ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 03/13/2014

ClinicalTrials.gov ID: NCT01197534

Study Identification

Unique Protocol ID:	D4300C00002
Brief Title:	Evaluation of Effectiveness of Two Dosing Regimens of Fostamatinib Compared to Placebo in Patients With Rheumatoid Arthritis (RA) Who Are Taking Disease Modifying Anti-rheumatic Drug (DMARD) But Not Responding. (OSKIRA - 2)
Official Title:	(OSKIRA-2): 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 an Inadequate Response to DMARDs
Secondary IDs:	2010-020744-35 [EudraCT Number]

Study Status

Record Verification:	March 2014
Overall Status:	Completed
Study Start:	September 2010
Primary Completion:	March 2013 [Actual]
Study Completion:	March 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:	Canada: Health Canada United States: Food and Drug Administration Czech Republic: State Institute for Drug Control Germany: Federal Institute for Drugs and Medical Devices India: Drugs Controller General of India Israel: Ministry of Health Italy: National Monitoring Centre for Clinical Trials - Ministry of Health Latvia: State Agency of Medicines Lithuania: State Medicine Control Agency - Ministry of Health Portugal: National Pharmacy and Medicines Institute Romania: National Medicines Agency Serbia and Montenegro: Agency for Drugs and Medicinal Devices South Africa: Medicines Control Council Spain: Agencia Española de Medicamentos y Productos Sanitarios Ukraine: Ministry of Health 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 disease modifying anti-rheumatic drug (DMARD) but not responding. The study will last for 1 year.
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: 913 [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, fostamatinib Placebo for 24 weeks followed by fostamatinib 100 mg 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
- Treatment with one the following disease modifying anti-rheumatic drug: methotrexate, sulfasalazine, hydroxychloroquine or chloroquine
- 4 or more swollen joints and 4 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 12 months 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 a TNF alpha antagonist, anakinra or previous treatment with other biological agent
- Severe renal impairment
- Neutropenia

Contacts/Locations

Study Officials: Neil MacKillop, MD PhD
Study Director
AstraZeneca

Locations: India
Research Site
Ahmedabad, Gujarat, India

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

Israel
Research Site
Ashkelon, Israel

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

Portugal
Research Site
Aveiro, Portugal

Romania
Research Site
Baia Mare, Romania

India
Research Site
Bangalore, Karnataka, India

Spain
Research Site
Barcelona, Spain

United Kingdom
Research Site
Basingstoke, United Kingdom

Israel
Research Site
Beer Yaakov, Israel

Serbia
Research Site
Belgrade, Serbia

United States, Alabama
Research Site
Birmingham, Alabama, United States

United States, Florida
Research Site

Boca Raton, Florida, United States

United States, Idaho
Research Site
Boise, Idaho, United States

Canada, Ontario
Research Site
Bowmanville, Ontario, Canada

Romania
Research Site
Brailari, Romania

United States, Florida
Research Site
Brandon, Florida, United States

Czech Republic
Research Site
Brno, Czech Republic

United States, New York
Research Site
Brooklyn, New York, United States

Czech Republic
Research Site
Bruntal, Czech Republic

Romania
Research Site
Bucharest, Romania

Research Site
Bucuresti, Romania

United Kingdom
Research Site
Cambridge, United Kingdom

United States, Georgia
Research Site
Canton, Georgia, United States

South Africa

Research Site
Cape Town, W Cape, South Africa

Czech Republic
Research Site
Ceska Lipa, Czech Republic

Research Site
Ceske Budejovice, Czech Republic

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

United States, Virginia
Research Site
Chesapeake, Virginia, United States

India
Research Site
Coimbatore, Tamil Nadu, India

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

Research Site
Cumberland, Maryland, United States

United States, Texas
Research Site
Dallas, Texas, United States

United States, Ohio
Research Site
Dayton, Ohio, United States

United States, Georgia
Research Site
Decatur, Georgia, United States

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

South Africa

Research Site
Durban, Kz-natal, South Africa

United States, North Carolina
Research Site
Durham, North Carolina, United States

United Kingdom
Research Site
Eastbourne, Sussex, United Kingdom

Canada, Alberta
Research Site
Edmonton, Alberta, Canada

United States, Kentucky
Research Site
Elizabethtown, Kentucky, United States

Germany
Research Site
Erlangen, Germany

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

India
Research Site
Gandhinagar, Gujarat, India

Spain
Research Site
Getafe, Spain

United States, Arizona
Research Site
Glendale, Arizona, United States

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

United States, Maryland
Research Site
Hagerstown, Maryland, United States

Israel
Research Site
Haifa, Israel

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Research Site
Hamburg, Germany

Canada, Ontario
Research Site
Hamilton, Ontario, Canada

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Hlucin, Czech Republic

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United States, Texas
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Houston, Texas, United States

United States, California
Research Site
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India
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United States, Florida
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Jacksonville, Florida, United States

Italy
Research Site
Jesi, AN, Italy

United States, Michigan
Research Site
Kalamazoo, Michigan, United States

United States, Montana
Research Site

Kalispell, Montana, United States

Lithuania
Research Site
Kaunas, Lithuania

South Africa
Research Site
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Israel
Research Site
Kfar-saba, Israel

Ukraine
Research Site
Kharkiv, Ukraine

Lithuania
Research Site
Klaipeda, Lithuania

Serbia
Research Site
Kragujevac, Serbia

Ukraine
Research Site
Kyiv, Ukraine

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

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Legnano, MI, Italy

Czech Republic
Research Site
Liberec, Czech Republic

Portugal
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Lucknow, India

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Research Site
Lutsk, Ukraine

Research Site
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Research Site
Macon, Georgia, United States

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Madurai, Tamil Nadu, India

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Manalapan, New Jersey, United States

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United States, Texas
Research Site
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United States, Florida
Research Site
Miami, Florida, United States

Canada, Ontario
Research Site
Mississauga, Ontario, Canada

Canada, Quebec
Research Site
Montreal, Quebec, Canada

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Muenchen, Germany

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Romania
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Ploiesti, Romania

South Africa
Research Site
Port Elizabeth, South Africa

Portugal
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Porto, Portugal

Czech Republic
Research Site
Praha, Czech Republic

Research Site
Praha 11, Czech Republic

Research Site
Praha 2, Czech Republic

Research Site
Praha 4, Czech Republic

South Africa
Research Site
Pretoria, Gauteng, South Africa

India
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Pune, Maharashtra, India

Canada, Quebec
Research Site
Quebec, Quebec, Canada

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Research Site
Ramat Gan, Israel

Research Site
Ramat-gan, Israel

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Research Site
Reading, Canada

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Research Site
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Research Site
Roslyn, New York, United States

United States, Texas
Research Site

San Antonio, Texas, United States

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Lithuania
Research Site
Siauliai, Lithuania

Ukraine
Research Site
Simferopol, Ukraine

Czech Republic
Research Site
Sokolov, Czech Republic

United Kingdom
Research Site
Solihull, West Midlands, United Kingdom

United States, Indiana
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South Bend, Indiana, United States

United States, Missouri
Research Site
St. Louis, Missouri, United States

South Africa
Research Site
Stellenbosch, South Africa

United Kingdom
Research Site
Stoke on Trent, United Kingdom

Research Site
Swindon, United Kingdom

United States, New York
Research Site
Syracuse, New York, United States

United States, Washington

Research Site
Tacoma, Washington, United States

United States, Florida
Research Site
Tampa, Florida, United States

Israel
Research Site
Tel Aviv, Israel

Czech Republic
Research Site
Terezin, Czech Republic

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Research Site
Toronto, Ontario, Canada

United States, California
Research Site
Torrance, California, United States

Canada, Quebec
Research Site
Trois-rivieres, Quebec, Canada

United States, Connecticut
Research Site
Trumbull, Connecticut, United States

United States, Arizona
Research Site
Tucson, Arizona, United States

Italy
Research Site
Udine, UD, Italy

India
Research Site
Vadodara, Gujarat, India

Latvia
Research Site
Valmiera, Latvia

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Research Site
Varese, VA, Italy

United States, Florida
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Venice, Florida, United States

Ukraine
Research Site
Vinnytsia, Ukraine

United States, District of Columbia
Research Site
Washington, District of Columbia, United States

United States, Pennsylvania
Research Site
West Reading, Pennsylvania, United States

Canada, Manitoba
Research Site
Winnipeg, Manitoba, Canada

Ukraine
Research Site
Zaporizhzhya, Ukraine

Research Site
Zaporyzhzhya, Ukraine

United States, Florida
Research Site
Zephyr Hills, Florida, United States

Czech Republic
Research Site
Zlin, Czech Republic

Latvia
Research Site
Liepaja, Latvia

References

Citations:

Links: URL: http://www.oskirastudy.com
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Study Data/Documents:

Study Results

Participant Flow

Recruitment Details	A total of 1632 patients were enrolled: 308, 300 & 305 were randomised to Groups A, B & C, respectively (308, 298 & 302 received at least 1 dose of investigational product).
Pre-Assignment Details	A total of 719 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Overall Study

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Started	308 [1]	298 [1]	302 [1]
Randomised But Did Not Receive Treatment	0 [2]	2 [3]	3 [4]
Completed	174 [5]	168 [5]	129 [5]
Not Completed	134	130	173
Not reported	16	10	16
Enrolment in long term extension	57	66	119
Severe non-compliance to protocol	3	4	1
Lack of therapeutic response	9	4	9
Dev. of study specific discont. criteria	13	6	2
Lost to Follow-up	1	4	2
Adverse Event	35	36	24

[1] Patients who received treatment
[2] Not applicable
[3] Adverse event / Other
[4] Eligibility criteria not fulfilled / Severe non-compliance to protocol
[5] 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Baseline Measures

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO	Total
Number of Participants	308	298	302	908
Age, Continuous [units: years] Mean (Standard Deviation)	53 (12.3)	54 (11.6)	53 (11.8)	53 (11.9)
Gender, Male/Female [units: Participants]				
Female	245	245	252	742
Male	63	53	50	166
Race/Ethnicity, Customized [units: Participants]				
White	254	235	241	730
Black or African American	6	15	8	29
Asian	16	13	20	49
American Indian or Alaska Native	0	2	1	3
Indian or Pakistani	25	31	28	84
Other	7	2	4	13

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Proportion of Patients With 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 CRP) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, CRP = C-reactive protein, DMARD = disease-modifying anti-rheumatic drug, 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
Proportion of Patients With ACR20 at Week 24, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	39.6	39.6	24.5

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	Week 24
	Method	Mantel Haenszel
	Comments	Treatment difference in proportion of responders using a Mantel Haenszel approach stratified by background use of DMARD and pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportions]
	Estimated Value	0.15

	Confidence Interval	(2-Sided) 95% 0.08 to 0.22
	Estimation Comments	[Not specified]

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	Week 24
	Method	Mantel Haenszel
	Comments	Treatment difference in proportion of responders using a Mantel Haenszel approach stratified by background use of DMARD and pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportions]
	Estimated Value	0.15
	Confidence Interval	(2-Sided) 95% 0.08 to 0.22
	Estimation Comments	[Not specified]

2. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving ACR20, Comparison Between Fostamatinib and Placebo at Week 1
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 CRP) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, CRP = C-reactive protein, DMARD = Disease-modifying anti-rheumatic drug, PO = orally, QD = once a day.
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
FOSTA 100 MG BID PO (Combined)	Dosing Group A and B combined
PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO (Combined)	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	606	302
Proportion of Patients Achieving ACR20, Comparison Between Fostamatinib and Placebo at Week 1 [units: Percentage of responders]	16.0	8.3

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO (Combined), PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 background use of DMARD and pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportion]
	Estimated Value	0.08

	Confidence Interval	(2-Sided) 95% 0.04 to 0.12
	Estimation Comments	[Not specified]

3. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving ACR50, Comparison Between Fostamatinib and Placebo at Week 24
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 CRP) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, CRP = C-reactive protein, DMARD = Disease-modifying anti-rheumatic drug, 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
Proportion of Patients Achieving ACR50, Comparison Between Fostamatinib and Placebo at Week 24 [units: Percentage of responders]	20.8	18.1	8.3

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 background use of DMARD and pooled country.
Method of Estimation	Estimation Parameter	Other [Weighted difference in proportions]
	Estimated Value	0.13
	Confidence Interval	(2-Sided) 95% 0.07 to 0.18
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Patients Achieving ACR50, 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 (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 background use of DMARD and pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportions]
	Estimated Value	0.10
	Confidence Interval	(2-Sided) 95% 0.05 to 0.15
	Estimation Comments	[Not specified]

4. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving ACR70, Comparison Between Fostamatinib and Placebo at Week 24
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 CRP) and the physician and patient's own assessments of disease activity, pain and physical function. BID = twice daily, CRP = C-reactive protein, DMARD = Disease-modifying anti-rheumatic drug, 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
Proportion of Patients Achieving ACR70, Comparison Between Fostamatinib and Placebo at Week 24	9.1	6.0	2.6

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
[units: Percentage of responders]			

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 background use of DMARD and pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportions]
	Estimated Value	0.07
	Confidence Interval	(2-Sided) 95% 0.03 to 0.10
	Estimation Comments	[Not specified]

Statistical Analysis 2 for Proportion of Patients Achieving ACR70, 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 (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	0.033
	Comments	[Not specified]
	Method	Mantel Haenszel
	Comments	95% confidence intervals and p-values are calculated using a Mantel Haenszel approach stratified by background use of DMARD and pooled country.

Method of Estimation	Estimation Parameter	Other [Weighted difference in proportions]
	Estimated Value	0.03
	Confidence Interval	(2-Sided) 95% 0.00 to 0.07
	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 CRP) 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. BID = twice daily, CI = confidence interval, CRP = C-reactive protein, DMARD = Disease-modifying anti-rheumatic drug, PO = orally, QD = once a day. Mean refers to change at Week 24.
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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
ACRn - Comparison Between Fostamatinib and Placebo at Week 24 [units: Percentage improvement from baseline] Mean (Standard Deviation)	20.75 (31.203)	18.31 (28.427)	9.84 (23.219)

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 presented for treatment comparison. Outcome 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 background use of DMARD and pooled country.

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 (24 WKS) THEN FOSTA 100 MG BID 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 presented for treatment comparison. Outcome 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 background use of DMARD and pooled country.

6. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving DAS28-CRP <2.6 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 patient's 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 a day.
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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Proportion of Patients Achieving DAS28-CRP <2.6 at Week 12, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	17.2	10.7	3.0

Statistical Analysis 1 for Proportion of Patients Achieving DAS28-CRP <2.6 at Week 12, Comparison Between Fostamatinib and Placebo

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals calculated using Logistic Regression with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	7.1
	Confidence Interval	(2-Sided) 95% 3.42 to 14.80
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

Statistical Analysis 2 for Proportion of Patients Achieving DAS28-CRP <2.6 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 (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals calculated using Logistic Regression with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	4.0
	Confidence Interval	(2-Sided) 95% 1.88 to 8.65
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

7. 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 patient's 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 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

	Description
PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
Proportion of Patients Achieving DAS28-CRP <2.6 at Week 24, Comparison Between Fostamatinib and Placebo [units: Percentage of responders]	41.3	12.8	2.3

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 (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals calculated using Logistic Regression with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	7.3
	Confidence Interval	(2-Sided) 95% 3.23 to 16.65
	Estimation Comments	An odds ratio >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 (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals calculated using Logistic Regression with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	6.4
	Confidence Interval	(2-Sided) 95% 2.81 to 14.71
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

8. Secondary Outcome Measure:

Measure Title	Proportion of Patients Achieving DAS28 EULAR Response at Week 24
Measure Description	Change in DAS28 was derived for each post baseline scheduled assessment and categorised using the European League Against Rheumatism (EULAR) response criteria. 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.
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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
Proportion of Patients Achieving DAS28 EULAR Response at Week 24 [units: Percentage of responders]			
No response	42.9	45.3	64.6
Moderate response	33.8	34.9	29.1
Good response	23.4	19.8	6.3

Statistical Analysis 1 for Proportion of Patients Achieving DAS28 EULAR Response at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 presented for treatment comparison. Outcome was not formally tested within the predefined multiplicity procedure.
	Method	Other [Proportional odds model]

	Comments	No Response, moderate response and good response are included in the model, with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.84
	Confidence Interval	(2-Sided) 95% 2.06 to 3.91
	Estimation Comments	An odds ratio > 1 indicates a benefit towards fostamatinib.

Statistical Analysis 2 for Proportion of Patients Achieving DAS28 EULAR Response at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 presented for treatment comparison. Outcome was not formally tested within the predefined multiplicity procedure.
	Method	Other [Proportional odds model]
	Comments	No Response, moderate response and good response are included in the model, with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.44
	Confidence Interval	(2-Sided) 95% 1.77 to 3.37
	Estimation Comments	An odds ratio > 1 indicates a benefit towards fostamatinib.

9. Secondary Outcome Measure:

Measure Title	HAQ-DI Response - Comparison of the Change(>=0.22) From Baseline Between Fostamatinib and Placebo at Week 24

Measure Description	HAQ-DI: Health Assessment Questionnaire – Disability Index, a measure of physical function. The HAQ-DI score is then 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. The HAQ-DI response is a reduction from baseline in HAQ-DI score 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	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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
HAQ-DI Response - Comparison of the Change(>=0.22) From Baseline Between Fostamatinib and Placebo at Week 24 [units: Percentage of responders]	46.1	42.3	26.5

Statistical Analysis 1 for HAQ-DI Response - Comparison of the Change(>=0.22) From Baseline Between Fostamatinib and Placebo at Week 24

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals calculated using Logistic Regression with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.4
	Confidence Interval	(2-Sided) 95% 1.73 to 3.46
	Estimation Comments	An odds ratio >1 indicates a benefit towards fostamatinib.

Statistical Analysis 2 for HAQ-DI Response - Comparison of the Change(>=0.22) 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 (24 WKS) THEN FOSTA 100 MG BID 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	Regression, Logistic
	Comments	Odds ratio and 95% confidence intervals calculated using Logistic Regression with treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Odds Ratio (OR)
	Estimated Value	2.1
	Confidence Interval	(2-Sided) 95%

		1.46 to 2.94
	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, 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 erosions and joint space narrowing and the results summed to give a value between 0 and 448. A higher value represents more serious progression of the disease. After disregarding ineligible records, patients with 2 or more non-missing values have 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, 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
Change From Baseline to Week 24 in mTSS, Comparison Between Fostamatinib and Placebo [units: Units on a scale] Mean (Standard Deviation)	0.64 (3.130)	0.37 (3.095)	1.16 (5.849)

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	This analysis is performed using an ANCOVA model on the ranks of the change from baseline, by pooled country and background use of DMARD, including a term for the ranks of the baseline score as a covariate.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.904
	Comments	As this is a non-parametric test, p-values alone are presented rather than an estimated treatment difference.
	Method	Cochran-Mantel-Haenszel
	Comments	Residuals from ANCOVA are analysed using a Cochran-Mantel-Haenszel approach, adjusting for the effects of pooled country and background use of DMARD.

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

Statistical Analysis Overview	Comparison Groups	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO, PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	This analysis is performed using an ANCOVA model on the ranks of the change from baseline, by pooled country and background use of DMARD, including a term for the ranks of the baseline score as a covariate.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]

Statistical Test of Hypothesis	P-Value	0.342
	Comments	As this is a non-parametric test, p-values alone are presented rather than an estimated treatment difference.
	Method	Cochran-Mantel-Haenszel
	Comments	Residuals from ANCOVA are analysed using a Cochran-Mantel-Haenszel approach, adjusting for the effects of pooled country and background use of DMARD.

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, 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 0-100. 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 mean of 50+/- 10. Higher scores represent 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. ANCOVA = analysis of covariance, BID = twice daily, DMARD = disease modifying antirheumatic drugs, 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302
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 (7.2)	4 (6.6)	2 (5.7)

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 (24 WKS) THEN FOSTA 100 MG BID PO

	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 presented for treatment comparison. Outcome was not formally tested within the predefined multiplicity procedure.
	Method	ANCOVA
	Comments	Including terms for baseline as continuous covariate and treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	2.47
	Confidence Interval	(2-Sided) 95% 1.47 to 3.48
	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 (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 presented for treatment comparison. Outcome was not formally tested within the predefined multiplicity procedure.
	Method	ANCOVA
	Comments	Including terms for baseline as continuous covariate and treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	1.64
	Confidence Interval	(2-Sided) 95% 0.63 to 2.65
	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, 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 0-100. 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 mean of 50+/- 10. Higher scores represent 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. ANCOVA = analysis of covariance, BID = twice daily, DMARD = disease modifying antirheumatic drugs, 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 (24 WKS) THEN FOSTA 100 MG BID PO	Dosing Group C

Measured Values

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
Number of Participants Analyzed	308	298	302

	FOSTA 100 MG BID PO	FOSTA 100 MG BID (4 WKS) THEN 150 MG QD PO	PLACEBO (24 WKS) THEN FOSTA 100 MG BID PO
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)	3 (7.5)	3 (8.4)	1 (6.3)

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 (24 WKS) THEN FOSTA 100 MG BID PO
	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 presented for treatment comparison. Outcome was not formally tested within the predefined multiplicity procedure.
	Method	ANCOVA
	Comments	Including terms for baseline as continuous covariate and treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	2.09
	Confidence Interval	(2-Sided) 95% 0.97 to 3.20
	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 (24 WKS) THEN FOSTA 100 MG BID PO

	Comments	Non-responder imputation has been applied following premature withdrawal, or increased dose of DMARD 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 presented for treatment comparison. Outcome was not formally tested within the predefined multiplicity procedure.
	Method	ANCOVA
	Comments	Including terms for baseline as continuous covariate and treatment, background use of DMARD and pooled country as factors.

Method of Estimation	Estimation Parameter	Other [Treatment difference]
	Estimated Value	1.96
	Confidence Interval	(2-Sided) 95% 0.83 to 3.08
	Estimation Comments	[Not specified]

Reported Adverse Events

Time Frame	52 weeks
Additional Description	For placebo treated patients time frame includes both placebo (24 weeks) and fostamatinib (28 weeks) treatment. 11 SAEs occurred during the 24 week placebo treated period.

Reporting Groups

	Description
FOSTA 100 MG BID	Dosing Group A
FOSTA 100 MG BID (4 WKS) THEN 150 MG QD	Dosing Group B
PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period	Dosing Group C

	Description
PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	

Serious Adverse Events

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	30/308 (9.74%)		25/298 (8.39%)		10/302 (3.31%)		10/302 (3.31%)	
Blood and lymphatic system disorders								
LEUKOPENIA [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
Cardiac disorders								
ANGINA PECTORIS [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
ATRIAL FIBRILLATION [A] †	2/308 (0.65%)	2	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
ATRIAL FLUTTER [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
CARDIAC ARREST [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
LEFT VENTRICULAR FAILURE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
MYOCARDIAL INFARCTION [A] †	1/308 (0.32%)	1	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
VENTRICULAR FIBRILLATION [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Eye disorders								
MACULAR HOLE [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Gastrointestinal disorders								
COLITIS [A] †	1/308 (0.32%)	1	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
COLITIS ULCERATIVE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
DIARRHOEA [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
GASTRITIS [A] †	2/308 (0.65%)	2	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
GASTRITIS EROSIVE [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
GASTRITIS HAEMORRHAGIC [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
LOWER GASTROINTESTINAL HAEMORRHAGE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
OESOPHAGITIS ULCERATIVE [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
PANCREATITIS CHRONIC [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
STOMATITIS [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
VOMITING [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
General disorders								
NON-CARDIAC CHEST PAIN [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Hepatobiliary disorders								

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
CHOLECYSTITIS ACUTE [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
CHOLELITHIASIS [A] †	0/308 (0%)	0	2/298 (0.67%)	2	0/302 (0%)	0	0/302 (0%)	0
HEPATOCELLULAR INJURY [A] †	0/308 (0%)	0	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
NON-ALCOHOLIC STEATOHEPATITIS [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Infections and infestations								
ACUTE SINUSITIS [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
ARTHRITIS BACTERIAL [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
ATYPICAL PNEUMONIA [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
BRONCHITIS [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
BRONCHITIS BACTERIAL [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
BRONCHITIS VIRAL [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
BURSITIS INFECTIVE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
DENGUE FEVER [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
DEVICE RELATED INFECTION [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
ENTEROCOLITIS BACTERIAL [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
ESCHERICHIA INFECTION [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
GASTROENTERITIS [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
GASTROENTERITIS BACTERIAL [A] †	1/308 (0.32%)	1	1/298 (0.34%)	1	1/302 (0.33%)	1	0/302 (0%)	0
GASTROINTESTINAL BACTERIAL INFECTION [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
HERPES SIMPLEX [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
INFLUENZA [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
PNEUMOCOCCAL SEPSIS [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
PNEUMONIA [A] †	0/308 (0%)	0	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
PNEUMONIA STREPTOCOCCAL [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
URINARY TRACT INFECTION BACTERIAL [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
Injury, poisoning and procedural complications								
CLAVICLE FRACTURE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
FEMORAL NECK FRACTURE [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
HIP FRACTURE [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
HUMERUS FRACTURE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
OVERDOSE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
ULNA FRACTURE [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Investigations								
ALANINE AMINOTRANSFERASE INCREASED [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
ASPARTATE AMINOTRANSFERASE INCREASED [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
BLOOD CREATINE PHOSPHOKINASE INCREASED [A] †	0/308 (0%)	0	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
Metabolism and nutrition disorders								
HYPOCALCAEMIA [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
HYPOKALAEMIA [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
OBESITY [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Musculoskeletal and connective tissue disorders								
MYOSITIS [A] †	0/308 (0%)	0	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
OSTEOARTHRITIS [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
PATHOLOGICAL FRACTURE [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
RHEUMATOID ARTHRITIS [A] †	1/308 (0.32%)	1	2/298 (0.67%)	2	0/302 (0%)	0	2/302 (0.66%)	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
BONE NEOPLASM MALIGNANT [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
METASTASES TO CENTRAL NERVOUS SYSTEM [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
METASTATIC BRONCHIAL CARCINOMA [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
PARATHYROID TUMOUR BENIGN [A] †	0/308 (0%)	0	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
RENAL ONCOCYTOMA [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
SQUAMOUS CELL CARCINOMA OF SKIN [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Nervous system disorders								
CAROTID ARTERY STENOSIS [A] †	0/308 (0%)	0	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
CONVULSION [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
LUMBAR RADICULOPATHY [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
SYNCOPE [A] †	1/308 (0.32%)	1	1/298 (0.34%)	1	0/302 (0%)	0	1/302 (0.33%)	1
Psychiatric disorders								

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
ANXIETY [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Renal and urinary disorders								
RENAL FAILURE ACUTE [A] †	1/308 (0.32%)	1	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
URINARY RETENTION [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
Reproductive system and breast disorders								
ENDOMETRIOSIS [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
MENORRHAGIA [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
UTERINE HAEMORRHAGE [A] †	0/308 (0%)	0	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
UTERINE POLYP [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
Respiratory, thoracic and mediastinal disorders								
ACUTE RESPIRATORY DISTRESS SYNDROME [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	0/302 (0%)	0
ALLERGIC BRONCHITIS [A] †	0/308 (0%)	0	0/298 (0%)	0	1/302 (0.33%)	1	0/302 (0%)	0
ASTHMA [A] †	1/308 (0.32%)	1	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
PULMONARY EMBOLISM [A] †	1/308 (0.32%)	1	0/298 (0%)	0	0/302 (0%)	0	1/302 (0.33%)	1
PULMONARY TOXICITY [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
RESPIRATORY FAILURE [A] †	1/308 (0.32%)	1	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
Vascular disorders								
DEEP VEIN THROMBOSIS [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (0%)	0
MALIGNANT HYPERTENSION [A] †	0/308 (0%)	0	1/298 (0.34%)	1	0/302 (0%)	0	0/302 (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		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Total	170/308 (55.19%)		152/298 (51.01%)		42/302 (13.91%)		77/302 (25.5%)	
Gastrointestinal disorders								
DIARRHOEA [A] †	44/308 (14.29%)	44	47/298 (15.77%)	47	15/302 (4.97%)	15	13/302 (4.3%)	13
NAUSEA [A] †	20/308 (6.49%)	20	17/298 (5.7%)	17	5/302 (1.66%)	5	7/302 (2.32%)	7
Infections and infestations								
NASOPHARYNGITIS [A] †	37/308 (12.01%)	37	29/298 (9.73%)	29	2/302 (0.66%)	2	16/302 (5.3%)	16

	FOSTA 100 MG BID		FOSTA 100 MG BID (4 WKS) THEN 150 MG QD		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - FOSTA Period		PLACEBO (24 WKS) THEN FOSTA 100 MG BID - Placebo Period	
	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events	Affected/ At Risk (%)	# Events
Investigations								
ALANINE AMINOTRANSFERASE INCREASED [A] †	21/308 (6.82%)	21	14/298 (4.7%)	14	2/302 (0.66%)	2	4/302 (1.32%)	4
ASPARTATE AMINOTRANSFERASE INCREASED [A] †	17/308 (5.52%)	17	13/298 (4.36%)	13	3/302 (0.99%)	3	4/302 (1.32%)	4
BLOOD PRESSURE INCREASED [A] †	15/308 (4.87%)	15	15/298 (5.03%)	15	1/302 (0.33%)	1	10/302 (3.31%)	10
Musculoskeletal and connective tissue disorders								
RHEUMATOID ARTHRITIS [A] †	19/308 (6.17%)	19	23/298 (7.72%)	23	1/302 (0.33%)	1	10/302 (3.31%)	10
Nervous system disorders								
HEADACHE [A] †	19/308 (6.17%)	19	12/298 (4.03%)	12	5/302 (1.66%)	5	9/302 (2.98%)	9
Vascular disorders								
HYPERTENSION [A] †	68/308 (22.08%)	68	55/298 (18.46%)	55	17/302 (5.63%)	17	16/302 (5.3%)	16

† 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.

The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

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