
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Philippines: 66
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Singapore: 16
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Thailand: 30
Country: Number of subjects enrolled	United States: 133

Worldwide total number of subjects	606
EEA total number of subjects	198

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)	552
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A screening period running up to 4 weeks before randomization was used to assess eligibility followed by a treatment period of two 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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks

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

Dosage and administration details:

Secukinumab (75 mg)

Arm title	Group 2

Arm description:

Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks

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

Dosage and administration details:

Secukinumab (150 mg)

Arm title	Group 3

Arm description:

Placebo i.v. at baseline, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12.
Patients on placebo who were responders remained on placebo until week 24.
At Week 24, these patients received either secukinumab 75 or 150 mg every 4 weeks, regardless of responder status (as dictated by the re-randomization).
• Patients on placebo who were non-responders were to be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 weeks.

Arm type	Placebo

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

Dosage and administration details:

Matching Placebo

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	202	202	202
Completed	155	167	154
Not completed	47	35	48
Adverse event, serious fatal	2	-	-
Consent withdrawn by subject	12	11	15
Physician decision	7	5	2
Adverse event, non-fatal	9	6	11
Pregnancy	-	-	1
Lost to follow-up	1	3	4
Protocol deviation	2	-	-
Lack of efficacy	14	10	15

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks	
Reporting group title	Group 2
Reporting group description:	
Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks	
Reporting group title	Group 3
Reporting group description:	
Placebo i.v. at baseline, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12. Patients on placebo who were responders remained on placebo until week 24. At Week 24, these patients received either secukinumab 75 or 150 mg every 4 weeks, regardless of responder status (as dictated by the re-randomization). • Patients on placebo who were non-responders were to be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 weeks.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	202	202	202
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	180	180	192
>=65 years	22	22	10
Gender, Male/Female Units: participants			
Female	118	106	106
Male	84	96	96

Reporting group values	Total		
Number of subjects	606		
Age Categorical Units: participants			
<=18 years	0		
Between 18 and 65 years	552		
>=65 years	54		
Gender, Male/Female Units: participants			
Female	330		
Male	276		

End points

End points reporting groups

Reporting group title	Group 1
Reporting group description:	
Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 75 mg s.c. starting at Week 8 and injected every 4 weeks	
Reporting group title	Group 2
Reporting group description:	
Secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4, then secukinumab 150 mg s.c. starting at Week 8 and injected every 4 weeks	
Reporting group title	Group 3
Reporting group description:	
Placebo i.v. at baseline, Weeks 2 and 4, then placebo s.c. starting at Week 8 and Week 12. Patients on placebo who were responders remained on placebo until week 24. At Week 24, these patients received either secukinumab 75 or 150 mg every 4 weeks, regardless of responder status (as dictated by the re-randomization). • Patients on placebo who were non-responders were to be re-randomized (1:1) at Week 16 to receive either secukinumab 75 mg or 150 mg s.c. every 4 weeks.	

Primary: Proportion of patients achieving ACR20 response criteria on secukinumab 75 or 150 mg vs. placebo

End point title	Proportion of patients achieving ACR20 response criteria on secukinumab 75 or 150 mg vs. placebo
End point description:	
A patient will be considered as responder according the ACR20 criteria if she/he has at least 20 % improvement in the two following measures:Tender joint count,Swollen joint count and at least 3 of the following 5 measures: Patient's assessment of PsA pain, Patient's global assessment disease activity,Physician's global assessment of disease activity, Health Assessment Questionnaire- Disability Index (HAQ-DI©) score ,Acute phase reactant (hsCRP or ESR)	
End point type	Primary
End point timeframe:	
Week 24	

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	202	202	
Units: % ACR 20 responders				
number (not applicable)	50	50	17.3	

Statistical analyses

Statistical analysis title	Patients acheiving ACR 20 response
Comparison groups	Group 1 v Group 3

Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.46
upper limit	8.85

Statistical analysis title	Patients acheiving ACR 20 response
Comparison groups	Group 2 v Group 3
Number of subjects included in analysis	404
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.37
upper limit	8.62

Secondary: Proportion of subjects achieving a PASI75 response in the subgroup of subjects who have ≥3% skin involvement with psoriasis at baseline

End point title	Proportion of subjects achieving a PASI75 response in the subgroup of subjects who have ≥3% skin involvement with psoriasis at baseline

End point description:

A 75% reduction in the Psoriasis Area and Severity Index (PASI) score (PASI 75) is the current benchmark of primary endpoints for most clinical trials with end points of psoriasis

End point type	Secondary

End point timeframe:

Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	108	109	
Units: % participants acheiving goal				
number (not applicable)	64.8	61.1	8.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects achieving a PASI90 response in the subgroup of subjects who have ≥3% skin involvement with psoriasis at baseline

End point title	Proportion of subjects achieving a PASI90 response in the subgroup of subjects who have ≥3% skin involvement with psoriasis at baseline

End point description:

A 90% reduction in the Psoriasis Area and Severity Index (PASI) score (PASI 90) is above the current benchmark of primary endpoints for most clinical trials with endpoints of psoriasis

End point type	Secondary

End point timeframe:

Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	108	108	109	
Units: % of participants acheiving goal				
number (not applicable)	49.1	45.4	3.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in DAS28-CRP for secukinumab 75 or 150 mg

End point title	Change from baseline in DAS28-CRP for secukinumab 75 or 150 mg

End point description:

DAS-CRP values range from 2.0 to 10.0 , While higher values mean a higher disease activity. A DAS-CRP below the value of 2.6 is interpreted as Remission. The DAS-CRP uses 28 different joints for its calculation: proximal interphalangeal joints (10 joints) metacarpophalangeal joints (10) wrists (2) elbows (2) shoulders (2) knees (2) With the above mentioned parameters, DAS-CRP is calculated as: $DAS-CRP=0.56 \times \sqrt{TEN28} + 0.28 \times \sqrt{SW28} + 0.36 \times \ln(CRP+1) + 0.014 \times SA+0.96$ With: TEN28: number of joints with tenderness upon touching SW28: number of swollen joints CRP: C-reactive Protein SA: subjective assessment of disease activity by the patient during the preceding 7 days on a scale between 0 and 100 ("0":no activity, "100": highest activity possible)

End point type	Secondary

End point timeframe:
Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	202	202	
Units: units on scale				
least squares mean (standard error)	-1.67 (± 0.085)	-1.62 (± 0.084)	-0.77 (± 0.123)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SF36-PCS for secukinumab 75 or 150 mg

End point title	Change from baseline in SF36-PCS for secukinumab 75 or 150 mg

End point description:

End point type	Secondary

End point timeframe:
Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	202	202	
Units: units on scale				
least squares mean (standard error)	5.41 (± 0.524)	5.91 (± 0.525)	1.82 (± 0.715)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in HAQ-DI for secukinumab 75 or 150 mg

End point title	Change from baseline in HAQ-DI for secukinumab 75 or 150 mg

End point description:
HAQ-DI score change from baseline using MMRM

End point type	Secondary

End point timeframe:
Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	202	202	
Units: units on a scale				
least squares mean (standard error)	-0.41 (± 0.036)	-0.4 (± 0.036)	-0.17 (± 0.047)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients achieving ACR50 response criteria on secukinumab 75 or 150 mg vs. placebo

End point title	Proportion of patients achieving ACR50 response criteria on secukinumab 75 or 150 mg vs. placebo

End point description:

ACR50 = 50 % improvement in at least 3 of the 5 measures(Patient's assessment of pain, Patient's global assessment of disease activity, Physician's global assessment of disease activity, Health Assessment Questionnaire (HAQ©) score, C-reactive protein (CRP)/Erythrocyte Sedimentation Rate (ESR) and 50 % improvement in the swollen and tender joint count.

End point type	Secondary

End point timeframe:

Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	202	202	
Units: % change				
number (not applicable)	30.7	34.7	7.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline for joint/bone structural damage (van der Heijde modified total Sharp score) for secukinumab 75 and 150 mg (pooled doses)

End point title	Change from baseline for joint/bone structural damage (van der Heijde modified total Sharp score) for secukinumab 75 and 150 mg (pooled doses)

End point description:

Joint structural damage change from baseline at Week 24 using non-parametric ANCOVA, Linear extrapolation. Estimate (for the difference in mean), SE are from a non-parametric ANCOVA model with

the change from baseline van der Heijde total modified Sharp score as the dependent variable, treatment and randomization stratum (TNFa status -naive or IR) as factors, and weight and baseline van der Heijde total modified Sharp score as covariates

End point type	Secondary

End point timeframe:

Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	202	202	202	
Units: units on a scale				
arithmetic mean (standard error)	0.02 (± 0.22)	0.13 (± 0.2)	0.57 (± 0.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with dactylitis in the subset of subjects who have dactylitis at baseline

End point title	Proportion of patients with dactylitis in the subset of subjects who have dactylitis at baseline

End point description:

End point type	Secondary

End point timeframe:

Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	104	116	
Units: % of baseline				
number (not applicable)	43.3	51.9	84.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with enthesitis in the subset of subjects who have enthesitis at baseline

End point title	Proportion of patients with enthesitis in the subset of subjects who have enthesitis at baseline

End point description:

End point type	Secondary

End point timeframe:

Week 24

End point values	Group 1	Group 2	Group 3	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	126	102	
Units: % participants				
number (not applicable)	51.2	54	87.2	

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 reported in this record are from date of 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	17.1

Reporting groups

Reporting group title	Any AIN457 75 mg

Reporting group description:

Secukinumab (75mg)

Reporting group title	Placebo

Reporting group description:

Placebo match (for 75 and 150 mg)

Reporting group title	Any AIN457 150 mg

Reporting group description:

Secukinumab (150 mg)

Serious adverse events	Any AIN457 75 mg	Placebo	Any AIN457 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 292 (10.96%)	11 / 202 (5.45%)	51 / 295 (17.29%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Haemangioma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Intraductal proliferative breast lesion			

subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	0 / 295 (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
Metastases to bone			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleomorphic adenoma			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schwannoma			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	2 / 295 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Hypertensive crisis			

subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	0 / 295 (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
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	2 / 295 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			

subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Respiratory, thoracic and mediastinal disorders			
Haemothorax			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Pleural effusion			
subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	0 / 295 (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 alveolar haemorrhage			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
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 embolism			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	0 / 295 (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			
Comminuted fracture			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Fibula fracture			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Laceration			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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

Pelvic fracture			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Procedural pain			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Skin abrasion			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic liver injury			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Ulna fracture			

subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
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			
Acute myocardial infarction			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	2 / 295 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Atrial fibrillation			
subjects affected / exposed	2 / 292 (0.68%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	2 / 295 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 292 (0.68%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Dizziness			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			

subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intracranial venous sinus thrombosis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic stroke			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	2 / 292 (0.68%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Ocular myasthenia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	2 / 295 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Crohn's disease			
subjects affected / exposed	1 / 292 (0.34%)	1 / 202 (0.50%)	0 / 295 (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
Dysphagia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral hernia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth ulceration			

subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Rectal haemorrhage			
subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	0 / 295 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	0 / 295 (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
Chronic hepatitis			

subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
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			
Rosacea			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	2 / 295 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	1 / 292 (0.34%)	1 / 202 (0.50%)	4 / 295 (1.36%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriatic arthropathy			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	4 / 295 (1.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scoliosis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovitis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Appendiceal abscess			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Cellulitis			

subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Diarrhoea infectious			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	2 / 295 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Lobar pneumonia			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Necrotising fasciitis			

subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Oesophageal candidiasis			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 292 (0.68%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Rash pustular			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Sepsis			
subjects affected / exposed	2 / 292 (0.68%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	2 / 292 (0.68%)	0 / 202 (0.00%)	0 / 295 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 292 (0.00%)	1 / 202 (0.50%)	0 / 295 (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
Typhoid fever			

subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Urinary tract infection bacterial			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Viral infection			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 292 (0.34%)	0 / 202 (0.00%)	0 / 295 (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
Hyponatraemia			

subjects affected / exposed	0 / 292 (0.00%)	0 / 202 (0.00%)	1 / 295 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Any AIN457 75 mg	Placebo	Any AIN457 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	175 / 292 (59.93%)	66 / 202 (32.67%)	183 / 295 (62.03%)
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 292 (7.19%)	5 / 202 (2.48%)	18 / 295 (6.10%)
occurrences (all)	21	6	18
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 292 (9.25%)	7 / 202 (3.47%)	25 / 295 (8.47%)
occurrences (all)	39	8	38
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	21 / 292 (7.19%)	6 / 202 (2.97%)	21 / 295 (7.12%)
occurrences (all)	31	7	27
Nausea			
subjects affected / exposed	16 / 292 (5.48%)	2 / 202 (0.99%)	11 / 295 (3.73%)
occurrences (all)	19	2	12
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 292 (4.79%)	6 / 202 (2.97%)	17 / 295 (5.76%)
occurrences (all)	16	9	19
Oropharyngeal pain			
subjects affected / exposed	15 / 292 (5.14%)	4 / 202 (1.98%)	11 / 295 (3.73%)
occurrences (all)	22	5	14
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	22 / 292 (7.53%)	1 / 202 (0.50%)	11 / 295 (3.73%)
occurrences (all)	22	1	11
Musculoskeletal and connective tissue disorders			

Psoriatic arthropathy			
subjects affected / exposed	15 / 292 (5.14%)	2 / 202 (0.99%)	14 / 295 (4.75%)
occurrences (all)	18	2	17
Back pain			
subjects affected / exposed	29 / 292 (9.93%)	2 / 202 (0.99%)	22 / 295 (7.46%)
occurrences (all)	35	2	25
Arthralgia			
subjects affected / exposed	20 / 292 (6.85%)	3 / 202 (1.49%)	17 / 295 (5.76%)
occurrences (all)	32	3	21
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 292 (4.79%)	6 / 202 (2.97%)	21 / 295 (7.12%)
occurrences (all)	17	7	26
Nasopharyngitis			
subjects affected / exposed	61 / 292 (20.89%)	11 / 202 (5.45%)	54 / 295 (18.31%)
occurrences (all)	106	12	99
Gastroenteritis			
subjects affected / exposed	8 / 292 (2.74%)	2 / 202 (0.99%)	20 / 295 (6.78%)
occurrences (all)	11	2	25
Sinusitis			
subjects affected / exposed	10 / 292 (3.42%)	4 / 202 (1.98%)	16 / 295 (5.42%)
occurrences (all)	16	4	17
Urinary tract infection			
subjects affected / exposed	14 / 292 (4.79%)	2 / 202 (0.99%)	17 / 295 (5.76%)
occurrences (all)	17	2	21
Upper respiratory tract infection			
subjects affected / exposed	52 / 292 (17.81%)	12 / 202 (5.94%)	60 / 295 (20.34%)
occurrences (all)	73	13	90
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	11 / 292 (3.77%)	5 / 202 (2.48%)	15 / 295 (5.08%)
occurrences (all)	12	5	15

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 for the conduct of the trial or the patient's treatment. 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. The section 'Serum biomarkers related to targeted pathway' had been included as a subsection of 'Pharmacogenetics,' but Serum biomarkers should be a separate section This is now corrected. Furthermore, a Sample Log for serum biomarkers is now included in this section. Additionally, we took the opportunity of this protocol amendment to correct typographical and formatting errors, and to clarify certain wordings.
18 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 alterin any way the treatment of study subjects. The wording of various sub-sections to "Data analysis" (Section 9) have been amended to reflect the rationale given above. Additionally, this protocol amendment includes the correction of typographical and formatting errors, and clarification of the wording in certain sections.
06 December 2013	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 PsA. These endpoints include but are not limited to PASI75, PASI90, DAS28- CRP, HAQ-DI, SF-36, dactylitis and enthesitis. Psoriatic arthritis (PsA) is a multifaceted chronic disabling disease that can present as different clinical phenotypes: peripheral arthritis, axial disease, skin and nail disease, dactylitis, and enthesitis, and hence defining outcome measures has been a challenge. In addition, the analysis is changed to include all subjects in Full Analysis Set (FAS) which includes TNFα inhibitor naïve as well as TNFα inhibitor inadequate responders (TNF-IR) rather than focusing only on the subset of subjects who are TNFα inhibitor naïve, as the FAS would be more representative of the general population of PsA patients. As the primary endpoint is at Week 24 and the analysis will be carried out after all subjects have completed Week 52 visit, there is no longer a need for the sponsor to be blinded past this time point. To mention only women of child bearing potential will undergo routine urine pregnancy tests (UPT). Thus this excludes postmenopausal women apart from sterile women from undergoing frequent UPT. This has been amended to avoid unnecessary UPT burden for women with confirmed menopause. 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