Clinical trial results:
(OSKIRA-4): A Phase IIB, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Fostamatinib Disodium Monotherapy Compared with Adalimumab Monotherapy in Patients with Active Rheumatoid Arthritis

Summary

EudraCT number	2010-023692-26
Trial protocol	GB DE CZ HU BG SK
Global end of trial date	17 July 2013

Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	D4300C00004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01264770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca Pharmaceuticals
Sponsor organisation address	Alderley Park, Macclesfield, United Kingdom,
Public contact	Neil Mackillop, AstraZeneca, information.center@astrazeneca.com
Scientific contact	Neil Mackillop, AstraZeneca, neil.mackillop@astrazeneca.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	27 November 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 October 2012
Global end of trial reached?	Yes
Global end of trial date	17 July 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study were:
• To evaluate the efficacy of 3 oral dosing regimens of fostamatinib compared with placebo when used as monotherapy in patients with active RA by assessment of the signs and symptoms of RA, as measured by Disease Activity Score based on a 28-joint count (DAS28) at Week 6.
• To evaluate whether the efficacy of 3 oral dosing regimens of fostamatinib were non-inferior to that of adalimumab when used as monotherapy in patients with active RA by assessment of the signs and symptoms of RA, as measured by DAS28 at Week 24.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.
Before enrolment of any patient into the study, the final clinical study protocol, including the final version of the informed consent form, was approved by the national regulatory authority or a notification to the national regulatory authority was done, according to local regulations. The study was approved or given a favourable opinion in writing by an Independent Ethics Committee (IEC) for each study centre. The investigator(s) at each centre ensured that the patient was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients were also notified that they were free to discontinue investigational product (IP) and/or withdraw from the study at any time. The patient was given the opportunity to ask questions and allowed time to consider the information provided.The patient’s signed and dated informed consent was obtained before conducting any procedure specifically for the study.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	24 January 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	Russian Federation: 53
Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Ukraine: 38
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Czech Republic: 33
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	South Africa: 13

Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Slovakia: 4
Worldwide total number of subjects	265
EEA total number of subjects	111

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)	241
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

452 patients were enrolled into the main study, 173 patients failed screening, 279 were randomised, 14 did not receive treatment (2, 5 and 2 for the fostamatinib doses, 3 for adalimumab and 2 for placebo). 265 were treated and are reported here as the full analysis set.

Pre-assignment

Screening details:

192 patients enrolled into a separate MRI sub-study (644 enrolled in total).

Period 1

Period 1 title	6 week placebo controlled study period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	FOSTA 100 MG BID PO

Arm description:

Dosing Group A

Arm type	Experimental
Investigational medicinal product name	Fostamatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100mg twice a day

Arm title	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO

Arm description:

Dosing Group B

Arm type	Experimental
Investigational medicinal product name	Fostamatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100mg twice daily for 4 weeks then 150gm once daily

Arm title	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO

Arm description:

Dosing Group C

Arm type	Experimental

Investigational medicinal product name	Fostamatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100mg twice daily for 4 weeks then 100mg once daily

Arm title	ADALIMUMAB 40 MG SC

Arm description:

Dosing Group D

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

40mg every 2 weeks

Arm title	PLACEBO

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Twice daily

Number of subjects in period 1	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO
Started	54	48	57
Completed	49	47	50
Not completed	5	1	7
Severe non-compliance to protocol	-	-	1
Adverse event, non-fatal	2	1	3
Dev. of study specific discont. criteria	-	-	-
e.g., change in circumstances	3	-	1
Randomised, but did not receive study drug	-	-	1
Lost to follow-up	-	-	1

Number of subjects in period 1	ADALIMUMAB 40 MG SC	PLACEBO
Started	54	52

Completed	54	48
Not completed	0	4
Severe non-compliance to protocol	-	-
Adverse event, non-fatal	-	-
Dev. of study specific discont. criteria	-	1
e.g., change in circumstances	-	3
Randomised, but did not receive study drug	-	-
Lost to follow-up	-	-

Period 2

Period 2 title	Week 6 to 24 active controlled period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	FOSTA 100 MG BID PO

Arm description:
Dosing Group A

Arm type	Experimental
Investigational medicinal product name	Fostamatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
100mg twice a day

Arm title	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO

Arm description:
Dosing Group B

Arm type	Experimental
Investigational medicinal product name	Fostamatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
100mg twice daily for 4 weeks then 150gm once daily

Arm title	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO

Arm description:
Dosing Group C

Arm type	Experimental

Investigational medicinal product name	Fostamatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100mg twice daily for 4 weeks then 100mg once daily

Arm title	ADALIMUMAB 40 MG SC

Arm description:

Dosing Group D

Arm type	Active comparator
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

40mg every 2 weeks

Arm title	PLACEBO (6 WKS) THEN FOSTA

Arm description:

Dosing Group E

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for 6 weeks then fostamatinib 100mg twice daily

Number of subjects in period 2	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO
Started	49	47	50
Completed	36	38	41
Not completed	13	9	9
Severe non-compliance to protocol	-	-	-
Lack of therapeutic response	1	-	2
Adverse event, non-fatal	5	6	5
Dev. of study specific discont. criteria	2	-	-
e.g., change in circumstances	5	3	2
Lost to follow-up	-	-	-

Number of subjects in period 2	ADALIMUMAB 40 MG SC	PLACEBO (6 WKS) THEN FOSTA
Started	54	48

Completed	48	38
Not completed	6	10
Severe non-compliance to protocol	1	-
Lack of therapeutic response	1	1
Adverse event, non-fatal	-	3
Dev. of study specific discont. criteria	-	1
e.g., change in circumstances	3	5
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	FOSTA 100 MG BID PO
Reporting group description:	
Dosing Group A	
Reporting group title	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO
Reporting group description:	
Dosing Group B	
Reporting group title	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO
Reporting group description:	
Dosing Group C	
Reporting group title	ADALIMUMAB 40 MG SC
Reporting group description:	
Dosing Group D	
Reporting group title	PLACEBO
Reporting group description: -	

Reporting group values	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO
Number of subjects	54	48	57
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	50	42	53
From 65-84 years	4	6	4
85 years and over	0	0	0
Age Continuous |			
Units: years			
arithmetic mean	50	50	50
standard deviation	± 11.5	± 12.6	± 11
Gender, Male/Female			
Units: Participants			
Female	38	39	48
Male	16	9	9
Race/Ethnicity, Customized			
Units: Subjects			
White	48	47	48
Black or African American	5	0	6
Asian	1	1	0
American Indian or Alaska Native	0	0	1
Indian or Pakistani	0	0	1

Other	0	0	1

Reporting group values	ADALIMUMAB 40 MG SC	PLACEBO	Total
Number of subjects	54	52	265
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	51	45	241
From 65-84 years	3	7	24
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	48	50	
standard deviation	± 12.4	± 12.7	-
Gender, Male/Female Units: Participants			
Female	45	40	210
Male	9	12	55
Race/Ethnicity, Customized Units: Subjects			
White	51	46	240
Black or African American	1	4	16
Asian	1	1	4
American Indian or Alaska Native	0	0	1
Indian or Pakistani	1	0	2
Other	0	1	2

Subject analysis sets

Subject analysis set title	Dosing Group B
Subject analysis set type	Full analysis
Subject analysis set description: FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	
Subject analysis set title	Dosing Group C
Subject analysis set type	Full analysis
Subject analysis set description: FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO	
Subject analysis set title	Dosing Group A
Subject analysis set type	Full analysis
Subject analysis set description: FOSTA 100 MG BID PO	
Subject analysis set title	Dosing Group D

Subject analysis set type	Full analysis
Subject analysis set description: ADALIMUMAB 40 MG SC	
Subject analysis set title	Dosing Group E
Subject analysis set type	Full analysis
Subject analysis set description: PLACEBO (COMBINED)	

Reporting group values	Dosing Group B	Dosing Group C	Dosing Group A
Number of subjects	48	57	54
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	53	50
From 65-84 years	6	4	4
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	50	50	50
standard deviation	± 12.6	± 11	± 11.5
Gender, Male/Female Units: Participants			
Female	39	48	38
Male	9	9	16
Race/Ethnicity, Customized Units: Subjects			
White	47	48	48
Black or African American	0	6	5
Asian	1	0	1
American Indian or Alaska Native	0	1	0
Indian or Pakistani	0	1	0
Other	0	1	0

Reporting group values	Dosing Group D	Dosing Group E	
Number of subjects	54	52	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	51	45	

From 65-84 years	3	7	
85 years and over	0	0	

Age Continuous | Units: years			
arithmetic mean	48	51	
standard deviation	± 12.4	± 11.6	
Gender, Male/Female Units: Participants			
Female	45	40	
Male	9	12	
Race/Ethnicity, Customized Units: Subjects			
White	51	46	
Black or African American	1	4	
Asian	1	1	
American Indian or Alaska Native	0	0	
Indian or Pakistani	1	0	
Other	0	1	

End points

End points reporting groups

Reporting group title	FOSTA 100 MG BID PO
Reporting group description: Dosing Group A	
Reporting group title	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO
Reporting group description: Dosing Group B	
Reporting group title	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO
Reporting group description: Dosing Group C	
Reporting group title	ADALIMUMAB 40 MG SC
Reporting group description: Dosing Group D	
Reporting group title	PLACEBO
Reporting group description: -	
Reporting group title	FOSTA 100 MG BID PO
Reporting group description: Dosing Group A	
Reporting group title	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO
Reporting group description: Dosing Group B	
Reporting group title	FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO
Reporting group description: Dosing Group C	
Reporting group title	ADALIMUMAB 40 MG SC
Reporting group description: Dosing Group D	
Reporting group title	PLACEBO (6 WKS) THEN FOSTA
Reporting group description: Dosing Group E	
Subject analysis set title	Dosing Group B
Subject analysis set type	Full analysis
Subject analysis set description: FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	
Subject analysis set title	Dosing Group C
Subject analysis set type	Full analysis
Subject analysis set description: FOSTA 100 MG BID (4 WKS) THEN 100 MG QD PO	
Subject analysis set title	Dosing Group A
Subject analysis set type	Full analysis
Subject analysis set description: FOSTA 100 MG BID PO	
Subject analysis set title	Dosing Group D
Subject analysis set type	Full analysis
Subject analysis set description: ADALIMUMAB 40 MG SC	
Subject analysis set title	Dosing Group E
Subject analysis set type	Full analysis

Subject analysis set description:

PLACEBO (COMBINED)

Primary: DAS28-CRP score - change from baseline to Week 6 compared to placebo

End point title	DAS28-CRP score - change from baseline to Week 6 compared to placebo

End point description:

DAS28-CRP: Disease Activity Score based on a count of swollen and tender joints (out of 28 joints), blood test measures of inflammation (CRP) and the patient's own assessment. Scores can take any positive value with a lower value indicating a better clinical condition. Mean changes from baseline in DAS28-CRP score are shown at each visit and are presented as decreases from baseline (defined as baseline minus post-baseline) with larger changes indicative of a better clinical condition. ANCOVA = analysis of covariance, BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, LS = least squares, n/a = not applicable, PO = orally, QD = once a day, SC = subcutaneous.

End point type	Primary

End point timeframe:

Baseline and 6 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group E
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	52
Units: Units on a scale				
arithmetic mean (standard deviation)	1.1 (± 0.92)	1.1 (± 1.01)	0.8 (± 0.96)	0.6 (± 1.14)

Statistical analyses

Statistical analysis title	DAS28 ANCOVA vs placebo

Statistical analysis description:

Change from baseline at Week 6. Non-responder imputation applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group E
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.56
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.23
upper limit	0.9

Statistical analysis title	DAS28 ANCOVA vs placebo

Statistical analysis description:

Change from baseline at Week 6. Non-responder imputation applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group E
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.12
upper limit	0.56

Statistical analysis title	DAS28 ANCOVA vs placebo

Statistical analysis description:

Change from baseline at Week 6. Non-responder imputation applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group E
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.49
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.14
upper limit	0.84

Primary: DAS28-CRP score - change from baseline to Week 24 compared to adalimumab

End point title	DAS28-CRP score - change from baseline to Week 24 compared to adalimumab

End point description:

DAS28-CRP: Disease Activity Score based on a count of swollen and tender joints (out of 28 joints), blood test measures of inflammation (CRP) and the patient's own assessment. Scores can take any positive value with a lower value indicating a better clinical condition. Mean changes from baseline in DAS28-CRP score are shown at each visit and are presented as decreases from baseline (defined as baseline minus post-baseline) with larger changes indicative of a better clinical condition. Non-responder imputation has been applied by carrying the baseline observation forward. ANCOVA = analysis of

covariance, BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, LS = least squares, n/a = not applicable, PO = orally, QD = once a day, SC = subcutaneous.

End point type	Primary

End point timeframe:

Baseline and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Units on a scale				
arithmetic mean (standard deviation)	1 (± 1.31)	1.1 (± 1.22)	1 (± 1.25)	1.8 (± 1.45)

Statistical analyses

Statistical analysis title	DAS28 ANCOVA vs adalimumab

Statistical analysis description:

Change from baseline at Week 24. Non-responder imputation applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.72
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.04
upper limit	-0.4

Notes:

[1] - For the comparison with adalimumab a non-inferiority margin of -0.6 in the mean change from baseline in DAS28-CRP at Week 24 was defined. The lower 80% confidence interval for treatment difference was below this value so non-inferiority could not be concluded. A p-value is also provided for a 2-sided test of superiority.

Statistical analysis title	DAS28 ANCOVA vs adalimumab

Statistical analysis description:

Change from baseline at Week 24. Non-responder imputation applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.02
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.61
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.94
upper limit	-0.27

Notes:

[2] - For the comparison with adalimumab a non-inferiority margin of -0.6 in the mean change from baseline in DAS28-CRP at Week 24 was defined. The lower 80% confidence interval for treatment difference was below this value so non-inferiority could not be concluded. A p-value is also provided for a 2-sided test of superiority.

Statistical analysis title	DAS28 ANCOVA vs adalimumab

Statistical analysis description:

Change from baseline at Week 24. Non-responder imputation applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.004
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	-0.72
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.04
upper limit	-0.4

Notes:

[3] - For the comparison with adalimumab a non-inferiority margin of -0.6 in the mean change from baseline in DAS28-CRP at Week 24 was defined. The lower 80% confidence interval for treatment difference was below this value so non-inferiority could not be concluded. A p-value is also provided for a 2-sided test of superiority.

Secondary: DAS28 EULAR response at Week 6

End point title	DAS28 EULAR response at Week 6

End point description:

Change in DAS28 was derived for each post baseline scheduled assessment and categorised using the European League Against Rheumatism (EULAR) response criteria. Non-responder imputation has been applied by carrying the baseline observation forward. bid = twice daily, DAS28 = Disease Activity Score based on a 28-joint count, DMARD = disease-modifying anti-rheumatic drug, OR = odds ratio, PO = orally, qd = once a day, SC = subcutaneous.

End point type	Secondary

End point timeframe:

6 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group E
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	52
Units: Percentage of responders				
number (not applicable)				
No response	37	33.3	57.9	67.3
Moderate response	53.7	47.9	35.1	25
Good response	9.3	18.8	7	7.7

Statistical analyses

Statistical analysis title	DAS28 EULAR response vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group E
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	3.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.59
upper limit	5.86

Statistical analysis title	DAS28 EULAR response vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group E
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	4.11

Confidence interval	
level	90 %
sides	2-sided
lower limit	2.1
upper limit	8.05

Statistical analysis title	DAS28 EULAR response vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group E
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.335
Method	Proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	1.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.76
upper limit	2.83

Secondary: DAS28 EULAR response at Week 24

End point title	DAS28 EULAR response at Week 24

End point description:

Change in DAS28 was derived for each post baseline scheduled assessment and categorised using the European League Against Rheumatism (EULAR) response criteria. Non-responder imputation has been applied by carrying the baseline observation forward. bid = twice daily, DAS28 = Disease Activity Score based on a 28-joint count, DMARD = disease-modifying anti-rheumatic drug, OR = odds ratio, PO = orally, qd = once a day, SC = subcutaneous.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Percentage of responders				
number (not applicable)				
No response	51.9	41.7	52.6	31.5
Moderate response	29.6	39.6	29.8	27.8
Good response	18.5	18.8	17.5	40.7

Statistical analyses

Statistical analysis title	DAS28 EULAR response vs adalimumab
Statistical analysis description:	
Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.	
Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	Proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	0.37
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.2
upper limit	0.68

Statistical analysis title	DAS28 EULAR response vs adalimumab
Statistical analysis description:	
Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.	
Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	Proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	0.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.26
upper limit	0.89

Statistical analysis title	DAS28 EULAR response vs adalimumab
Statistical analysis description:	
Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or	

for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	0.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.2
upper limit	0.65

Secondary: Proportion of patients achieving ACR20 up to Week 24

End point title	Proportion of patients achieving ACR20 up to Week 24

End point description:

ACR20: American College of Rheumatology 20% response criteria, based on count of swollen and tender joints (out of 28 joints), blood test measures of inflammation (such as CRP) and the physician and patient's own assessments of disease activity, pain and physical function. Non-responder imputation has been applied by carrying the baseline observation forward. BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, n/a = not applicable, PO = orally, qd = once a day, SC = subcutaneous.

End point type	Secondary

End point timeframe:

6 and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Percentage of responders				
number (not applicable)				
Week 6	48.1	47.9	38.6	53.7
Week 24	40.7	56.3	35.1	59.3

End point values	Dosing Group E			
Subject group type	Subject analysis set			
Number of subjects analysed	52[4]			
Units: Percentage of responders				
number (not applicable)				
Week 6	19.2			
Week 24	44.2			

Notes:

[4] - Week 24 placebo data is after switch to fostamatinib (doses combined)

Statistical analyses

Statistical analysis title	ACR20 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group E
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.17
upper limit	0.4

Notes:

[5] - Week 6

Statistical analysis title	ACR20 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group E
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [6]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.18
upper limit	0.43

Notes:

[6] - Week 6

Statistical analysis title	ACR20 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or

for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group E
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007 [7]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.07
upper limit	0.31

Notes:

[7] - Week 6

Statistical analysis title	ACR20 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049 [8]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.16
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.3
upper limit	-0.03

Notes:

[8] - Week 24

Statistical analysis title	ACR20 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.803 [9]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.02

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.16
upper limit	0.12

Notes:

[9] - Week 24

Statistical analysis title	ACR20 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [10]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.37
upper limit	-0.1

Notes:

[10] - Week 24

Secondary: Proportion of patients achieving ACR50 up to Week 24

End point title	Proportion of patients achieving ACR50 up to Week 24

End point description:

ACR50: American College of Rheumatology 50% response criteria, based on count of swollen and tender joints (out of 28 joints), blood test measures of inflammation (such as CRP) and the physician and patient's own assessments of disease activity, pain and physical function. Non-responder imputation has been applied by carrying the baseline observation forward. BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, n/a = not applicable, PO = orally, qd = once a day, SC = subcutaneous.

End point type	Secondary

End point timeframe:

6 and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Percentage of responders				
number (not applicable)				
Week 6	13	12.5	7	25.9
Week 24	20.4	18.8	12.3	31.5

End point values	Dosing Group E			
Subject group type	Subject analysis set			
Number of subjects analysed	52[11]			
Units: Percentage of responders				
number (not applicable)				
Week 6	3.8			
Week 24	23.1			

Notes:

[11] - Week 24 placebo data is after switch to fostamatinib (doses combined)

Statistical analyses

Statistical analysis title	ACR50 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group E
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059 [12]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.01
upper limit	0.18

Notes:

[12] - Week 6

Statistical analysis title	ACR50 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group E
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.071 [13]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.09

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.01
upper limit	0.17

Notes:

[13] - Week 6

Statistical analysis title	ACR50 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group E
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.758 [14]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.05
upper limit	0.07

Notes:

[14] - Week 6

Statistical analysis title	ACR50 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.114 [15]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.12
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.24
upper limit	0

Notes:

[15] - Week 24

Statistical analysis title	ACR50 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078 [16]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.26
upper limit	-0.01

Notes:

[16] - Week 24

Statistical analysis title	ACR50 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [17]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.32
upper limit	-0.09

Notes:

[17] - Week 24

Secondary: Proportion of patients achieving ACR70 up to Week 24

End point title	Proportion of patients achieving ACR70 up to Week 24

End point description:

ACR70: American College of Rheumatology 70% response criteria, based on count of swollen and tender joints (out of 28 joints), blood test measures of inflammation (such as CRP) and the physician and patient's own assessments of disease activity, pain and physical function. Non-responder imputation has been applied by carrying the baseline observation forward. BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, n/a = not applicable, PO = orally, qd = once a day, SC = subcutaneous.

End point type	Secondary

End point timeframe:

6 and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Percentage of responders				
number (not applicable)				
Week 6	1.9	4.2	1.8	7.4
Week 24	9.3	10.4	3.5	20.4

End point values	Dosing Group E			
Subject group type	Subject analysis set			
Number of subjects analysed	52[18]			
Units: Percentage of responders				
number (not applicable)				
Week 6	3.8			
Week 24	5.8			

Notes:

[18] - Week 24 placebo data is after switch to fostamatinib (doses combined)

Statistical analyses

Statistical analysis title	ACR70 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group E
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46 [19]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.07
upper limit	0.03

Notes:

[19] - Week 6

Statistical analysis title	ACR70 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group E
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903 [20]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.05
upper limit	0.06

Notes:

[20] - Week 6

Statistical analysis title	ACR70 vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group E
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.172 [21]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.08
upper limit	0.01

Notes:

[21] - Week 6

Statistical analysis title	ACR70 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.082 [22]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.11

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.21
upper limit	-0.01

Notes:

[22] - Week 24

Statistical analysis title	ACR70 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092 [23]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.21
upper limit	0

Notes:

[23] - Week 24

Statistical analysis title	ACR70 vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [24]
Method	Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-0.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.27
upper limit	-0.08

Notes:

[24] - Week 24

Secondary: ACRn - comparison between fostamatinib and placebo at Week 6

End point title	ACRn - comparison between fostamatinib and placebo at Week 6

End point description:

ACRn: American College of Rheumatology Index of RA improvement, based on smallest percentage improvement in the count of swollen joints (out of 28 joints), count of tender joints (out of 28 joints) or in blood test measures of inflammation (such as CRP) or the physician and patient's own asessment of disease activity, pain and physical function. Scores are reported as a percentage improvement on a scale of -100 to +100, with larger values representing a better clinical outcome and negative values a worsening of clinical condition. Non-responder imputation has been applied by carrying the baseline observation forward. BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, n/a = not applicable, PO = orally, qd = once a day, SC = subcutaneous. Mean refers to change at Week 6. Treatment difference: difference between fostamatinib and placebo groups.

End point type	Secondary

End point timeframe:

Baseline and 6 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group E
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	52
Units: Percentage change from baseline				
arithmetic mean (standard deviation)	16.6 (± 30.682)	15.07 (± 33.334)	6.48 (± 32.237)	-6.49 (± 35.159)

Statistical analyses

Statistical analysis title	ACRn vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group E
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Van Elteren
Parameter estimate	Treatment difference
Point estimate	23.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	9.57
upper limit	40

Statistical analysis title	ACRn vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group E

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.234
Method	Van Elteren
Parameter estimate	Treatment difference
Point estimate	5.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.2
upper limit	21.68

Statistical analysis title	ACRn vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group E
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Van Elteren
Parameter estimate	Treatment difference
Point estimate	22.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	7.84
upper limit	38.34

Secondary: ACRn - comparison between fostamatinib and adalimumab at Week 24

End point title	ACRn - comparison between fostamatinib and adalimumab at Week 24

End point description:

ACRn: American College of Rheumatology Index of RA improvement, based on smallest percentage improvement in the count of swollen joints (out of 28 joints), count of tender joints (out of 28 joints) or in blood test measures of inflammation (such as CRP) or the physician and patient's own asessment of disease activity, pain and physical function. Scores are reported as a percentage improvement on a scale of -100 to +100, with larger values representing a better clinical outcome and negative values a worsening of clinical condition. Non-responder imputation has been applied by carrying the baseline observation forward. BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, n/a = not applicable, PO = orally, qd = once a day, SC = subcutaneous. Mean refers to change at Week 24. Treatment difference: difference between fostamatinib and adalimumab groups.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Percentage change from baseline				
arithmetic mean (standard deviation)	18.35 (± 34.355)	22.03 (± 32.361)	11.49 (± 26.916)	31.21 (± 39.187)

Statistical analyses

Statistical analysis title	ACRn vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Van Elteren
Parameter estimate	Treatment difference
Point estimate	-13.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	-25.01
upper limit	0

Statistical analysis title	ACRn vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.207
Method	Van Elteren
Parameter estimate	Treatment difference
Point estimate	-9.49

Confidence interval	
level	90 %
sides	2-sided
lower limit	-25
upper limit	6.96

Statistical analysis title	ACRn vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Van Elteren
Parameter estimate	Treatment difference
Point estimate	-19.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	-30.01
upper limit	-6.25

Secondary: HAQ-DI - comparison of the change from baseline between fostamatinib and placebo at Week 6

End point title	HAQ-DI - comparison of the change from baseline between fostamatinib and placebo at Week 6

End point description:

HAQ-DI: Health Assessment Questionnaire - Disability Index, a measure of physical function. The HAQ-DI score is calculated by summing the category scores from 8 sub-categories (ie, scores for patient ability in dressing and grooming, rising, eating, walking, hygiene, reach, grip and common daily activities) and dividing by the number of categories completed. The HAQ-DI score takes values between 0 and 3, with a higher score indicating greater disability. Non-responder imputation has been applied by carrying the baseline observation forward. ANCOVA = analysis of covariance, BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, LS = least squares, n/a = not applicable, PO = orally, qd = once a day, SC = subcutaneous.

End point type	Secondary

End point timeframe:

Baseline and 6 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group E
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	52
Units: Units on a scale				
arithmetic mean (standard deviation)	0.3 (± 0.35)	0.3 (± 0.54)	0.2 (± 0.43)	0.1 (± 0.52)

Statistical analyses

Statistical analysis title	HAQ-DI vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group E
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.007
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.09
upper limit	0.38

Statistical analysis title	HAQ-DI vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group E
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.07
upper limit	0.37

Statistical analysis title	HAQ-DI vs placebo

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group E
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0.29

Secondary: HAQ-DI - comparison of the change from baseline between fostamatinib and adalimumab at Week 24

End point title	HAQ-DI - comparison of the change from baseline between fostamatinib and adalimumab at Week 24

End point description:

HAQ-DI: Health Assessment Questionnaire - Disability Index, a measure of physical function. The HAQ-DI score is calculated by summing the category scores from 8 sub-categories (ie, scores for patient ability in dressing and grooming, rising, eating, walking, hygiene, reach, grip and common daily activities) and dividing by the number of categories completed. The HAQ-DI score takes values between 0 and 3, with a higher score indicating greater disability. Non-responder imputation has been applied by carrying the baseline observation forward. ANCOVA = analysis of covariance, BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, LS = least squares, n/a = not applicable, PO = orally, qd = once a day, SC = subcutaneous.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Units on a scale				
arithmetic mean (standard deviation)	0.3 (± 0.57)	0.4 (± 0.56)	0.2 (± 0.45)	0.5 (± 0.53)

Statistical analyses

Statistical analysis title	HAQ-DI vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or

for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.36
upper limit	-0.04

Statistical analysis title	HAQ-DI vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.158
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.31
upper limit	0.02

Statistical analysis title	HAQ-DI vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.32

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.47
upper limit	-0.16

Secondary: SF-36 - comparison of the change in PCS from baseline between fostamatinib and adalimumab at Week 24

End point title	SF-36 - comparison of the change in PCS from baseline between fostamatinib and adalimumab at Week 24

End point description:

SF-36: 36 item short form health survey, as a measure of health-related quality of life. Scores for 8 sub-domains (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Function, Role-Emotional and Mental Health) are derived and normalised to a scale of 0 to 100. The physical and mental component scores (PCS and MCS) are derived by multiplying each of these 8 scores by a constant, summing them and standardising against a population with a mean of 50, standard deviation of 10. A higher score represents a better quality of life. Mean changes from baseline score are presented as increases from baseline (defined as post-baseline minus baseline); larger changes indicate a better clinical condition. Mean refers to change in scores at Week 24. ANCOVA = analysis of covariance, BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, IR = inadequate response, LS = least squares, PO = orally, QD = once a day, QoL = quality of life, SC = subcutaneous

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Units on a scale				
arithmetic mean (standard deviation)	4 (± 7.3)	5 (± 7.2)	4 (± 7.4)	7 (± 8.4)

Statistical analyses

Statistical analysis title	SF-36 PCS vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.77

Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.08
upper limit	-0.45

Statistical analysis title	SF-36 PCS vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.99
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.29
upper limit	-0.7

Statistical analysis title	SF-36 PCS vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.33
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.73
upper limit	1.06

Secondary: SF-36 - comparison of the change in MCS from baseline between fostamatinib and adalimumab at Week 24

End point title	SF-36 - comparison of the change in MCS from baseline

	between fostamatinib and adalimumab at Week 24

End point description:

SF-36: 36 item short form health survey, as a measure of health-related quality of life. The SF-36 scores for 8 sub-domains (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Function, Role-Emotional and Mental Health) are derived and normalised to a scale of 0 to 100. The physical and mental component scores (PCS and MCS) are derived by multiplying each of these 8 scores by a constant, summing them and standardising against a population with a mean of 50, standard deviation of 10. A higher score represents a better quality of life. Mean changes from baseline score are presented as increases from baseline (defined as post-baseline minus baseline); larger changes indicate a better clinical condition. Mean refers to change in score at Week 24. ANCOVA = analysis of covariance, BID = twice daily, DMARD = disease modifying antirheumatic drugs, PO = orally, QD = once daily.

End point type	Secondary

End point timeframe:

Baseline and 24 weeks

End point values	Dosing Group A	Dosing Group B	Dosing Group C	Dosing Group D
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	48	57	54
Units: Units on a scale				
arithmetic mean (standard deviation)	3 (± 9.3)	3 (± 11.5)	2 (± 10)	4 (± 9.8)

Statistical analyses

Statistical analysis title	SF-36 MCS vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group A v Dosing Group D
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.568
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.95
upper limit	1.92

Statistical analysis title	SF-36 MCS vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group B v Dosing Group D
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.66
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.69
upper limit	1.38

Statistical analysis title	SF-36 MCS vs adalimumab

Statistical analysis description:

Non-responder imputation has been applied following premature withdrawal, or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

Comparison groups	Dosing Group C v Dosing Group D
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.38
upper limit	0.43

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 weeks

Adverse event reporting additional description:

For placebo treated patients time frame includes both placebo(6 weeks) and fostamatinib(18 weeks) treatment. 1 SAE occurred in these treatment arms began during the 6 week placebo treated period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	ADALIMUMAB 40mg SC
Reporting group description:	
Dosing Group D	
Reporting group title	FOSTA 100mg BID (4WKS) THEN 100mg QD
Reporting group description:	
Dosing Group C	
Reporting group title	FOSTA 100mg BID
Reporting group description:	
Dosing Group A	
Reporting group title	FOSTA 100 MG BID (4WKS) THEN 150 MG QD
Reporting group description:	
Dosing Group B	
Reporting group title	PLACEBO(6WKS) THEN FOSTA 100mgBID THEN 150mgQD-FOSTA period
Reporting group description:	
Dosing Group G	
Reporting group title	PLACEBO(6WKS) THEN FOSTA 100mgBID THEN 150mgQD-Placebo period
Reporting group description:	
Dosing Group G	
Reporting group title	PLACEBO(6WKS) THEN FOSTA 100mgBID- FOSTA Period
Reporting group description:	
Dosing Group F	
Reporting group title	PLACEBO(6WKS) THEN FOSTA 100mgBID- Placebo Period
Reporting group description:	
Dosing Group F	

Serious adverse events	ADALIMUMAB 40mg SC	FOSTA 100mg BID (4WKS) THEN 100mg QD	FOSTA 100mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 54 (7.41%)	4 / 57 (7.02%)	5 / 54 (9.26%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cardiac myxoma			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	0 / 54 (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
Multiple myeloma			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ligament injury NOS	Additional description: Rupture		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	0 / 54 (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
Concussion, unspecified			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	0 / 54 (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
Meniscus injury	Additional description: Lesion		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Essential hypertension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertensive crisis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left Bundle Branch Block			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure (NOS)	Additional description: Congestive		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	0 / 54 (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
Cor Pulmonale Acute			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	0 / 54 (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
Pericarditis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain localized	Additional description: Upper		
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	0 / 54 (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
Inguinal hernia, without mention of obstruction or gangrene			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	0 / 54 (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			
Asthma NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	0 / 54 (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 embolism			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	1 / 57 (1.75%)	0 / 54 (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
Endocrine disorders			
Hyperadrenalism			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Chronic sinusitis, unspecified			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	1 / 54 (1.85%)
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			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis, unspecified	Additional description: Chronic		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	FOSTA 100 MG BID (4WKS) THEN 150 MG QD	PLACEBO(6WKS) THEN FOSTA 100mgBID THEN 150mgQD- FOSTA period	PLACEBO(6WKS) THEN FOSTA 100mgBID THEN 150mgQD- Placebo period
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 25 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cardiac myxoma			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 25 (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
Multiple myeloma			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
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			
Ligament injury NOS	Additional description: Rupture		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 25 (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
Concussion, unspecified			

alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Meniscus injury	Additional description: Lesion		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Essential hypertension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Hypertensive crisis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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 disorders			
Angina			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Left Bundle Branch Block			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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 failure (NOS)	Additional description: Congestive		
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Cor Pulmonale Acute			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Pericarditis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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 localized	Additional description: Upper		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Inguinal hernia, without mention of obstruction or gangrene			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Respiratory, thoracic and mediastinal disorders			
Asthma NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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 embolism			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Endocrine disorders			
Hyperadrenalism			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Infections and infestations			
Chronic sinusitis, unspecified			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Gastroenteritis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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
Pyelonephritis, unspecified	Additional description: Chronic		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (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	PLACEBO(6WKS) THEN FOSTA 100mgBID- FOSTA Period	PLACEBO(6WKS) THEN FOSTA 100mgBID- Placebo Period	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cardiac myxoma			
alternative dictionary used:			

MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple myeloma			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ligament injury NOS	Additional description: Rupture		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion, unspecified			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury	Additional description: Lesion		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Essential hypertension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Bundle Branch Block			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure (NOS)	Additional description: Congestive		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor Pulmonale Acute			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain localized	Additional description: Upper		
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, without mention of obstruction or gangrene			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperadrenalism			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Chronic sinusitis, unspecified			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis, unspecified	Additional description: Chronic		
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ADALIMUMAB 40mg SC	FOSTA 100mg BID (4WKS) THEN 100mg QD	FOSTA 100mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 54 (27.78%)	19 / 57 (33.33%)	30 / 54 (55.56%)
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	2 / 57 (3.51%)	3 / 54 (5.56%)
occurrences (all)	1	2	3
Hepatic enzyme increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	2 / 57 (3.51%)	3 / 54 (5.56%)
occurrences (all)	1	2	3
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	5 / 54 (9.26%)	5 / 57 (8.77%)	7 / 54 (12.96%)
occurrences (all)	5	5	7
Blood and lymphatic system disorders			
Leukopenia NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Neutropenia			
alternative dictionary used:			

MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Gastrointestinal disorders			
Diarrhoea NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	12 / 57 (21.05%)	9 / 54 (16.67%)
occurrences (all)	1	12	9
Dyspepsia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	3 / 54 (5.56%)	1 / 57 (1.75%)	0 / 54 (0.00%)
occurrences (all)	3	1	0
Nausea			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 54 (1.85%)	0 / 57 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Vomiting alone			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Nephrolithiasis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 54 (3.70%)	0 / 57 (0.00%)	3 / 54 (5.56%)
occurrences (all)	2	0	3
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1

Influenza			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 54 (0.00%)	0 / 57 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Nasopharyngitis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	4 / 54 (7.41%)	1 / 57 (1.75%)	1 / 54 (1.85%)
occurrences (all)	4	1	1

Non-serious adverse events	FOSTA 100 MG BID (4WKS) THEN 150 MG QD	PLACEBO(6WKS) THEN FOSTA 100mgBID THEN 150mgQD- FOSTA period	PLACEBO(6WKS) THEN FOSTA 100mgBID THEN 150mgQD- Placebo period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 48 (41.67%)	13 / 25 (52.00%)	1 / 25 (4.00%)
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
Hepatic enzyme increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	1 / 48 (2.08%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	3 / 48 (6.25%)	7 / 25 (28.00%)	0 / 25 (0.00%)
occurrences (all)	3	7	0
Blood and lymphatic system disorders			
Leukopenia NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
alternative dictionary used: MedDRA 15.1			

subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	13 / 48 (27.08%)	4 / 25 (16.00%)	0 / 25 (0.00%)
occurrences (all)	13	4	0
Dyspepsia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nausea			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 48 (4.17%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Vomiting alone			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 48 (4.17%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	2	1	0
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Influenza			

alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 48 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 48 (4.17%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences (all)	2	1	0

Non-serious adverse events	PLACEBO(6WKS) THEN FOSTA 100mgBID- FOSTA Period	PLACEBO(6WKS) THEN FOSTA 100mgBID- Placebo Period	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 27 (40.74%)	3 / 27 (11.11%)	
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Hepatic enzyme increased			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	4 / 27 (14.81%)	0 / 27 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Leukopenia NOS			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
alternative dictionary used: MedDRA 15.1			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			

Diarrhoea NOS alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 3 / 27 (11.11%) 3	 0 / 27 (0.00%) 0	
Dyspepsia alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 0 / 27 (0.00%) 0	
Nausea alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 2 / 27 (7.41%) 2	 0 / 27 (0.00%) 0	
Vomiting alone alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 1 / 27 (3.70%) 1	 0 / 27 (0.00%) 0	
Renal and urinary disorders Nephrolithiasis alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 0 / 27 (0.00%) 0	
Musculoskeletal and connective tissue disorders Rheumatoid arthritis alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 4 / 27 (14.81%) 4	 0 / 27 (0.00%) 0	
Infections and infestations Bronchitis alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 0 / 27 (0.00%) 0	
Influenza alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 2 / 27 (7.41%) 2	

Nasopharyngitis alternative dictionary used: MedDRA 15.1 subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0	 1 / 27 (3.70%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2011	Added an imaging sub-study. This was reported separately. Restrictions for males wishing to father a child or donate sperm were removed.
28 September 2011	Patient discontinuing treatment were to be contacted every 12 weeks up to week 24 to collect follow-up safety outcomes data. All week 24 assessments were to be completed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported