ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 02/27/2014

ClinicalTrials.gov ID: NCT01197755

Study Identification

Unique Protocol ID:	D4300C00003
Brief Title:	Evaluation of Effectiveness of Two Dosing Regimens of Fostamatinib Compared to Placebo in Patients With Rheumatoid Arthritis (RA) Who Are Taking Methotrexate and Have Had Inadequate Response to Single TNF-alpha Antagonist (OSKIRA - 3)
Official Title:	(OSKIRA-3): A Phase III, Multi-centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study of Two Dosing Regimens of Fostamatinib Disodium in Rheumatoid Arthritis Patients With Inadequate Response to a TNF-alpha Antagonist
Secondary IDs:	2010-020745-27 [EudraCT Number]

Study Status

Record Verification:	February 2014
Overall Status:	Completed
Study Start:	September 2010
Primary Completion:	February 2013 [Actual]
Study Completion:	February 2013 [Actual]

Sponsor/Collaborators

Sponsor:	AstraZeneca
Responsible Party:	Sponsor
Collaborators:	

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? Yes Delayed Posting? No
IND/IDE Protocol?:	Yes
IND/IDE Information:	Grantor: CDER IND/IDE Number: 69197 Serial Number: Has Expanded Access? No
Review Board:	Approval Status: Board Name: Board Affiliation: Phone: Email:
Data Monitoring?:	Yes
Plan to Share Data?:	
Oversight Authorities:	Argentina: National Administration of Drugs, Food & Medical Technology (ANMAT) Australia: Department of Health and Ageing Therapeutic Goods Administration Belgium: Federal Agency for Medicinal Products and Health Products Brazil: National Health Surveillance Agency Canada: Health Canada Czech Republic: State Institute for Drug Control France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Germany: Federal Institute for Drugs and Medical Devices Hungary: National Institute of Pharmacy Israel: Ministry of Health Italy: National Monitoring Centre for Clinical Trials - Ministry of Health Mexico: Federal Commission for Sanitary Risks Protection Portugal: National Pharmacy and Medicines Institute South Africa: Medicines Control Council Spain: Agencia Española de Medicamentos y Productos Sanitarios United Kingdom: Medicines and Healthcare Products Regulatory Agency United States: Food and Drug Administration

Study Description

Brief Summary:	The purpose of the study is to evaluate the effectiveness of two dosing regimens of fostamatinib compared to placebo, in patients with rheumatoid arthritis (RA) who are taking methotrexate and have had an inadequate response to a single TNF-alpha antagonist. The study will last for approximately six months.
Detailed Description:	Sub-study: Full title: Optional Genetic Research

Date: 18 June 2010

Version: 1

Objectives: To collect and store, with appropriate consent ,DNA samples for future exploratory research into genes/genetic variation that may influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib disodium and/or methotrexate; and/or susceptibility to, progression of and prognosis of RA

Conditions

Conditions: Rheumatoid Arthritis

Keywords: Rheumatoid Arthritis

Study Design

Study Type: Interventional

Primary Purpose: Treatment

Study Phase: Phase 3

Intervention Model: Parallel Assignment

Number of Arms: 3

Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)

Allocation: Randomized

Endpoint Classification: Safety/Efficacy Study

Enrollment: 323 [Actual]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Dosing Regimen A Oral Treatment	Drug: fostamatinib fostamatinib 100 mg twice daily
Experimental: Dosing Regimen B Oral Treatment	Drug: fostamatinib fostamatinib 100 mg twice daily/150 mg once daily
Placebo Comparator: Dosing Regimen C Oral Treatment	Drug: placebo Placebo twice daily

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age: 18 Years

Maximum Age:

Gender: Both

Accepts Healthy Volunteers?: No

Criteria: Inclusion Criteria:

- Active rheumatoid arthritis (RA) diagnosed after the age of 16
- Currently taking methotrexate
- 6 or more swollen joints and 6 or more tender/painful joints (from 28 joint count) and either Erythrocyte Sedimentation Rate (ESR) blood result of 28mm/h or more, or C-Reactive Protein (CRP) blood result of 10mg/L or more
- At least one of the following: documented history of positive rheumatoid factor (blood test), current presence of rheumatoid factor (blood test), radiographic erosion within 12months prior to study enrolment, presence of serum anti-cyclic citrullinated peptide antibodies (blood test)

Exclusion Criteria:

- Females who are pregnant or breast feeding
- Poorly controlled hypertension
- Liver disease or significant liver function test abnormalities
- Certain inflammatory conditions (other than rheumatoid arthritis), connective tissue diseases or chronic pain disorders
- Recent or significant cardiovascular disease
- Significant active or recent infection including tuberculosis
- Previous failure to respond to anakinra or previous treatment with biological agent (other than TNF alpha antagonists including rituximab, abatacept and tocilizumab)
- Severe renal impairment
- Neutropenia

Contacts/Locations

Study Officials: Neil MacKillop, MD PhD
Study Director
AstraZeneca

Locations: Argentina
Research Site
Buenos Aires, Caba, Argentina

Research Site
Cordoba, CRD, Argentina

Research Site
Rosario, Santa Fe, Argentina

Research Site
San Miguel de Tucuman, TUC, Argentina

Research Site
Buenos Aires, Argentina

Research Site
Ciudad de Buenos Aires, Argentina

Research Site
Quilmes, Argentina

Research Site
Rosario, Argentina

Research Site
San Juan, Argentina

Research Site
San Miguel de Tucuman, Argentina

Belgium
Research Site
Brussels, Belgium, Belgium

Research Site
Gent, Belgium, Belgium

Research Site
Liege, Belgium, Belgium

Research Site
Yvoir, Belgium

Brazil
Research Site
Porto Alegre, Brasil, Brazil

Research Site
Goiania, GO, Brazil

Research Site
Curitiba, PR, Brazil

Research Site
Sao Paulo, SP, Brazil

Canada, Newfoundland and Labrador
Research Site
St John's, Newfoundland and Labrador, Canada

Canada, Ontario
Research Site
Mississauga, Ontario, Canada

Research Site
Toronto, Ontario, Canada

Canada, Quebec
Research Site
Pointe-claire, Quebec, Canada

Research Site
Rimouski, Quebec, Canada

Czech Republic
Research Site
Bruntal, Czech Republic

Research Site
Ceske Budejovice, Czech Republic

Research Site
Hlucin, Czech Republic

Research Site
Ostrava-trebovice, Czech Republic

Research Site
Praha, Czech Republic

Research Site
Praha 2, Czech Republic

Research Site
Zlin, Czech Republic

France
Research Site
Orleans Cedex 1, France

Germany
Research Site
Hamburg, HH, Germany

Research Site
Aachen, Nordrhein Westfalen, Germany

Research Site
Leipzig, SN, Germany

Research Site
Erlangen, Germany

Research Site
Frankfurt, Germany

Research Site
Hamburg, Germany

Research Site
Heidelberg, Germany

Research Site
Muenchen, Germany

Hungary
Research Site
Budapest, Hungary

Israel
Research Site
Ashkelon, Israel

Research Site
Haifa, Israel

Research Site
Kfar Saba, Israel

Research Site
Ramat Gan, Israel

Research Site
Tel-hashomer, Israel

Italy
Research Site
Jesi, AN, Italy

Research Site
Ferrara, FE, Italy

Mexico
Research Site
Chihuahua, Chihuahua, Mexico

Research Site
Obrergon, SON, Mexico

Research Site
DF, Mexico

Research Site
Monterrey, Mexico

Research Site
Saltillo, Mexico

Portugal
Research Site
Lisboa, Portugal

Research Site
Porto, Portugal

South Africa
Research Site
Cape Town, South Africa

Research Site
Pretoria, South Africa

Research Site
Stellenbosch, South Africa

Spain
Research Site
Barcelona, Spain

United Kingdom
Research Site
Reading, Berkshire, United Kingdom

Research Site
Warrington, Cheshire, United Kingdom

Research Site
Maidstone, Kent, United Kingdom

Research Site
Eastbourne, Sussex, United Kingdom

Research Site
Cambridge, United Kingdom

Research Site
Christchurch, United Kingdom

Research Site
Ipswich, United Kingdom

Research Site
London, United Kingdom

Research Site
Nottingham, United Kingdom

Research Site
Westcliff-on-the Sea, United Kingdom

Research Site
Wirral, United Kingdom

United States, Alabama
Research Site
Anniston, Alabama, United States

Research Site
Huntsville, Alabama, United States

Research Site
Tuscaloosa, Alabama, United States

United States, Arkansas
Research Site

Hot Springs, Arkansas, United States

United States, Arizona
Research Site
Mesa, Arizona, United States

Research Site
Scottsdale, Arizona, United States

United States, California
Research Site
La Jolla, California, United States

Research Site
Long Beach, California, United States

Research Site
Santa Maria, California, United States

Research Site
Torrance, California, United States

Research Site
Tustin, California, United States

United States, Colorado
Research Site
Colorado Springs, Colorado, United States

United States, Connecticut
Research Site
Bridgeport, Connecticut, United States

Research Site
Trumbull, Connecticut, United States

United States, Delaware
Research Site
Lewes, Delaware, United States

United States, Florida
Research Site
Jacksonville, Florida, United States

Research Site
Ocala, Florida, United States

Research Site
Orlando, Florida, United States

Research Site
Tampa, Florida, United States

Research Site
Venice, Florida, United States

Research Site
Zephyr Hills, Florida, United States

United States, Georgia
Research Site
Atlanta, Georgia, United States

Research Site
Canton, Georgia, United States

United States, Iowa
Research Site
Cedar Rapids, Iowa, United States

United States, Idaho
Research Site
Idaho Falls, Idaho, United States

United States, Kentucky
Research Site
Bowling Green, Kentucky, United States

Research Site
Elizabethtown, Kentucky, United States

United States, Massachusetts
Research Site
Fall River, Massachusetts, United States

Research Site
Worcester, Massachusetts, United States

United States, Maryland
Research Site
Crofton, Maryland, United States

United States, Michigan

Research Site
Lansing, Michigan, United States

United States, Missouri
Research Site
Florissant, Missouri, United States

Research Site
Richmond Heights, Missouri, United States

United States, Mississippi
Research Site
Flowood, Mississippi, United States

United States, North Carolina
Research Site
Charlotte, North Carolina, United States

Research Site
Durham, North Carolina, United States

Research Site
Greensboro, North Carolina, United States

United States, New Mexico
Research Site
Las Cruces, New Mexico, United States

United States, New York
Research Site
Albany, New York, United States

Research Site
Brooklyn, New York, United States

Research Site
Olean, New York, United States

Research Site
Roslyn, New York, United States

Research Site
Smithtown, New York, United States

United States, Ohio
Research Site

Dayton, Ohio, United States

Research Site
Mayfield Village, Ohio, United States

United States, Oregon
Research Site
Lake Oswego, Oregon, United States

United States, Pennsylvania
Research Site
Duncansville, Pennsylvania, United States

Research Site
Philadelphia, Pennsylvania, United States

Research Site
Pittsburgh, Pennsylvania, United States

Research Site
West Reading, Pennsylvania, United States

United States, South Carolina
Research Site
Charleston, South Carolina, United States

United States, Tennessee
Research Site
Hixson, Tennessee, United States

Research Site
Memphis, Tennessee, United States

Research Site
Nashville, Tennessee, United States

United States, Texas
Research Site
Austin, Texas, United States

Research Site
Dallas, Texas, United States

Research Site
Houston, Texas, United States

Research Site
San Antonio, Texas, United States

United States, Washington
Research Site
Tacoma, Washington, United States

United States, Texas
Research Site
Amarillo, Texas, United States

United States, Florida
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Brandon, Florida, United States

United States, Illinois
Research Site
Decatur, Illinois, United States

United States, California
Research Site
Glendale, California, United States

United States, South Carolina
Research Site
Greenville, South Carolina, United States

United States, California
Research Site
Palo Alto, California, United States

United States, New York
Research Site
Rochester, New York, United States

United States, California
Research Site
Upland, California, United States

References

Citations:

Links: URL: http://www.oskirastudy.com
Description Aimed at US participants

URL: http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_MED_6111&studyid=419&fil...
Description Related Info

URL: http://filehosting.pharmacm.com/DownloadService.ashx?client=CTR_MED_6111&studyid=1201&fi...
Description Related Info

Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	A total of 638 patients were enrolled: 105, 108 & 110 were randomised to Groups A, B & C respectively (105, 108 & 109 received at least 1 dose of investigational product).
Pre-Assignment Details	A total of 315 patients failed screening.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Overall Study

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Started	105 [1]	108 [1]	109 [1]
Randomised But Did Not Receive Treatment	0	0	1 [2]
Completed	67 [3]	65 [3]	55 [3]
Not Completed	38	43	54
Adverse Event	8	10	10
Study-specific discontinuation criteria	2	1	0
Entered the long-term extension study	18	21	35

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Lack of therapeutic response	0	7	4
Severe non-compliance to the protocol	2	1	2
Withdrawal by Subject	1	0	0
Lost to Follow-up	0	0	1
eg, change in circumstances	7	3	2

[1] Patients who received treatment
[2] Severe non-compliance to the protocol
[3] Number of patients who completed treatment includes patients who had a dose reduction.

Baseline Characteristics

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Baseline Measures

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO	Total
Number of Participants	105	108	109	322
Age, Continuous [units: years] Mean (Standard Deviation)	54 (11.9)	51 (12.0)	53 (13.0)	53 (12.3)
Gender, Male/Female [units: Participants]				
Female	89	87	85	261
Male	16	21	24	61

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO	Total
Race/Ethnicity, Customized [units: Participants]				
White	86	92	91	269
Black or African American	9	5	9	23
Asian	0	1	0	1
American Indian or Alaska Native	1	4	1	6
Indian or Pakistani	2	0	1	3
Other	7	6	7	20

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Proportion of Patients Achieving ACR20 at Week 24, Comparison Between Fostamatinib and Placebo
Measure 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 C-Reactive Protein) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, PO = orally, QD = once daily.
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
Proportion of Patients Achieving ACR20 at Week 24, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	36.2	27.8	21.1

Statistical Analysis 1 for Proportion of Patients Achieving ACR20 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.004
	Comments	Week 24
	Method	Mantel Haenszel
	Comments	Treatment difference in proportion of responders at Week 24 with a Mantel-Haenszel approach stratified by pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.17
	Confidence Interval	(2-Sided) 95% 0.05 to 0.28
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Patients Achieving ACR20 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.168
	Comments	Week 24
	Method	Mantel Haenszel
	Comments	Treatment difference in proportion of responders at Week 24 with a Mantel-Haenszel approach stratified by pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.07
	Confidence Interval	(2-Sided) 95% -0.03 to 0.18
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving ACR20 at Week 1, Comparison Between Fostamatinib and Placebo
Measure 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 C-Reactive Protein) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, PO = orally, QD = once daily.
Time Frame	1 week
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
PLACEBO PO	Dosing Group C
Dosing Group A and B Combined PO	Fostamatinib 100 mg BID (combined)

Measured Values

	PLACEBO PO	Dosing Group A and B Combined PO
Number of Participants Analyzed	109	213
Proportion of Patients Achieving ACR20 at Week 1, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	3.7	25.4

Statistical Analysis 1 for Proportion of Patients Achieving ACR20 at Week 1, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	PLACEBO PO, Dosing Group A and B Combined PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Mantel Haenszel
	Comments	95% confidence intervals and p-values are calculated using a Mantel-Haenszel approach stratified by pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.22
	Confidence Interval	(2-Sided) 95% 0.16 to 0.29
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving ACR50 at Week 24, Comparison Between Fostamatinib and Placebo
Measure 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 C-Reactive Protein) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, PO = orally, QD = once daily.

Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
Proportion of Patients Achieving ACR50 at Week 24, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	18.1	13.0	8.3

Statistical Analysis 1 for Proportion of Patients Achieving ACR50 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.014
	Comments	[Not specified]
	Method	Mantel Haenszel

	Comments	95% confidence intervals and p-values are calculated using a Mantel-Haenszel approach stratified by pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.10
	Confidence Interval	(2-Sided) 95% 0.02 to 0.19
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Patients Achieving ACR50 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.180
	Comments	Nominal p-value presented for Group B comparison. Formal statistical testing could not be carried out due to the predefined multiplicity procedure (primary variable comparison of Group B versus Group C was non-significant).
	Method	Mantel Haenszel
	Comments	95% confidence intervals and p-values are calculated using a Mantel-Haenszel approach stratified by pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.05
	Confidence Interval	(2-Sided) 95% -0.02 to 0.12
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving ACR70 at Week 24, Comparison Between Fostamatinib and Placebo

Measure 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 C-Reactive Protein) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, PO = orally, QD = once daily.
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
Proportion of Patients Achieving ACR70 at Week 24, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	14.3	2.8	2.8

Statistical Analysis 1 for Proportion of Patients Achieving ACR70 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	Mantel Haenszel
	Comments	95% confidence intervals and p-values are calculated using a Mantel-Haenszel approach stratified by pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.12
	Confidence Interval	(2-Sided) 95% 0.06 to 0.19
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Patients Achieving ACR70 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.891
	Comments	Nominal p-value presented for Group B comparison. Formal statistical testing could not be carried out due to the predefined multiplicity procedure (primary variable comparison of Group B versus Group C was non-significant).
	Method	Mantel Haenszel
	Comments	95% confidence intervals and p-values are calculated using a Mantel-Haenszel approach stratified by pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.00
	Confidence Interval	(2-Sided) 95% -0.04 to 0.04
	Estimation Comments	[Not specified]

5. Secondary Outcome Measure:

Measure Title	ACRn - Comparison Between Fostamatinib and Placebo at Week 24
Measure 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 C-Reactive Protein) or the physician or patient's own assessments 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. Mean refers to change at Week 24. BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, PO = orally, QD = once a day.
Time Frame	Baseline and 24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
ACRn - Comparison Between Fostamatinib and Placebo at Week 24 [units: Percentage improvement from baseline] Mean (Standard Deviation)	16.25 (36.994)	13.00 (24.718)	5.87 (26.726)

Statistical Analysis 1 for ACRn - Comparison Between Fostamatinib and Placebo at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO

	Comments	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.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.010
	Comments	Nominal p-value presented for treatment comparison. ACRn was not formally tested within the predefined multiplicity procedure. As this is a non-parametric test p-values alone are presented rather than an estimated treatment difference.
	Method	Other [Van Elteren]
	Comments	P-values are estimated using the Van Elteren test stratified by pooled country.

Method of Estimation	Estimation Parameter	
	Estimated Value	
	Estimation Comments	[Not specified]

Statistical Analysis 2 for ACRn - Comparison Between Fostamatinib and Placebo at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	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.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.019
	Comments	Nominal p-value presented for treatment comparison. ACRn was not formally tested within the predefined multiplicity procedure. As this is a non-parametric test p-values alone are presented rather than an estimated treatment difference.
	Method	Other [Van Elteren]
	Comments	P-values are estimated using the Van Elteren test stratified by pooled country.

6. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving DAS28-CRP <2.6 at Week 24, Comparison Between Fostamatinib and Placebo
Measure 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 patients' own assessment. Scores can take any positive value with a lower value indicating a better clinical condition. A DAS28-CRP score of <2.6 is indicative of remission of RA symptoms. BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, OR = odds ratio, PO = orally, QD = once daily.
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
Proportion of Patients Achieving DAS28-CRP <2.6 at Week 24, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	11.4	7.4	3.7

Statistical Analysis 1 for Proportion of Patients Achieving DAS28-CRP <2.6 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.023
	Comments	[Not specified]
	Method	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals are calculated using Logistic Regression with treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	4.1
	Confidence Interval	(2-Sided) 95% 1.21 to 13.91
	Estimation Comments	An odds ratio of >1 indicates a benefit towards fostamatinib.

Statistical Analysis 2 for Proportion of Patients Achieving DAS28-CRP <2.6 at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.197
	Comments	Nominal p-value presented for Group B comparison. Formal statistical testing could not be carried out due to the predefined multiplicity procedure (primary variable comparison of Group B versus Group C was non-significant).
	Method	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals are calculated using Logistic Regression with treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.3

	Confidence Interval	(2-Sided) 95% 0.65 to 8.23
	Estimation Comments	An odds ratio of >1 indicates a benefit towards fostamatinib.

7. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving DAS28-CRP <=3.2 at Week 12, Comparison Between Fostamatinib and Placebo
Measure 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 patients' own assessment. Scores can take any positive value with a lower value indicating a better clinical condition. A DAS28-CRP score of <=3.2 indicates low disease activity. BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, OR = odds ratio, PO = orally, QD = once daily.
Time Frame	12 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
Proportion of Patients Achieving DAS28-CRP <=3.2 at Week 12, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	18.1	20.4	5.5

Statistical Analysis 1 for Proportion of Patients Achieving DAS28-CRP <=3.2 at Week 12, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.005
	Comments	[Not specified]
	Method	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals are calculated using Logistic Regression with treatment and pooled country as factors.
Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	4.1
	Confidence Interval	(2-Sided) 95% 1.54 to 10.92
	Estimation Comments	An odds ratio of >1 indicates a benefit towards fostamatinib.

Statistical Analysis 2 for Proportion of Patients Achieving DAS28-CRP <=3.2 at Week 12, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	0.002
	Comments	Nominal p-value presented for Group B comparison. Formal statistical testing could not be carried out due to the predefined multiplicity procedure (primary variable comparison of Group B versus Group C was non-significant).
	Method	Regression, Logistic

	Comments	Odds ratio and 95% confidence intervals are calculated using Logistic Regression with treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	4.7
	Confidence Interval	(2-Sided) 95% 1.79 to 12.30
	Estimation Comments	An odds ratio of >1 indicates a benefit towards fostamatinib.

8. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving DAS28-CRP EULAR Response at Week 24, Comparison Between Fostamatinib and Placebo
Measure Description	Change from baseline in DAS28-CRP at Week 24 was categorised using the European League Against Rheumatism (EULAR) response criteria. BID = twice daily, CRP = C-reactive protein, 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.
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
Proportion of Patients Achieving DAS28-CRP EULAR Response at Week 24, Comparison Between Fostamatinib and Placebo			

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
[units: Percentage of responders]			
No response	46.7	54.6	67.9
Moderate response	29.5	34.3	26.6
Good response	23.8	11.1	5.5

Statistical Analysis 1 for Proportion of Patients Achieving DAS28-CRP EULAR Response at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	<0.001
	Comments	Nominal p value only. This was not included in the pre-defined multiplicity testing procedure.
	Method	Other [Proportional odds model]
	Comments	No response, moderate response and good response are included in the proportional odds model with treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	3.27
	Confidence Interval	(2-Sided) 95% 1.86 to 5.76
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

Statistical Analysis 2 for Proportion of Patients Achieving DAS28-CRP EULAR Response at Week 24, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data

	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.028
	Comments	Nominal p-value only. This was not included in the pre-defined multiplicity testing procedure.
	Method	Other [Proportional odds model]
	Comments	No response, moderate response and good response are included in the proportional odds model with treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.89
	Confidence Interval	(2-Sided) 95% 1.07 to 3.31
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

9. Secondary Outcome Measure:

Measure Title	Proportion of Patients With a HAQ-DI Response at Week 24 - Comparison Between Fostamatinib and Placebo
Measure 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, hygeine, 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. A HAQ-DI response is a reduction from baseline in HAQ-DI greater than or equal to the minimally important difference (0.22). BID = twice daily, DMARD = disease-modifying anti-rheumatic drug, OR = odds ratio, PO = orally, QD = once a day.
Time Frame	24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A

	Description
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	105	108	109
Proportion of Patients With a HAQ-DI Response at Week 24 - Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	41.9	31.5	23.9

Statistical Analysis 1 for Proportion of Patients With a HAQ-DI Response at Week 24 - Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	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.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.004
	Comments	[Not specified]
	Method	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals are calculated using logistic regression with treatment and pooled country as factors

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.4
	Confidence Interval	(2-Sided) 95% 1.33 to 4.45
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

Statistical Analysis 2 for Proportion of Patients With a HAQ-DI Response at Week 24 - Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	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.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.186
	Comments	Nominal p-value presented for Group B comparison. Formal statistical testing could not be carried out due to the predefined multiplicity procedure (primary variable comparison of Group B versus Group C was non-significant).
	Method	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals are calculated using logistic regression with treatment and pooled country as factors

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	1.5
	Confidence Interval	(2-Sided) 95% 0.82 to 2.79
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

10. Secondary Outcome Measure:

Measure Title	Change From Baseline to Week 24 in mTSS Score, Comparison Between Fostamatinib and Placebo
Measure Description	mTSS: modified total sharp score, a measure of structural progression based upon X-rays. Hand and foot joints are scored for eroisions and joint space narrowing and the results summed to give a value between 0 and 488. A higher value represents more serious progression of the disease. After disregarding ineligible records, patients with 2 or more non-missing values had missing data imputed via linear extrapolation/interpolation methods. Patients with only 1 result were excluded from the analysis. ANCOVA = Analysis of covariance, BID = twice daily, IP = investigational product, PO = orally, QD = once a day.
Time Frame	Baseline and 24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes patients who received at least 1 dose of IP. Patients were analysed by randomised treatment in accordance with the intention to treat principle. Measurements at 2 timepoints are required for a patient to be included in the analysis; therefore patients with only 1 result have been excluded from the analysis population.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	81	87	88
Change From Baseline to Week 24 in mTSS Score, Comparison Between Fostamatinib and Placebo [units: Units on a scale] Mean (Standard Deviation)	0.80 (2.636)	0.18 (3.455)	0.84 (1.989)

Statistical Analysis 1 for Change From Baseline to Week 24 in mTSS Score, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.729
	Comments	Nominal p-value only. This was not included in the pre-defined multiplicity procedure. As this is a non-parametric test p-values alone are presented rather than an estimated treatment difference.
	Method	ANCOVA
	Comments	This was performed on the ranks of the change from baseline, by pooled country, including a term for the ranks of the baseline score as covariate.

Statistical Analysis 2 for Change From Baseline to Week 24 in mTSS Score, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	[Not specified]
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.019
	Comments	Nominal p-value only. This was not included in the pre-defined multiplicity procedure. As this is a non-parametric test p-values alone are presented rather than an estimated treatment difference.
	Method	ANCOVA
	Comments	This was performed on the ranks of the change from baseline, by pooled country, including a term for the ranks of the baseline score as covariate.

11. Secondary Outcome Measure:

Measure Title	SF-36 - Comparison of the Change in PCS From Baseline Between Fostamatinib and Placebo at Week 24
Measure 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 antirheumatic drugs, PO = orally, QD = once daily
Time Frame	Baseline and 24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A

	Description
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	104	108	109
SF-36 - Comparison of the Change in PCS From Baseline Between Fostamatinib and Placebo at Week 24 [units: Units on a scale] Mean (Standard Deviation)	5 (8.3)	4 (7.4)	2 (6.2)

Statistical Analysis 1 for SF-36 - Comparison of the Change in PCS From Baseline Between Fostamatinib and Placebo at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.009
	Comments	[Not specified]
	Method	ANCOVA
	Comments	Improvement from baseline, including terms for baseline as a continuous covariate and treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	2.60
	Confidence Interval	(2-Sided) 95% 0.65 to 4.56

	Estimation Comments	[Not specified]

Statistical Analysis 2 for SF-36 - Comparison of the Change in PCS From Baseline Between Fostamatinib and Placebo at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.118
	Comments	[Not specified]
	Method	ANCOVA
	Comments	Improvement from baseline, including terms for baseline as a continuous covariate and treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	1.53
	Confidence Interval	(2-Sided) 95% -0.39 to 3.44
	Estimation Comments	[Not specified]

12. Secondary Outcome Measure:

Measure Title	SF-36 - Comparison of the Change in MCS From Baseline Between Fostamatinib and Placebo at Week 24
Measure 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.
Time Frame	Baseline and 24 weeks
Safety Issue?	No

Analysis Population Description

The full analysis set includes those patients who received at least 1 dose of investigational product. Patients were analysed by randomised treatment in accordance with the intention to treat principle.

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO PO
Number of Participants Analyzed	104	108	109
SF-36 - Comparison of the Change in MCS From Baseline Between Fostamatinib and Placebo at Week 24 [units: Units on a scale] Mean (Standard Deviation)	2 (8.6)	2 (7.0)	2 (7.3)

Statistical Analysis 1 for SF-36 - Comparison of the Change in MCS From Baseline Between Fostamatinib and Placebo at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.487
	Comments	[Not specified]
	Method	ANCOVA
	Comments	Improvement from baseline, including terms for baseline as a continuous covariate and treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	0.67
	Confidence Interval	(2-Sided) 95% -1.23 to 2.58
	Estimation Comments	[Not specified]

Statistical Analysis 2 for SF-36 - Comparison of the Change in MCS From Baseline Between Fostamatinib and Placebo at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of methotrexate or any DMARD initiation, or for 8 weeks following receipt of any parenteral steroids, or for patients with no post baseline data.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.516
	Comments	[Not specified]
	Method	ANCOVA
	Comments	Improvement from baseline, including terms for baseline as a continuous covariate and treatment and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	0.62
	Confidence Interval	(2-Sided) 95% -1.26 to 2.51
	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	[Not specified]

Reporting Groups

	Description
FOSTA 100 MG BID PO	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	Dosing Group B
PLACEBO PO	Dosing Group C

Serious Adverse Events

	FOSTA 100 MG BID PO		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO		PLACEBO PO	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	7/105 (6.67%)		7/108 (6.48%)		6/109 (5.5%)	
Blood and lymphatic system disorders						
ANAEMIA [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
Cardiac disorders						
ACUTE CORONARY SYNDROME [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
ARTERIOSCLEROSIS CORONARY ARTERY [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
CARDIAC FAILURE CONGESTIVE [A] †	0/105 (0%)	0	1/108 (0.93%)	1	0/109 (0%)	0
CARDIO-RESPIRATORY ARREST [A] †	0/105 (0%)	0	1/108 (0.93%)	1	0/109 (0%)	0
CORONARY ARTERY OCCLUSION [A] †	0/105 (0%)	0	1/108 (0.93%)	1	0/109 (0%)	0
Gastrointestinal disorders						
CROHN'S DISEASE [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
DIARRHOEA [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
GASTRIC ULCER [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
GASTRITIS [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
VOMITING [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
General disorders						

	FOSTA 100 MG BID PO		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO		PLACEBO PO	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
NON-CARDIAC CHEST PAIN [A] †	1/105 (0.95%)	1	1/108 (0.93%)	1	0/109 (0%)	0
Hepatobiliary disorders						
CHOLECYSTITIS [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
Infections and infestations						
DIVERTICULITIS [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
ESCHERICHIA URINARY TRACT INFECTION [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
GASTROENTERITIS [A] †	1/105 (0.95%)	1	2/108 (1.85%)	2	0/109 (0%)	0
GASTROENTERITIS BACTERIAL [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
HERPES PHARYNGITIS [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	2
OROPHARYNGEAL CANDIDIASIS [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
Metabolism and nutrition disorders						
DIABETES MELLITUS [A] †	0/105 (0%)	0	0/108 (0%)	0	1/109 (0.92%)	1
HYPOKALAEMIA [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
HYPONATRAEMIA [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
RENAL CELL CARCINOMA [A] †	0/105 (0%)	0	1/108 (0.93%)	1	0/109 (0%)	0
Nervous system disorders						
SYNCOPE [A] †	0/105 (0%)	0	1/108 (0.93%)	1	0/109 (0%)	0
TRANSIENT GLOBAL AMNESIA [A] †	1/105 (0.95%)	1	0/108 (0%)	0	0/109 (0%)	0

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.1

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	FOSTA 100 MG BID PO		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO		PLACEBO PO	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	51/105 (48.57%)		49/108 (45.37%)		46/109 (42.2%)	
Gastrointestinal disorders						
DIARRHOEA [A] †	21/105 (20%)	23	29/108 (26.85%)	31	7/109 (6.42%)	8
FLATULENCE [A] †	6/105 (5.71%)	7	2/108 (1.85%)	2	4/109 (3.67%)	4
NAUSEA [A] †	4/105 (3.81%)	5	7/108 (6.48%)	8	9/109 (8.26%)	9
VOMITING [A] †	1/105 (0.95%)	1	6/108 (5.56%)	6	4/109 (3.67%)	4
General disorders						
FATIGUE [A] †	0/105 (0%)	0	0/108 (0%)	0	6/109 (5.5%)	6
Infections and infestations						
NASOPHARYNGITIS [A] †	6/105 (5.71%)	6	4/108 (3.7%)	5	4/109 (3.67%)	4
UPPER RESPIRATORY TRACT INFECTION [A] †	6/105 (5.71%)	7	2/108 (1.85%)	2	1/109 (0.92%)	1
Musculoskeletal and connective tissue disorders						
ARTHRALGIA [A] †	6/105 (5.71%)	6	0/108 (0%)	0	5/109 (4.59%)	5
RHEUMATOID ARTHRITIS [A] †	4/105 (3.81%)	5	6/108 (5.56%)	9	11/109 (10.09%)	11
Nervous system disorders						
DIZZINESS [A] †	7/105 (6.67%)	9	6/108 (5.56%)	6	2/109 (1.83%)	2
HEADACHE [A] †	8/105 (7.62%)	8	9/108 (8.33%)	9	11/109 (10.09%)	12
Vascular disorders						

	FOSTA 100 MG BID PO		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO		PLACEBO PO	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
HYPERTENSION [A] †	14/105 (13.33%)	15	15/108 (13.89%)	15	9/109 (8.26%)	11

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA 15.1

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There is NOT an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

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