Clinical trial results:
A Phase 2, Open-Label, Non-Comparative, Multi-Center Extension Study to Evaluate the Long-term Safety and Efficacy of ASP015K in Subjects Previously Enrolled in a Phase 2 ASP015K Rheumatoid Arthritis Study

Summary

EudraCT number	2011-006021-23
Trial protocol	HU BE CZ BG PL
Global end of trial date	25 March 2016

Results information

Result version number	v1 (current)
This version publication date	09 March 2017
First version publication date	09 March 2017

Trial information

Trial identification

Sponsor protocol code	015K-CL-RA25

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01711814
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development, Inc. (APGD)
Sponsor organisation address	1 Astellas Way, Northbrook , IL, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), Astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, Inc. (APGD), Astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this phase 2 extension study was to evaluate the long-term safety and efficacy of ASP015K in patients with rheumatoid arthritis (RA) who had completed one of two 12-week double-blind, placebo-controlled phase 2b studies: Study 015K-CL-RA21 (wherein patients received ASP015K or placebo plus a weekly dose of 7.5 to 25 mg of methotrexate (MTX)) or Study 015K-CL-RA22 (wherein patients received ASP015K or placebo).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 256
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Czech Republic: 52
Country: Number of subjects enrolled	Hungary: 40
Country: Number of subjects enrolled	Poland: 138
Country: Number of subjects enrolled	Colombia: 23
Country: Number of subjects enrolled	Mexico: 74
Worldwide total number of subjects	611
EEA total number of subjects	258

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)	508
From 65 to 84 years	102
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This extension study was conducted at 51 contracted sites in a total of 8 countries in 3 geographic regions: North America (United States 20 sites), Europe (Belgium 2 sites, Bulgaria 3 sites, Czech Republic 4 sites, Hungary 6 sites, Poland 7 sites) and Latin America (Colombia 5 sites, Mexico 4 sites).

Pre-assignment

Screening details:

Participants in this extension study 015k-CL-RA25 (shortened to RA25 for ease of reading) rolled over from either 015K-CL-RA21 (shortened to RA21 for ease of reading) or 015K-CL-RA22 (shortened to RA22 for ease of reading). Baseline of RA25 was the last procedure in RA21/RA22 prior to dosing (Visit day 1) of RA25.

Period 1

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

Blinding implementation details:

This was an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	RA21/RA22 Placebo

Arm description:

Participants who received placebo in studies RA21 or RA22 received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received open-label ASP015K 100 mg daily. Study drug should have been taken as close to the same time each day as possible. Study drug was to be administered orally with approximately 240 mL (8 oz.) of water, and must have been taken with food.

Arm title	RA21/RA22 ASP015K 25 mg

Arm description:

Participants who previously completed RA21 or RA22 study and received ASP015K 25 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received open-label ASP015K 100 mg daily. Study drug should have been taken as close to the same time each day as possible. Study drug was to be administered orally with approximately 240 mL (8 oz.) of water, and must have been taken with food.

Arm title	RA21/RA22 ASP015K 50 mg

Arm description:

Participants who previously completed RA21 or RA22 study and received ASP015K 50 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received open-label ASP015K 100 mg daily. Study drug should have been taken as close to the same time each day as possible. Study drug was to be administered orally with approximately 240 mL (8 oz.) of water, and must have been taken with food.

Arm title	RA21/RA22 ASP015K 100 mg

Arm description:

Participants who previously completed RA21 or RA22 study and received ASP015K 100 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received open-label ASP015K 100 mg daily. Study drug should have been taken as close to the same time each day as possible. Study drug was to be administered orally with approximately 240 mL (8 oz.) of water, and must have been taken with food.

Arm title	RA21/RA22 ASP015K 150 mg

Arm description:

Participants who previously completed RA21 or RA22 study and received ASP015K 150 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Arm type	Experimental
Investigational medicinal product name	ASP015K
Investigational medicinal product code	ASP015K
Other name	Peficitinib (USAN)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received open-label ASP015K 100 mg daily. Study drug should have been taken as close to the same time each day as possible. Study drug was to be administered orally with approximately 240 mL (8 oz.) of water, and must have been taken with food.

Number of subjects in period 1	RA21/RA22 Placebo	RA21/RA22 ASP015K 25 mg	RA21/RA22 ASP015K 50 mg
Started	116	112	124
Completed	66	60	61
Not completed	50	52	63
Protocol violation	-	-	-
Death	-	-	-
Withdrawal by participant	16	16	25

Miscellaneous	-	-	1
Adverse event	9	10	6
Met discontinuation criteria	8	10	14
Did not meet ACR20 response by week 13	6	5	5
Lost to follow-up	4	2	3
Site closure	2	5	1
Lack of efficacy	5	4	8

Number of subjects in period 1	RA21/RA22 ASP015K 100 mg	RA21/RA22 ASP015K 150 mg
Started	128	131
Completed	67	65
Not completed	61	66
Protocol violation	1	-
Death	1	1
Withdrawal by participant	18	21
Miscellaneous	-	1
Adverse event	12	4
Met discontinuation criteria	13	17
Did not meet ACR20 response by week 13	4	9
Lost to follow-up	1	3
Site closure	2	4
Lack of efficacy	9	6

Baseline characteristics

Reporting groups	
Reporting group title	RA21/RA22 Placebo
Reporting group description:	
Participants who received placebo in studies RA21 or RA22 received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.	
Reporting group title	RA21/RA22 ASP015K 25 mg
Reporting group description:	
Participants who previously completed RA21 or RA22 study and received ASP015K 25 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.	
Reporting group title	RA21/RA22 ASP015K 50 mg
Reporting group description:	
Participants who previously completed RA21 or RA22 study and received ASP015K 50 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.	
Reporting group title	RA21/RA22 ASP015K 100 mg
Reporting group description:	
Participants who previously completed RA21 or RA22 study and received ASP015K 100 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.	
Reporting group title	RA21/RA22 ASP015K 150 mg
Reporting group description:	
Participants who previously completed RA21 or RA22 study and received ASP015K 150 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.	

Reporting group values	RA21/RA22 Placebo	RA21/RA22 ASP015K 25 mg	RA21/RA22 ASP015K 50 mg
Number of subjects	116	112	124
Age categorical			
Units: Subjects			

Age continuous			
Age values were based on all enrolled participants.			
Units: years			
arithmetic mean	52.4	52.2	53.3
standard deviation	± 12.14	± 11.48	± 11.53
Gender categorical			
Gender values were based on all enrolled participants.			
Units:			
Male	17	19	22
Female	99	93	102

Reporting group values	RA21/RA22 ASP015K 100 mg	RA21/RA22 ASP015K 150 mg	Total
Number of subjects	128	131	611
Age categorical			
Units: Subjects			

Age continuous			
Age values were based on all enrolled participants.			
Units: years			
arithmetic mean	54.5	54.2	

standard deviation	± 12.05	± 12.39	-

Gender categorical			
Gender values were based on all enrolled participants.			
Units:			
Male	22	27	107
Female	106	104	504

Subject analysis sets

Subject analysis set title	Total RA25
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who enrolled in the RA25 extension study. Participants received open-label ASP015K 100 mg daily for up to 104 weeks.

Reporting group values	Total RA25		
Number of subjects	611		
Age categorical Units: Subjects			

Age continuous			
Age values were based on all enrolled participants.			
Units: years			
arithmetic mean	53.4		
standard deviation	± 11.93		
Gender categorical			
Gender values were based on all enrolled participants.			
Units:			
Male	107		
Female	504		

End points

End points reporting groups

Reporting group title	RA21/RA22 Placebo

Reporting group description:

Participants who received placebo in studies RA21 or RA22 received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 25 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 25 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 50 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 50 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 100 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 100 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 150 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 150 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Subject analysis set title	Total RA25
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who enrolled in the RA25 extension study. Participants received open-label ASP015K 100 mg daily for up to 104 weeks.

Primary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)[1]

End point description:

Analysis population consisted of the Safety Analysis Set (SAF). SAF was defined as all participants who were enrolled & received at least 1 dose of study drug. AE is defined as any untoward medical occurrence in a participant administered a study drug or has undergone study procedures & which does not necessarily have a causal relationship with this treatment. A treatment-emergent adverse event (TEAE) was defined as an AE that started or worsened in severity after first dose of study drug in RA25, excluding events continuing from the preceding study (RA21 or RA22). AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v4.03, where Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life-threatening & Grade 5 = Death related to AE. A drug-related TEAE was defined as any TEAE with at least a possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

End point type	Primary

End point timeframe:

Up to 104 weeks. Date of last evaluation was 25 Mar 2016.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses applicable for this end point.

End point values	RA21/RA22 Placebo	RA21/RA22 ASP015K 25 mg	RA21/RA22 ASP015K 50 mg	RA21/RA22 ASP015K 100 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	116	112	124	128
Units: Participants				
TEAE	80	85	98	101
Drug-related TEAE	39	38	49	47
Death	0	0	0	1
Serious Adverse Event (SAE)	14	11	14	25
Drug-related SAE	5	6	5	5
TEAE ≥ Grade 3 in severity	13	10	15	23
TEAE leading to permanent discontinuation	9	9	8	11
Drug-related TEAE leading to permanent disc.	8	7	5	3
SAE leading to permanent discontinuation	2	1	3	5
Drug-related SAE leading to permanent disc.	2	1	3	1

End point values	RA21/RA22 ASP015K 150 mg	Total RA25		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	131	611		
Units: Participants				
TEAE	99	463		
Drug-related TEAE	49	222		
Death	1	2		
Serious Adverse Event (SAE)	16	80		
Drug-related SAE	3	24		
TEAE ≥ Grade 3 in severity	17	78		
TEAE leading to permanent discontinuation	6	43		
Drug-related TEAE leading to permanent disc.	4	27		
SAE leading to permanent discontinuation	2	13		
Drug-related SAE leading to permanent disc.	1	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 104 weeks. Date of last evaluation was 25 Mar 2016.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	RA21/RA22 Placebo

Reporting group description:

Participants who previously completed RA21 or RA22 study and received placebo, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 25 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 25 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 50 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 50 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 100 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 100 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	RA21/RA22 ASP015K 150 mg

Reporting group description:

Participants who previously completed RA21 or RA22 study and received ASP015K 150 mg, received open-label ASP015K 100 mg daily in this RA25 extension study for up to 104 weeks.

Reporting group title	Total RA25

Reporting group description:

All participants who enrolled in the RA25 extension study. Participants received open-label ASP015K 100 mg daily for up to 104 weeks.

Serious adverse events	RA21/RA22 Placebo	RA21/RA22 ASP015K 25 mg	RA21/RA22 ASP015K 50 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 116 (12.07%)	11 / 112 (9.82%)	14 / 124 (11.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Benign salivary gland neoplasm			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Thyroid cancer			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (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
Thrombosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Arthrodesis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposuction			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device complication			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Perforated ulcer			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudocyst			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (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
Endometriosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (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
Metrorrhagia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ovarian cyst			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Haemoptysis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Lung infiltration			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pulmonary thrombosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
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 failure			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (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
Transaminases increased			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (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			
Femoral neck fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			

subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Operative haemorrhage			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			

subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia supraventricular			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			

subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Pericarditis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Leukocytosis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (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
Abdominal pain upper			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Colitis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal sphincter insufficiency			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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

Pancreatitis acute			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Hand deformity			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			

subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	3 / 124 (2.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Cellulitis staphylococcal			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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
Clostridial infection			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster ophthalmic			
subjects affected / exposed	1 / 116 (0.86%)	0 / 112 (0.00%)	0 / 124 (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	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 116 (0.00%)	1 / 112 (0.89%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	1 / 124 (0.81%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 116 (0.00%)	0 / 112 (0.00%)	0 / 124 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	RA21/RA22 ASP015K 100 mg	RA21/RA22 ASP015K 150 mg	Total RA25
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 128 (19.53%)	16 / 131 (12.21%)	80 / 611 (13.09%)
number of deaths (all causes)	1	1	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign salivary gland neoplasm			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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 leiomyoma			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthrodesis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liposuction			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 128 (0.78%)	1 / 131 (0.76%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device complication			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Perforated ulcer			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pseudocyst			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial hyperplasia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometriosis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Menorrhagia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 128 (0.78%)	2 / 131 (1.53%)	4 / 611 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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 infiltration			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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 failure			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			

subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Operative haemorrhage			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Spinal compression fracture			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon injury			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			

subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 128 (0.78%)	1 / 131 (0.76%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia supraventricular			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Coronary artery disease			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			

subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 128 (1.56%)	0 / 131 (0.00%)	3 / 611 (0.49%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			

subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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 upper			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal sphincter insufficiency			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	3 / 611 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand deformity			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	2 / 128 (1.56%)	0 / 131 (0.00%)	6 / 611 (0.98%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis staphylococcal			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	2 / 611 (0.33%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster ophthalmic			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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 bacterial			

subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
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 staphylococcal			
subjects affected / exposed	0 / 128 (0.00%)	0 / 131 (0.00%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 128 (2.34%)	0 / 131 (0.00%)	3 / 611 (0.49%)
occurrences causally related to treatment / all	3 / 3	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 128 (0.00%)	1 / 131 (0.76%)	1 / 611 (0.16%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 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	RA21/RA22 Placebo	RA21/RA22 ASP015K 25 mg	RA21/RA22 ASP015K 50 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 116 (50.86%)	54 / 112 (48.21%)	70 / 124 (56.45%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	9 / 116 (7.76%)	4 / 112 (3.57%)	4 / 124 (3.23%)
occurrences (all)	10	8	4
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 116 (2.59%)	4 / 112 (3.57%)	7 / 124 (5.65%)
occurrences (all)	3	4	7
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 116 (5.17%)	5 / 112 (4.46%)	6 / 124 (4.84%)
occurrences (all)	7	5	7
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 116 (2.59%)	2 / 112 (1.79%)	2 / 124 (1.61%)
occurrences (all)	3	3	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 116 (6.03%)	3 / 112 (2.68%)	7 / 124 (5.65%)
occurrences (all)	10	4	7
Nausea			
subjects affected / exposed	8 / 116 (6.90%)	2 / 112 (1.79%)	5 / 124 (4.03%)
occurrences (all)	10	2	5
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	6 / 116 (5.17%)	4 / 112 (3.57%)	6 / 124 (4.84%)
occurrences (all)	6	4	9
Infections and infestations			
Bronchitis			
subjects affected / exposed	12 / 116 (10.34%)	10 / 112 (8.93%)	12 / 124 (9.68%)
occurrences (all)	17	12	14
Influenza			
subjects affected / exposed	3 / 116 (2.59%)	3 / 112 (2.68%)	6 / 124 (4.84%)
occurrences (all)	3	4	10
Nasopharyngitis			
subjects affected / exposed	7 / 116 (6.03%)	9 / 112 (8.04%)	12 / 124 (9.68%)
occurrences (all)	7	11	16
Pharyngitis			
subjects affected / exposed	1 / 116 (0.86%)	6 / 112 (5.36%)	4 / 124 (3.23%)
occurrences (all)	1	6	4
Sinusitis			
subjects affected / exposed	4 / 116 (3.45%)	3 / 112 (2.68%)	2 / 124 (1.61%)
occurrences (all)	6	4	2
Upper respiratory tract infection			
subjects affected / exposed	19 / 116 (16.38%)	9 / 112 (8.04%)	15 / 124 (12.10%)
occurrences (all)	24	12	21
Urinary tract infection			
subjects affected / exposed	14 / 116 (12.07%)	9 / 112 (8.04%)	8 / 124 (6.45%)
occurrences (all)	19	13	8

Urinary tract infection bacterial subjects affected / exposed occurrences (all)	5 / 116 (4.31%) 5	5 / 112 (4.46%) 7	3 / 124 (2.42%) 4
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all)	5 / 116 (4.31%) 6	8 / 112 (7.14%) 9	11 / 124 (8.87%) 11

Non-serious adverse events	RA21/RA22 ASP015K 100 mg	RA21/RA22 ASP015K 150 mg	Total RA25
Total subjects affected by non-serious adverse events subjects affected / exposed	69 / 128 (53.91%)	58 / 131 (44.27%)	310 / 611 (50.74%)
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	4 / 128 (3.13%) 5	7 / 131 (5.34%) 8	28 / 611 (4.58%) 35
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	5 / 128 (3.91%) 6	7 / 131 (5.34%) 7	26 / 611 (4.26%) 27
Nervous system disorders Headache subjects affected / exposed occurrences (all)	12 / 128 (9.38%) 13	3 / 131 (2.29%) 3	32 / 611 (5.24%) 35
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	9 / 128 (7.03%) 10	2 / 131 (1.53%) 2	18 / 611 (2.95%) 20
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	7 / 128 (5.47%) 15 8 / 128 (6.25%) 9	3 / 131 (2.29%) 4 2 / 131 (1.53%) 2	27 / 611 (4.42%) 40 25 / 611 (4.09%) 28
Musculoskeletal and connective tissue disorders Rheumatoid arthritis			

subjects affected / exposed	5 / 128 (3.91%)	3 / 131 (2.29%)	24 / 611 (3.93%)
occurrences (all)	6	3	28
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 128 (2.34%)	5 / 131 (3.82%)	42 / 611 (6.87%)
occurrences (all)	3	6	52
Influenza			
subjects affected / exposed	10 / 128 (7.81%)	5 / 131 (3.82%)	27 / 611 (4.42%)
occurrences (all)	10	5	32
Nasopharyngitis			
subjects affected / exposed	10 / 128 (7.81%)	4 / 131 (3.05%)	42 / 611 (6.87%)
occurrences (all)	16	6	56
Pharyngitis			
subjects affected / exposed	7 / 128 (5.47%)	3 / 131 (2.29%)	21 / 611 (3.44%)
occurrences (all)	9	4	24
Sinusitis			
subjects affected / exposed	4 / 128 (3.13%)	7 / 131 (5.34%)	20 / 611 (3.27%)
occurrences (all)	4	7	23
Upper respiratory tract infection			
subjects affected / exposed	17 / 128 (13.28%)	17 / 131 (12.98%)	77 / 611 (12.60%)
occurrences (all)	21	20	98
Urinary tract infection			
subjects affected / exposed	15 / 128 (11.72%)	6 / 131 (4.58%)	52 / 611 (8.51%)
occurrences (all)	20	9	69
Urinary tract infection bacterial			
subjects affected / exposed	7 / 128 (5.47%)	8 / 131 (6.11%)	28 / 611 (4.58%)
occurrences (all)	8	9	33
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	5 / 128 (3.91%)	9 / 131 (6.87%)	38 / 611 (6.22%)
occurrences (all)	6	10	42

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2012	• Dosing instructions revised to state "take with food" • Safety follow-up period extended to 30 days • Clarified inclusion criterion regarding eligibility for women of child-bearing potential • Clarified discontinuation criterion for symptomatic CPK elevation • Corrected the description of study drug packaging and labeling • Other clarifications and administrative changes made. These changes to the protocol were included prior to the enrollment of any patients in RA25.
22 June 2012	• Updated planned study period in accordance with revised timelines • Updated planned number of patients • Provided clearly defined laboratory exclusion criteria • Included changes in allowed and prohibited concomitant medications • Clarified definition of efficacy end points and efficacy data to be summarized • Clarified dosing instructions and requirements for dose reduction • Corrected instructions for performing joint assessments • Added requirement for estimated glomerular filtration rate (eGFR) calculation by central laboratory at all visits • Other clarifications and administrative changes made. These changes to the protocol were included prior to the enrollment of any patients in RA25.
15 August 2012	• Updated planned study period to reflect more accurate timelines per regulatory feedback • Added IEC to approval required for Informed Consent • Revised inclusion criteria to specify completion of phase 2 study and included the time period allowed to roll over into the extension study • Clarified exclusion criteria such that patients who discontinue study drug prior to week 12 visit in phase 2 study will not be eligible • Updated Schedule of Assessments and statistical methods • Updated allowed doses of oral morphine • Clarified timepoints when Disease Activity Score (DAS) in 28 joints (DAS28) is performed • Updated blood volumes collected during first and second years of study • Other clarifications and administrative changes made. These changes to the protocol were included prior to the enrollment of any patients in RA25.

02 April 2013	• Revised inclusion criteria regarding use of contraceptives, and limitations on ova donation for women of child-bearing potential and sperm donation for men • Added inclusion criteria that patients agree not to participate in another interventional trial while on treatment in RA25 • Clarified that waivers to inclusion and exclusion criteria would not be allowed • Added exclusion criteria for patients with significant lymphopenia and discontinuation criteria to mandate patients discontinue study drug in presence of severe lymphopenia • Revised exclusion criteria for laboratory values to be consistent with discontinuation laboratory criteria for RA21 and RA22 • Modified criteria for continuing study treatment from "requiring achievement of an American College of Rheumatology response (ACR20) by week 13" to "requiring a 20% improvement in tender and swollen joint counts • Added azathioprine and minocycline to prohibited medications list • Allowed chloroquine to list of DMARDs • Added absolute lymphocyte count to criteria for reduction and/or permanent discontinuation of study drug • Revised definition of SAEs to include safety events of interest and their reporting requirements • Other clarifications and administrative changes made. These changes to the protocol were made after the enrollment of 129 patients in RA25. Changes did not affect the overall outcome of the study.
10 July 2014	• Revised discontinuation criteria for CPK and serum creatinine • Revised increase and reduction in dose of study drug to allow patients to re-escalate back to 100 mg during the study • Revised laboratory testing levels for CPK elevations and timeframe required for rechecks • Updated background section to include final results from RA21 and RA22 studies • Revised criteria to include additional instructions for discontinuing patients whose laboratory values met the Hematology Threshold Criteria • Clarifications and other administrative changes made. These changes to the protocol were made after the enrollment of 611 patients in RA25. Changes did not affect the overall outcome of the study.
24 March 2015	• Removed biomarker analysis and optional mRNA samples from study design • Added additional discontinuation criteria to mandate that those patients who had not achieved low disease activity, experienced moderate or high disease activity for 2 consecutive visits after achieving low disease activity or remission, received a diagnosis of congenital short QT syndrome or experienced a QTc < 300 ms would be discontinued • Added calculation of Clinical Disease Activity Index (CDAI) to arthritis assessments • Clarifications and other administrative changes made. These changes to the protocol were made after the enrollment of 611 patients in RA25. Changes did not affect the overall outcome of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported