Clinical trial results:
A randomized, double-blind, placebo-controlled study of secukinumab to demonstrate the efficacy at 24 weeks and to assess the safety, tolerability and long term efficacy up to 2 years in patients with active rheumatoid arthritis who have an inadequate response to anti-TNF agents (CAIN457F2302) and A three year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in patients with active rheumatoid arthritis (CAIN457F2302E1)

Summary

EudraCT number	2011-000275-13
Trial protocol	HU GB BE IT
Global end of trial date	26 May 2015

Results information

Result version number	v1 (current)
This version publication date	10 June 2016
First version publication date	10 June 2016

Trial information

Trial identification

Sponsor protocol code	CAIN457F2302/CAIN457F2302E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01377012
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	26 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of core study CAIN457F2302 was to demonstrate that the efficacy of secukinumab 75 mg or 150 mg at Week 24 is superior to placebo in patients with active RA based on the proportion of patients achieving an ACR20 response.
The primary objective of the extension study CAIN457F2302E1 was to evaluate the long term efficacy of secukinumab 150 mg with respect to ACR20, ACR50 and ACR70 response over time.

However, This study was terminated early by the Sponsor (unrelated to safety) due to the results of study AIN457F2309, which indicated the efficacy of AIN457 was not comparable to the currently available RA treatment, abatacept, thus leading to closing of the AIN457 RA program

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	30 August 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: 48
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Colombia: 29
Country: Number of subjects enrolled	Guatemala: 31
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Hungary: 54
Country: Number of subjects enrolled	India: 49
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Japan: 154
Country: Number of subjects enrolled	Mexico: 73
Country: Number of subjects enrolled	Panama: 10
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Turkey: 1

Country: Number of subjects enrolled	United States: 145
Worldwide total number of subjects	637
EEA total number of subjects	82

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)	535
From 65 to 84 years	102
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At baseline, participants were randomized to 1 of 3 treatment groups. Placebo non- responders at week 16 were re-randomized to receive AIN457 75mg or AIN457 150mg. Placebo responders at Week16 were re-randomized to receive AIN457 75mg or AIN457 150mg at Week 24.

Period 1

Period 1 title	Core Study
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	AIN457 10mg/kg-75mg

Arm description:

Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. 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 and solution for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4 then secukinumab 75mg every 4 weeks

Arm title	AIN457 10mg/kg-150mg

Arm description:

Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. 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 and solution for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4 then secukinumab 150mg every 4 weeks

Arm title	Placebo

Arm description:

Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status (>= 20% reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at 24 weeks

Arm type	Placebo

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

Dosage and administration details:

placebo i.v. at baseline, Weeks 2 and 4 then placebo s.c. starting at Week 8 and injected every 4 weeks

Number of subjects in period 1	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Started	210	213	214
Completed	76	81	80
Not completed	134	132	134
Adverse event, serious fatal	1	1	1
Consent withdrawn by subject	15	23	18
Physician decision	5	4	10
No Longer require treatment	-	-	1
Technical problems	1	-	-
Adverse event, non-fatal	10	14	13
Pregnancy	-	-	1
Study terminated by sponsor	47	54	46
Non-Compliant with study treatment	-	-	1
Lost to follow-up	7	5	4
Protocol deviation	7	3	2
Lack of efficacy	41	28	37

Period 2

Period 2 title	Extension Study, weeks 104-260
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	AIN457 10mg/kg-75mg

Arm description:

Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks up to Week 100, then AIN457 150 mg s.c. starting at week 104

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

Dosage and administration details:

secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4 then secukinumab 75 up to Week 100, then secukinumab 150 mg starting at Week 104

Arm title	AIN457 10mg/kg-150mg

Arm description:

Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. 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 and solution for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

secukinumab i.v. (10 mg/kg) at baseline, Weeks 2 and 4 then secukinumab 150mg every 4 weeks

Arm title	Placebo

Arm description:

Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status (>= 20% reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24

Arm type	Placebo
Investigational medicinal product name	Secukinumab
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Subcutaneous use, Intravenous use

Dosage and administration details:

placebo i.v. at baseline, Weeks 2 and 4 then placebo s.c. starting at Week 8 and injected every 4 weeks. injected every 4 weeks. Treatment was switched to active treatment at Week 16 or Week 24

Number of subjects in period 2[1]	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Started	57	71	68
Completed	0	0	0
Not completed	57	71	68
Consent withdrawn by subject	1	-	3
Physician decision	1	-	-
Adverse event, non-fatal	-	2	1

Study terminated by sponsor	52	69	63
Lost to follow-up	-	-	1
Lack of efficacy	3	-	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: This study includes a core phase (CAIN457F2302) and extension phase (CAIN457F2302E1).

Baseline characteristics

Reporting groups	
Reporting group title	AIN457 10mg/kg-75mg
Reporting group description:	
Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks	
Reporting group title	AIN457 10mg/kg-150mg
Reporting group description:	
Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status (>= 20% reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at 24 weeks	

Reporting group values	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo
Number of subjects	210	213	214
Age, Customized Units: Particpants			
In Utero	0	0	0
Preterm Newborn Infants	0	0	0
0-<28 days	0	0	0
28 days - <2 years	0	0	0
2 years - <12 years	0	0	0
12 years - <18 years	0	0	0
18 years - < 65 years	177	176	182
65 years - <85 years	33	37	32
>=85 years	0	0	0
Age continuous Units: years			
median	53.3	53.2	52.2
standard deviation	± 12.27	± 11.62	± 11.55
Gender, Male/Female Units: Participants			
Female	186	188	182
Male	24	25	32

Reporting group values	Total		
Number of subjects	637		
Age, Customized Units: Particpants			
In Utero	0		
Preterm Newborn Infants	0		
0-<28 days	0		
28 days - <2 years	0		
2 years - <12 years	0		
12 years - <18 years	0		
18 years - < 65 years	535		

65 years - <85 years	102		
>=85 years	0		

Age continuous Units: years median standard deviation	-		
Gender, Male/Female Units: Participants			
Female	556		
Male	81		

End points

End points reporting groups

Reporting group title	AIN457 10mg/kg-75mg
Reporting group description:	
Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks	
Reporting group title	AIN457 10mg/kg-150mg
Reporting group description:	
Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status (>= 20% reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at 24 weeks	
Reporting group title	AIN457 10mg/kg-75mg
Reporting group description:	
Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks up to Week 100, then AIN457 150 mg s.c. starting at week 104	
Reporting group title	AIN457 10mg/kg-150mg
Reporting group description:	
Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status (>= 20% reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment at week 24	

Primary: Core Study: Percentage of participants achieving an American College of Rheumatology Response 20 (ACR20) at week 24

End point title	Core Study: Percentage of participants achieving an American College of Rheumatology Response 20 (ACR20) at week 24
End point description:	
ACR20 response was defined as having a positive clinical response to treatment (individual improvement) in disease activity if the participant had at least 20% improvement in tender 68-joint count, swollen 66-joint count and at least 3 of the following 5 measures: patient's assessment of RA pain, patient's global assessment of disease activity, physician's global assessment of disease activity, subject self-assessed disability (Health Assessment Questionnaire [HAQ-DI] score), and/or acute phase reactant (high sensitivity c-reactive protein (hsCRP) or erythrocyte sedimentation rate (ESR). The ACR20 response results at week 24 used non-responder imputation.	
End point type	Primary
End point timeframe:	
Week 24	

End point values	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	210	213	214	
Units: Percentage of Participants				
number (not applicable)	35.2	35.2	19.6	

Statistical analyses

Statistical analysis title	Percentage of participants ACR20 response
Comparison groups	AIN457 10mg/kg-75mg v Placebo
Number of subjects included in analysis	424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	3.4

Statistical analysis title	Percentage of participants ACR20 response
Comparison groups	AIN457 10mg/kg-150mg v Placebo
Number of subjects included in analysis	427
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	3.4

Secondary: Change from baseline and week 24 in Stanford Health Assessment Questionnaire Disability Index (HAQ-DI)

End point title	Change from baseline and week 24 in Stanford Health Assessment Questionnaire Disability Index (HAQ-DI)

End point description:

The HAQ-DI assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip and usual activities. The stem of each item asks 'Over the past week, "are you able to..." perform a particular task'. Each item is scored on a 4 point scale from 0 - 3, representing normal, no difficulty (0), some difficulty (1), much difficulty (2) and unable to do (3). The disability index score is calculated as the mean of the available category scores, ranging from 0 to 3. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	171	188	71	
Units: Score on a scale				
least squares mean (standard error)	-0.35 (± 0.039)	-0.35 (± 0.038)	-0.24 (± 0.051)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From baseline at week 24 in van der Heijde total modified Sharp score

End point title	Change From baseline at week 24 in van der Heijde total modified Sharp score

End point description:

Separate radiographs of each hand/wrist and each foot were taken at baseline and Week 24. The radiographs were assessed using the van der Heijde modified Sharp score. The change in the Van der Heijde modified Sharp score is calculated against the baseline value

End point type	Secondary

End point timeframe:

Week 24

End point values	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	67	83	
Units: Score on a scale				
arithmetic mean (standard error)	0.59 (± 0.62)	0.83 (± 0.68)	1.73 (± 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients achieving major clinical response (continuous six-month period of ACR70 response) at week 52

End point title	Percentage of patients achieving major clinical response (continuous six-month period of ACR70 response) at week 52

End point description:

End point type	Secondary

End point timeframe:

52 week

End point values	AIN457 10mg/kg-75mg	AIN457 10mg/kg-150mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	210	213	214	
Units: Participants				
number (not applicable)	2.4	0.9	1.4	

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	18.1

Reporting groups

Reporting group title	Any AIN457 75 mg

Reporting group description:

Participants received AIN457 i.v. (10 mg/kg) at Baseline (BSL), Weeks 2 and 4 then AIN457 75 mg s.c. at Week 8 and injected every 4 weeks or switched from placebo to AIN457 75 mg at week 16 or week 24

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo to AIN457 until week 16 or week 24 based on responder status (>= 20% reduction in tender and swollen joint count). Non-responders were switched to active treatment at week 16. Responders were switched to active treatment

Reporting group title	Any AIN457 150 mg

Reporting group description:

Participants received AIN457 i.v. (10 mg/kg) at BSL, Weeks 2 and 4 then AIN457 150 mg s.c. at Week 8 and injected every 4 weeks or switched from placebo to AIN457 75 mg at week 16 or week 24 or was in the extension study (AIN457 150 mg only)

Serious adverse events	Any AIN457 75 mg	Placebo	Any AIN457 150 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 301 (10.96%)	9 / 214 (4.21%)	48 / 392 (12.24%)
number of deaths (all causes)	3	1	2
number of deaths resulting from adverse events	1	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			

subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Femoral artery occlusion			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 301 (0.33%)	1 / 214 (0.47%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Non-cardiac chest pain			
subjects affected / exposed	1 / 301 (0.33%)	1 / 214 (0.47%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sudden death			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Ovarian cyst ruptured			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 301 (0.66%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Pulmonary oedema			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Acute psychosis			

subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Anxiety			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Occult blood positive			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Transaminases increased			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Animal bite			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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

Femur fracture			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
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	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Atrial fibrillation			

subjects affected / exposed	1 / 301 (0.33%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Myocardial infarction			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Myocardial ischaemia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Nervous system disorders			
Carotid artery insufficiency			
subjects affected / exposed	1 / 301 (0.33%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Carotid artery occlusion			

subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebellar embolism			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral artery embolism			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (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
Cerebral ischaemia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (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
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dizziness			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (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
Encephalomalacia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Headache			

subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Hypoaesthesia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (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
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Lumbar radiculopathy			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Syncope			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Macular degeneration			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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 hernia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Colitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
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 gastrointestinal haemorrhage			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 301 (0.66%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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 and subcutaneous tissue disorders			

Skin ulcer			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus ureteric			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Acquired claw toe			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Joint range of motion decreased			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Osteoarthritis			
subjects affected / exposed	1 / 301 (0.33%)	1 / 214 (0.47%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Osteoporosis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Rheumatoid arthritis			
subjects affected / exposed	2 / 301 (0.66%)	1 / 214 (0.47%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 301 (0.00%)	1 / 214 (0.47%)	0 / 392 (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
Bronchitis			

subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	5 / 392 (1.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gastroenteritis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Gastroenteritis bacterial			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Helicobacter gastritis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Herpes zoster			

subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint tuberculosis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Pneumonia			
subjects affected / exposed	4 / 301 (1.33%)	2 / 214 (0.93%)	2 / 392 (0.51%)
occurrences causally related to treatment / all	3 / 4	1 / 2	2 / 2
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Psoas abscess			

subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Pyelonephritis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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	0 / 301 (0.00%)	0 / 214 (0.00%)	3 / 392 (0.77%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Soft tissue infection			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Staphylococcal osteomyelitis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Urosepsis			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	1 / 392 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Hypoalbuminaemia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Hypoglycaemia			
subjects affected / exposed	1 / 301 (0.33%)	0 / 214 (0.00%)	0 / 392 (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
Metabolic acidosis			
subjects affected / exposed	0 / 301 (0.00%)	0 / 214 (0.00%)	1 / 392 (0.26%)
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: 2 %

Non-serious adverse events	Any AIN457 75 mg	Placebo	Any AIN457 150 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	187 / 301 (62.13%)	94 / 214 (43.93%)	227 / 392 (57.91%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 301 (5.98%)	5 / 214 (2.34%)	12 / 392 (3.06%)
occurrences (all)	18	5	13
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	7 / 301 (2.33%)	1 / 214 (0.47%)	8 / 392 (2.04%)
occurrences (all)	11	1	10
Pyrexia			

subjects affected / exposed	8 / 301 (2.66%)	4 / 214 (1.87%)	13 / 392 (3.32%)
occurrences (all)	9	4	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 301 (2.99%)	4 / 214 (1.87%)	18 / 392 (4.59%)
occurrences (all)	9	4	23
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 301 (1.00%)	6 / 214 (2.80%)	12 / 392 (3.06%)
occurrences (all)	4	6	17
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 301 (2.33%)	3 / 214 (1.40%)	10 / 392 (2.55%)
occurrences (all)	8	3	10
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 301 (1.66%)	2 / 214 (0.93%)	10 / 392 (2.55%)
occurrences (all)	5	2	14
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 301 (1.99%)	3 / 214 (1.40%)	8 / 392 (2.04%)
occurrences (all)	6	3	9
Headache			
subjects affected / exposed	14 / 301 (4.65%)	10 / 214 (4.67%)	18 / 392 (4.59%)
occurrences (all)	19	10	20
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 301 (2.99%)	5 / 214 (2.34%)	11 / 392 (2.81%)
occurrences (all)	11	5	14
Lymphopenia			
subjects affected / exposed	6 / 301 (1.99%)	4 / 214 (1.87%)	7 / 392 (1.79%)
occurrences (all)	8	6	7
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 301 (0.66%)	2 / 214 (0.93%)	8 / 392 (2.04%)
occurrences (all)	2	2	8
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	6 / 301 (1.99%)	5 / 214 (2.34%)	13 / 392 (3.32%)
occurrences (all)	6	5	15
Dental caries			
subjects affected / exposed	4 / 301 (1.33%)	1 / 214 (0.47%)	11 / 392 (2.81%)
occurrences (all)	4	1	15
Diarrhoea			
subjects affected / exposed	14 / 301 (4.65%)	6 / 214 (2.80%)	22 / 392 (5.61%)
occurrences (all)	15	7	30
Nausea			
subjects affected / exposed	6 / 301 (1.99%)	6 / 214 (2.80%)	15 / 392 (3.83%)
occurrences (all)	6	6	17
Dyspepsia			
subjects affected / exposed	6 / 301 (1.99%)	1 / 214 (0.47%)	7 / 392 (1.79%)
occurrences (all)	6	1	7
Stomatitis			
subjects affected / exposed	6 / 301 (1.99%)	1 / 214 (0.47%)	8 / 392 (2.04%)
occurrences (all)	9	1	12
Vomiting			
subjects affected / exposed	4 / 301 (1.33%)	5 / 214 (2.34%)	8 / 392 (2.04%)
occurrences (all)	4	5	8
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	6 / 301 (1.99%)	3 / 214 (1.40%)	8 / 392 (2.04%)
occurrences (all)	6	4	9
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 301 (6.31%)	7 / 214 (3.27%)	16 / 392 (4.08%)
occurrences (all)	25	16	18
Back pain			
subjects affected / exposed	6 / 301 (1.99%)	7 / 214 (3.27%)	11 / 392 (2.81%)
occurrences (all)	6	8	12
Muscle spasms			
subjects affected / exposed	3 / 301 (1.00%)	4 / 214 (1.87%)	9 / 392 (2.30%)
occurrences (all)	4	4	10
Myalgia			

subjects affected / exposed	5 / 301 (1.66%)	0 / 214 (0.00%)	8 / 392 (2.04%)
occurrences (all)	5	0	9
Rheumatoid arthritis			
subjects affected / exposed	20 / 301 (6.64%)	11 / 214 (5.14%)	17 / 392 (4.34%)
occurrences (all)	27	11	24
Infections and infestations			
Bronchitis			
subjects affected / exposed	15 / 301 (4.98%)	1 / 214 (0.47%)	31 / 392 (7.91%)
occurrences (all)	19	1	42
Conjunctivitis			
subjects affected / exposed	4 / 301 (1.33%)	0 / 214 (0.00%)	8 / 392 (2.04%)
occurrences (all)	4	0	8
Cystitis			
subjects affected / exposed	4 / 301 (1.33%)	0 / 214 (0.00%)	15 / 392 (3.83%)
occurrences (all)	6	0	24
Gastroenteritis			
subjects affected / exposed	4 / 301 (1.33%)	2 / 214 (0.93%)	13 / 392 (3.32%)
occurrences (all)	4	2	14
Herpes zoster			
subjects affected / exposed	8 / 301 (2.66%)	1 / 214 (0.47%)	9 / 392 (2.30%)
occurrences (all)	8	1	9
Influenza			
subjects affected / exposed	11 / 301 (3.65%)	2 / 214 (0.93%)	10 / 392 (2.55%)
occurrences (all)	11	2	10
Nasopharyngitis			
subjects affected / exposed	49 / 301 (16.28%)	14 / 214 (6.54%)	63 / 392 (16.07%)
occurrences (all)	70	16	110
Pharyngitis			
subjects affected / exposed	23 / 301 (7.64%)	5 / 214 (2.34%)	18 / 392 (4.59%)
occurrences (all)	36	5	22
Sinusitis			
subjects affected / exposed	6 / 301 (1.99%)	3 / 214 (1.40%)	8 / 392 (2.04%)
occurrences (all)	7	4	9
Upper respiratory tract infection			
subjects affected / exposed	25 / 301 (8.31%)	10 / 214 (4.67%)	39 / 392 (9.95%)
occurrences (all)	34	11	58

Urinary tract infection subjects affected / exposed occurrences (all)	28 / 301 (9.30%) 36	8 / 214 (3.74%) 9	33 / 392 (8.42%) 42
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	6 / 301 (1.99%) 6	2 / 214 (0.93%) 2	9 / 392 (2.30%) 13

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was terminated early by the Sponsor (unrelated to safety) due to the results of study AIN457F2309, which indicated the efficacy of AIN457 was not comparable to the currently available RA treatment

Notes: