AstraZeneca

Revised Clinical Study Protocol

Drug Substance	Fostamatinib
Study Code	D4300C00004
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Date	

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca Research and Development site representative

The following Amendment(s) and Administrative Changes are included in this revised protocol:

Amendment No.	Date of Amendment	Local Amendment No.	Date of local Amendment
1			
2			
3			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
1			

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PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

Study centres and number of patients planned

In total it is planned to randomise approximately 370 patients across approximately 150-200 centres. An adequate number of patients will be randomised to ensure that approximately 250 patients (approximately 50 patients in each of the 5 dose regimens) will receive their randomised treatment in the main study. Ninety patients will receive randomised treatment in the sub-study.

Study period	Phase of development
Estimated date of first patient enrolled	IIB
Estimated date of last patient completed	

Objectives

Primary objective

The primary objectives of this study are:

- To evaluate the efficacy of 3 oral dosing regimens of fostamatinib compared with placebo when used as monotherapy in patients with active rheumatoid arthritis (RA) by assessment of:

  - The signs and symptoms of RA, as measured by Disease Activity Score based on a 28 joint count (DAS28) at Week 6.

- To evaluate whether the efficacy of 3 oral dosing regimens of fostamatinib are non-inferior to that of adalimumab (Humira®) when used as monotherapy in patients with active RA by assessment of:

  - The signs and symptoms of RA, as measured by DAS28 at Week 24.

Secondary objectives

The secondary objectives of the study are:

- To further assess the efficacy of fostamatinib measured by DAS28, DAS28 response criteria, American College of Rheumatology 20% response criteria (ACR20), ACR 50% response criteria (ACR50), ACR 70% response criteria (ACR70), ACR-N and the individual components of the ACR score.

- To assess physical function status of patients after administration of fostamatinib using the Health Assessment Questionnaire - Disability Index (HAQ-DI).

- To investigate the effects of fostamatinib on health-related quality of life using the 36-item Short Form Health Survey (SF-36) questionnaire.

Safety objectives

- To evaluate the safety and tolerability of fostamatinib taken as monotherapy in patients with active RA.

- To investigate the relationship between variations in the gene encoding uridine diphosphate (UDP) glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) and the safety and tolerability of fostamatinib in the study population.

Exploratory objectives

- To investigate the pharmacokinetics (PK) of R406 (the active metabolite of fostamatinib) and/or the PK of R788 (fostamatinib) or other metabolites and to investigate the relationship between systemic exposure to these metabolites and adverse events (AEs), safety parameters and efficacy outcomes. This may be described in a separate report.

- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib and/or adalimumab; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers. This may be described in a separate report.

- To investigate systemic biomarker profiles in RA patients. This may be described in a separate report.

Study design

The study is a 24-week, multi-centre, randomised, double-blind (administrator unblinded), placebo-controlled (for 6 weeks), parallel group study to investigate the efficacy and safety of fostamatinib monotherapy in patients with active RA.

Eligible patients will include those who are not currently receiving disease-modifying anti-rheumatic drug (DMARDs; DMARD naïve, intolerant to DMARDs or have had an inadequate response to DMARDs). There is no minimum or maximum number of patients in each subgroup but randomisation will be stratified by DMARD naive versus DMARD-inadequate response (IR)/intolerant. Patients must not have used DMARDs within 6 weeks prior to Visit 1 in order to be eligible to participate in the study.

Patients will be randomised to receive 1 of 3 oral dosing regimens of fostamatinib, adalimumab by subcutaneous injection or a matching placebo regimen. Oral study treatment will be taken on a once or twice daily basis and adalimumab/placebo will be administered by injection in the clinic once every 2 weeks. A double-dummy blinding technique will be used to ensure neither patient nor investigator will know which treatment the patient is receiving. Since an exact placebo match for adalimumab is not available, each site will be required to appoint an unblinded administrator for the injection, who will be independent of the rest of the on-site study team.

It is planned to randomise up to approximately 370 patients in total. An adequate number of patients will be randomised to ensure that approximately 250 patients (approximately 50 patients in each of the 5 dose regimens) will receive their randomised treatment in the main study. At randomisation, the patients allocated to placebo will be assigned to switch to fostamatinib at Week 6 (100 mg fostamatinib *bid* up to Week 24; or 100 mg fostamatinib *bid* for 4 weeks, followed by fostamatinib 150 mg *qd* up to Week 24).

Selected sites will also participate in an imaging sub-study, where approximately 90 OSKIRA-4 patients will be asked to provide consent to undergo MRI assessments in addition to their main study assessments described in this main protocol.

Patients who successfully complete the scheduled treatment period will be offered the opportunity to receive fostamatinib therapy in a long-term follow-up extension study (OSKIRA-X: Protocol D4300C00005).

Target subject population

Male and female patients aged 18 or over, with active RA who are not currently receiving DMARDs (DMARD naive, intolerant to DMARDs or have had an inadequate response to DMARDs).

Investigational products, dosage and mode of administration

Fostamatinib (oral), adalimumab (injection).

Dosing Group A:	Fostamatinib 100 mg *bid* for 24 weeks plus placebo injection every 2 weeks.
Dosing Group B:	Fostamatinib induction and maintenance: induction of response with 100 mg *bid* for 4 weeks, followed by *qd* maintenance dosing with 150 mg up to Week 24, plus placebo injection every 2 weeks.
Dosing Group C:	Fostamatinib induction and maintenance: induction of response with 100 mg *bid* for 4 weeks, followed by *qd* maintenance dosing with 100 mg up to Week 24, plus placebo injection every 2 weeks.
Dosing Group D:	Adalimumab 40 mg by subcutaneous injection every 2 weeks for 24 weeks, plus placebo to fostamatinib twice daily.
Dosing Group E:	Placebo *bid* for 6 weeks followed by switch to fostamatinib (100 mg fostamatinib *bid*; or 100 mg fostamatinib *bid* for 4 weeks, followed by fostamatinib 150 mg *qd* for the remaining 14 weeks up to Week 24) plus placebo injection every 2 weeks. NB: Patients will be assigned to their fostamatinib regimen at randomisation.

Patients will take study treatment as a monotherapy, ie, without any background DMARD regimen.

It is recognised that some AEs may require reduction of the fostamatinib dose. A reduced dosing regimen of fostamatinib 100 mg *qd* is available. Patients who have their dose reduced will remain on this dose for the remainder of the study and into the long-term extension, if applicable. Where fostamatinib dose reduction is required, the original treatment allocation will remain blinded, although patients will be aware of the switch to a reduced regimen. Patients on regimen C who meet the criteria for a dose reduction after Week 4 will need to be withdrawn since they are already taking 100 mg *qd* and no further dose reduction is available. This will entail unblinding of the patient via the interactive voice response system (IVRS). Dose reductions are not permitted for adalimumab injection, however due to the blinded nature of the study reduction of the placebo dose for patients on regimen D may occur.

Treatment will continue for 24 weeks unless any of the criteria for discontinuation are met.

Outcome variables:

Efficacy

- Primary outcome variables:
  - DAS28 score at Week 6

- DAS28 score at Week 24

- Secondary outcome variables:
  - DAS28 score, DAS28 response criteria, DAS low disease activity, DAS28 remission, clinically important change in DAS28 score
  - ACR20, ACR50, ACR70, ACR-N, individual components of ACR (swollen joint count, tender joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function, as measured by the HAQ-DI, C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR])
  - HAQ-DI score; HAQ-DI response, individual dimensions of HAQ-DI.

Patient reported outcomes

In addition to the HAQ-DI, patient's global assessment of disease activity Visual Analogue Scale (VAS) and pain VAS, which are also components of the ACR score, and the SF-36 will also be completed by patients during the study.

Pharmacokinetic

Blood samples for determination of R406 plasma concentrations will be obtained at Weeks 4 and 24 (sparse sampling).

Pharmacokinetic/Pharmacodynamic

A population PK/pharmacodynamic (PD) analysis will be undertaken to investigate the relationship between plasma drug concentrations/exposure and safety and/or efficacy outcomes, the results of which may be reported separately.

Safety

Safety outcomes will include AEs, vital signs, electrocardiogram (ECG), clinical chemistry (including total cholesterol, high density lipoprotein [HDL]/ low density lipoprotein [LDL]), haematology, urinalysis and physical examination. An independent Safety Review Committee (SRC) will be constituted to review accumulating safety data on an ongoing basis. Adverse event monitoring will include independent adjudication of cardiovascular (CV) events.

Genetics

Variation in the gene encoding UGT1A1, including *UGT1A1*28*, will be characterised. Genotype at the *UGT1A1* locus is known to contribute to a spectrum of hyperbilirubinaemias, including Gilbert's syndrome (Strassburg, CP, Kalthoff S, Ehmer U. Variability and function of family 1 Uridine-5'-diphosphate glucuronosyltransferases (UGT1A). Crit Rev Clin Lab Sci 2008;45(6):485-530). Fostamatinib is an inhibitor of UGT1A1. Given this, *UGT1A1* genotype data will be used to aid interpretation of bilirubin levels throughout the fostamatinib

clinical programme. Additional exploratory analyses of other genetic factors that may influence the absorption, distribution, metabolism and excretion, efficacy, safety and tolerability of fostamatinib and adalimumab, and progression and prognosis of RA and associated biomarkers, may also be investigated.

Biomarkers

Serum and plasma samples will be collected for optional exploratory biomarker analysis.

Statistical methods

A sample size of approximately 250 patients in total (approximately 50 in each arm) provides at least 85% power to detect a difference (between fostamatinib and placebo) in the mean change from baseline in DAS28-CRP of 0.7 at Week 6, and to confirm non-inferiority between fostamatinib and adalimumab at Week 24.

The full analysis set will be used as the primary population for reporting efficacy and safety data. This comprises all patients randomised into the study who receive at least 1 dose of investigational product and will be analysed according to randomised treatment (intention-to-treat principle).

The primary endpoints in this study are the signs and symptoms of RA, as measured by DAS28 at Week 6 and DAS28 at Week 24. The primary endpoints will be analysed using an analysis of covariance (ANCOVA) model on the change from baseline, including terms for baseline as a continuous covariate and treatment, DMARD naivety (DMARD naive vs DMARD IR/intolerant) and country as factors. Results will be presented in terms of the adjusted means for each treatment group, and estimates of treatment difference, associated confident interval (CI) and p-value for each treatment comparison.

Safety data and tolerability data will be assessed in terms of AEs, ECG data and changes in laboratory data, body weight and vital signs.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% response criteria
ACR50	American College of Rheumatology 50% response criteria
ACR70	American College of Rheumatology 70% response criteria
AE	Adverse event (see definition in Section 6.4.1)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
anti-CCP	Anti-cyclic citrullinated protein
AST	Aspartate aminotransferase
bid	Latin: *bis in die* = twice daily
BP	Blood pressure
CI	Confidence interval
CPMP	Committee for Proprietary Medicinal Products
CRO	Contract Research Organisation
CRP	C-reactive protein
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CV	Cardiovascular
CYP2C8	Cytochrome P450 isoenzyme 2C8
CYP3A4	Cytochrome P450 isoenzyme 3A4
DAE	Discontinuation due to adverse event
DAS	Disease Activity Score
DAS28	Disease Activity Score based on a 28 joint count
DMARD	Disease-modifying anti-rheumatic drug
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
E-code	Enrolment number

Abbreviation or special term	Explanation
eCRF	Electronic case report form
ESR	Erythrocyte sedimentation rate
Ethics Committee	Synonymous to institutional review board and independent ethics committee
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GH	General health
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HRQoL	Health-related quality of life
IB	Investigator's brochure
ICH	International Conference on Harmonisation
International Co-ordinating investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally.
IL-1	Interleukin 1
IR	inadequate response
ITP	Idiopathic thrombocytopenic purpura
IVRS/IWRS	Interactive voice/web response system used to manage allocation of patients to study treatment
LDL	Low Density Lipoprotein
LIMS	Laboratory Information Management System
LSLV	Last subject's last visit
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCP	Metacarpophalangeal
MCS	Mental component score
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase

Abbreviation or special term	Explanation
MRI	Magnetic Resonance Imaging
NSAID	Non steroidal anti-inflammatory drug
OAE	Other significant adverse event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 11.2.1)
OSKIRA	Short name given to the late phase clinical development programme for fostamatinib, based on acronym: Oral Syk Inhibition in Rheumatoid Arthritis. Individual Phase III studies are numbered OSKIRA-1, OSKIRA-2 etc. OSKIRA-X refers to the long-term extension study.
PCS	Physical component score
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
(e)PRO	(electronic) patient reported outcome
qd	Latin: *quaque die* = once a day
RA	Rheumatoid arthritis
RDW	Red blood cell distribution width
RF	Rheumatoid factor
RNA	Ribonucleic acid
SAE	Serious adverse event (see definition in Section 6.4.2)
SAP	Statistical analysis plan
SD	Standard deviation
SDV	Source data verification
SF-36	36-item Short Form Health Survey
SLE	Systemic lupus erythematosus
SRC	Safety Review Committee
syk	Spleen Tyrosine Kinase
TB	Tuberculosis
TNF-α	Tumour necrosis factor-alpha
UDP	Uridine diphosphate
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1 – a member of the family of enzymes that catalyze the glucuronidation of various compounds, including endogenous compounds such as bilirubin
ULN	Upper limit of normal
VAS	Visual analogue scale

Abbreviation or special term	Explanation
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterised by inflammation in the synovium of joints, which is associated with cartilage destruction and erosion of juxta-articular bone. The clinical onset of RA may be acute, but is often insidious involving gradual progression to polyarticular involvement with symptoms including pain and symmetrical stiffness and swelling of peripheral joints. It is the most common form of inflammatory polyarthritis with a substantial effect in terms of cost, disability and lost productivity. The prevalence of the disorder varies with race and locality; the average population prevalence is approximately 1% (Silman and Pearson 2002).

The pathogenesis of RA is complex and numerous cell populations have been implicated including B-cells, T-cells, monocytes, macrophages, mast cells, dendritic cells and fibroblasts. These cells play a key role in inflammation by releasing lipid mediators of inflammation, cytokines, nitric oxide, reactive oxygen intermediates, matrix metalloproteinases (MMPs) and proinflammatory cytokines (Weinblatt et al 2008).

Traditionally, RA has been treated with a combination of anti-inflammatory agents and disease-modifying anti-rheumatic drugs (DMARDs). While therapeutic options have improved, particularly with the introduction of biological approaches neutralising cytokines such as tumour necrosis factor (TNF) and interleukin-1(IL-1) which have been shown to both control signs and symptoms of joint inflammation and retard progression of joint destruction, targeting other mediators and pathways might improve the overall response rate. Although TNF-α antagonists and other biologic therapies represent an important advance in the management of patients with RA, there remains a significant unmet medical need for effective novel oral therapies given the significant non-responder rates, well-documented systemic toxicities and parenteral route of administration.

Spleen tyrosine kinase (syk) is a key enzyme in intra-cellular signalling of various immune cells implicated in the destruction of bone and cartilage that characterises RA. Spleen tyrosine kinase expression has been detected in RA synovium; increased levels of phosphorylated syk have been seen in RA synovial tissue as compared with tissue from patient with osteoarthritis; and syk activation is important in tumor necrosis factor induced cytokine and MMP production in RA fibroblast-like synoviocytes (Weinblatt et al 2008). Therefore inhibition of syk signalling could affect disease activity and has the potential to be a successful approach for the treatment of RA. AstraZeneca and Rigel Pharmaceuticals are co-developing fostamatinib (R935788, R788) for the treatment of RA. Fostamatinib, an orally bio-available small molecule, is the pro-drug of R940406 (R406). R406 has been shown to be a potent syk inhibitor. Fostamatinib has been selected for development rather than the active metabolite, R406, due to its more favourable physiochemical properties and rapid and extensive conversion to R406.

1.1.1 R406 and fostamatinib pharmacokinetics

Several Phase I studies have been conducted in healthy volunteers to determine the pharmacokinetics (PK), pharmacodynamics (PD) and safety of single and multiple doses of R406 and the pro-drug fostamatinib. Fostamatinib is rapidly converted to R406 and consequently is virtually undetectable after 2 hours. Following administration of fostamatinib, maximum concentration of R406 occurs within 1-2 hours and the plasma half-life is approximately 17 hours. Exposure is relatively dose proportional over the dose range 80 mg to 250 mg after which there is little increase in exposure. There is a 2- to 2.5-fold increase in exposure following dosing for 7 days. Co-administration of fostamatinib with a high fat/high calorie meal lowered and delayed the peak concentration but had little effect on overall exposure. R406 is a substrate for cytochrome P450 isoenzyme 3A4 (CYP3A4) and R406 exposure (area under plasma concentration-time curve) was increased 2-fold during co-administration with the probe CYP3A4 inhibitor ketoconazole.

1.1.2 Efficacy of fostamatinib in RA

The efficacy of fostamatinib in RA has been evaluated in 3 double-blind, randomised placebo-controlled Phase II clinical trials (C788-006, C788-010 and C788-011); 592 patients with active RA were treated with doses ranging from 100 mg to 300 mg per day over 3 to 6 months. In addition, around 600 patients from these studies have been subsequently included in 2 open-label extension studies (C788-006X and C788-012). The results of these studies are described briefly below and further details can be found in the Investigator's Brochure (IB).

The primary efficacy endpoint for the randomised controlled trials was the proportion of patients who achieved an American College of Rheumatology 20% response criteria (ACR20) response on completion of the 3 month (C788-006, C788-011) or 6 month (C788-010) treatment period. Studies C788-006 and C788-010 were conducted in patients with an inadequate response to methotrexate and fostamatinib was added to a stable dose of methotrexate. In both these studies statistically significant and clinically relevant efficacy was demonstrated at total daily doses of 150 mg or greater compared with placebo patients. The onset of a clinically significant effect occurred as early as 1 week after initiation of therapy and once achieved was maintained throughout the treatment period.

Study C788-006 (Weinblatt et al 2008), (treatment arms: fostamatinib 50 mg *bid*, 100 mg *bid*,150 mg *bid* or placebo) demonstrated that 50 mg *bid* has no greater efficacy than placebo and that 100 mg *bid* is the maximum well-tolerated dose. While 150 mg *bid* was associated with numerically greater ACR response rates than 100 mg *bid* there were higher rates of adverse effects at the higher dose, especially gastrointestinal (GI) intolerance and neutropenia.

Study C788-010 was a large and robust 6-month study of fostamatinib 100 mg *bid* or 150 mg *qd* versus placebo). The efficacy results are shown in Table 1.

Table 1 Percentage of patients achieving ACR response in Study C788-010

Treatment	(N)	ACR 20	ACR 50	ACR 70
Placebo	153	35%	19%	10%
150 mg *qd*	152	57% **	32% *	14%
100 mg *bid*	152	66% **	43% **	28% **

** P<0.001, *P<0.01 (compared to placebo)

While the 150 mg *qd* dose had significantly greater efficacy than placebo on the majority of measures, the efficacy appears to be less than that observed for the 100 mg *bid* dose.

Study C788-011 (treatment arms: fostamatinib 100 mg *bid* or placebo) was conducted in a more refractory RA patient population who had failed one or more biologic agents and were also on various background DMARD treatments. This 3-month study failed to demonstrate any difference in ACR response between patients who received fostamatinib (100 mg *bid*) and those who received placebo. The placebo ACR response rate in the study was much higher than in other studies in similar patient populations and in addition there was evidence of baseline imbalance and a markedly heterogeneous study population. These findings make the result difficult to interpret. Some evidence of efficacy for fostamatinib is suggested by an improvement compared with placebo in the acute phase responses (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and in synovitis and osteitis measured using magnetic resonance imaging (MRI) techniques. Whilst it is possible that in this refractory population 3 months of treatment with fostamatinib 100 mg *bid* is insufficient to significantly improve the symptoms and signs of RA, considering the efficacy profiles demonstrated in studies C788-006 and C788-010 and the difficulties in interpreting the data from study C788-011, it is more likely that the failure to demonstrate an ACR20 improvement is a spurious result.

1.1.3 Safety and tolerability of fostamatinib

Refer to the IB for full details of safety findings to date. The safety profile has been studied in healthy volunteers, in chronically ill patients with idiopathic thrombocytopenic purpura (ITP), in severely ill patients with lymphoma, and predominantly in patients with RA. This is discussed in greater detail in the IB, as are the adverse events (AEs) in the other diseases that have been studied. The AE profile seen in the studies conducted to date has generally been dose-dependent. AEs include increases in blood pressure (BP), elevations of liver enzymes (mainly transaminases), reductions in neutrophil counts and GI disturbances including nausea and diarrhoea. Elevations of bilirubin may be due to an inhibition of the glucuronidation process similar to the effect seen in patients with Gilbert's syndrome. To date these effects have been reversible and manageable with appropriate dose reduction and/or ancillary therapy allowing most patients affected by these events to stay on therapy. Appropriate measures have been included in this protocol and other Phase III protocols to minimize the likelihood of these events and to manage them effectively when they arise. Due to the potential for reproductive toxicity, adequate contraceptive precautions are required (refer to Section 5.1).

1.2 Research hypothesis

In patients who are DMARD naïve, DMARD intolerant, or have had an inadequate response to DMARDs, fostamatinib given as a monotherapy will result in improvements in signs and symptoms of RA that are greater than placebo and non-inferior to adalimumab.

1.3 Rationale for conducting this study

This study is designed to establish the optimum dose for fostamatinib when given as a monotherapy in a mixed population of either DMARD naive patients or patients who have had an inadequate response (IR), or intolerance, to DMARDs. This is part of a programme of studies to support registration of fostamatinib for the treatment of RA.

Regulatory agencies in US and Europe have suggested that data to demonstrate that fostamatinib is active in the treatment of RA without concomitant treatments would be helpful to the overall evaluation of the fostamatinib program. This study is designed to provide preliminary information and may lead to confirmatory studies.

1.4 Benefit/risk and ethical assessment

Refer to the IB for an overall risk/benefit assessment.

Fostamatinib is a potent syk inhibitor with potential as an anti-inflammatory/ immunomodulatory agent through its inhibition of the Fc receptor, B cell receptor and immunoglobulin-like receptor signalling pathways. To date, encouraging evidence of efficacy has been shown in double-blind Phase II studies with statistically significant clinically meaningful improvements in indices of RA for fostamatinib vs placebo, albeit mixed results were obtained in 1 study of refractory patients (patients who had previously failed 1 or more biologic agent).

Fostamatinib has been studied in healthy volunteers and patient populations. Notwithstanding the different underlying clinical situations, the safety profile has been consistent across these groups. As of

the RA program: ~200 patient years from double-blind studies and ~580 patient-years in open-label studies. The overall pattern of adverse effects includes dose-related effects on BP, neutrophil counts and GI complaints, as well as sporadic effects on liver transaminases, all of which are reversible and manageable with appropriate dose reduction or ancillary therapy.

There was no imbalance of serious cardiovascular (CV) AEs/death in the placebo-controlled phase of studies to suggest an excess of serious vascular events in the fostamatinib treatment arms. Cardiovascular event rates in the ongoing open-label study are reviewed by an independent data monitoring board.

Minimising patient risk, by implementing conservative eligibility criteria with due consideration to the toxicology data and growing experience in humans and RA patients together with toxicity management advice (eg, for hypertension) is provided for in this

protocol. An independent Safety Review Committee (SRC) will be constituted to review accumulating safety data on an ongoing basis throughout the Phase III program (see Section 12.4).

Adverse events will be collected throughout the study and, with the long-term extension study, monitoring patients for safety outcomes over a prolonged period of time will be possible. Pre-defined CV events will be reviewed by a blinded independent CV adjudication panel which will provide reports to the SRC.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objectives of this study are:

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

2.2 Secondary objectives

The secondary objectives of the study are:

- To further assess the efficacy of fostamatinib measured by DAS28, DAS28 response criteria, ACR20, ACR 50% response criteria (ACR50), ACR 70% response criteria (ACR70), ACR-N and the individual components of the ACR score.
- To assess physical function status of patients after administration of fostamatinib using the Health Assessment Questionnaire - Disability Index (HAQ-DI).
- To investigate the effects of fostamatinib on health-related quality of life using the 36-item Short Form Health Survey (SF-36) questionnaire.

2.3 Safety objectives

- To evaluate the safety and tolerability of fostamatinib taken as monotherapy in patients with active RA.

- To investigate the relationship between variations in the gene encoding uridine diphosphate (UDP) glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) and the safety and tolerability of fostamatinib in the study population.

2.4 Exploratory objectives

- To investigate the PK of R406 (the active metabolite of fostamatinib) and/or the PK of R788 (fostamatinib) or other metabolites and to investigate the relationship between systemic exposure to these metabolites and AEs, safety parameters and efficacy outcomes. This may be described in a separate report.

- To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib and/or adalimumab; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers. This may be described in a separate report.

- To investigate systemic biomarker profiles in RA patients. This may be described in a separate report.

3. STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

The study is a 24-week, multi-centre, randomised, double-blind (administrator unblinded), placebo-controlled (for 6 weeks), parallel group study to investigate the efficacy and safety of fostamatinib monotherapy in patients with active RA.

Eligible patients will include those who are who are not currently receiving DMARDs (DMARD naive, intolerant to DMARDs or have had an inadequate response to DMARDs). There is no minimum or maximum number of patients in each subgroup but randomisation will be stratified by DMARD naive versus DMARD- IR/intolerant. Patients must not have used DMARDs within 6 weeks prior to Visit 1 in order to be eligible to participate in the study.

Patients will be randomised to receive 1 of 3 oral dosing regimens of fostamatinib, a dosing regimen of adalimumab, or a matching placebo regimen.

Dosing Group A: Fostamatinib 100 mg *bid* for 24 weeks plus placebo injection every 2 weeks.

Dosing Group B: Fostamatinib induction and maintenance: induction of response with 100 mg *bid* for 4 weeks, followed by *qd* maintenance dosing with 150 mg up to Week 24, plus placebo injection every 2 weeks.

Dosing Group C: Fostamatinib induction and maintenance: induction of response with 100 mg *bid* for 4 weeks, followed by *qd* maintenance dosing with 100 mg up to Week 24, plus placebo injection every 2 weeks.

Dosing Group D: Adalimumab 40 mg by subcutaneous injection every 2 weeks for 24 weeks, plus placebo to fostamatinib twice daily.

Dosing Group E: Placebo *bid* for 6 weeks followed by switch to fostamatinib (100 mg fostamatinib *bid*; or 100 mg fostamatinib *bid* for 4 weeks, followed by fostamatinib 150 mg *qd* for the remaining 14 weeks up to Week 24) plus placebo injection every 2 weeks. NB: Patients will be assigned to their fostamatinib regimen at randomisation.

It is recognised that some AEs may require reduction of the fostamatinib dose. A reduced dosing regimen of fostamatinib 100 mg *qd* is available. Where fostamatinib dose reduction is required, the original treatment allocation will remain blinded, although patients will be aware of the switch to a reduced regimen. Patients on regimen C who meet the criteria for a dose reduction after Week 4 will need to be withdrawn since they are already taking 100 mg *qd* and no further dose reduction is available (see Section 5.8.1). Patients who have their dose reduced will remain on this dose for the remainder of the study. Dose reductions are not permitted for adalimumab injection, however due to the blinded nature of the study reduction of the placebo dose for patients on regimen D may occur (see Table 4).

Patients will be followed for DAS28 response and safety parameters as described in Table 2. An experienced, independent joint assessor, blinded to other study assessments as well as the dosing regimen, will be identified at each site to perform the swollen and tender joint counts.

If necessary, in order to control symptoms of RA, patients may have intramuscular, intravenous or intra-articular corticosteroid injections of up to 80 mg methyl prednisolone (or equivalent) according to the schedule in Section 5.6.

It is planned to randomise up to approximately 370 patients in total. An adequate number of patients will be randomised in the main study to ensure that approximately 250 patients (approximately 50 patients in each of the 5 dose regimens) will receive their randomised treatment. Ninety patients will receive randomised treatment in the sub-study. It is anticipated that approximately 560 patients will need to be screened in order to achieve this. Recruitment of patients will take place across approximately 150-200 centres in approximately 10-15 countries. Additional countries may be considered, so as to recruit the target number of patients in the required timeframe. The distribution of patients across countries and centres will depend on the final distribution of study centres.

Visit schedule

This study has 16 scheduled visits as shown in Figure 1. The study procedures to be undertaken at each visit are shown in Table 2.

Patients may return for unscheduled visits should their medical condition warrant urgent attention. Patients withdrawn from the study prematurely should undergo assessments as scheduled for the Week 24 final study visit. All patients (including those who have discontinued investigational products) will have an additional follow-up visit 4 weeks after their last dose of investigational products unless they continue into the long-term extension study.

The interval between Visit 1 (screening) and Visit 2 (treatment start) should be no more than 28 days. Patients should be randomised via the interactive voice response system (IVRS) or an associated interactive web response system (IWRS) as soon as possible after eligibility has been established based on Visit 1 assessments, as investigational products will be shipped to the study centre after patient randomisation. To allow for delivery of investigational products to the site, patients should be randomised approximately 7-10 days prior to Visit 2. Eligibility must still be confirmed at Visit 2 prior to dispensing of investigational products, even though patients have already been randomised. If a patient fails to meet eligibility criteria at Visit 2, they must not be given investigational products and must be withdrawn. Subsequent visits should be scheduled as close as possible to the pre-planned schedule, relative to Visit 2. Visits for primary efficacy assessment at Week 24 should be scheduled within ±5 days of the scheduled date as measured relative to the first dose.

Selected sites will also participate in an imaging sub-study, where approximately 90 OSKIRA-4 patients will be asked to provide consent to undergo MRI assessments in addition to their main study assessments described in this main protocol. The patients participating in the sub-study will be randomised to Dosing Groups A, D or E only. The analysis of the main OSKIRA-4 study will be performed when approximately 250 randomised patients who have received treatment have completed the main study as described above; this may include some or all patients participating in the sub-study. The sub-study will continue recruiting until the target number of sub-study subjects has been reached, which may continue beyond the end of the main study. If this occurs, the analysis of the main study will be updated with data from all additional patients. Participating sites will receive further details of the sub-study in a separate protocol appendix.

Long-term Extension Study

Patients who successfully complete the scheduled treatment period may be offered the opportunity to receive fostamatinib therapy in the long-term extension follow-up study (protocol D4300C00005). The treatment blind will not be broken for these patients until completion of this study.

The dose of fostamatinib that patients receive in the extension study will depend on their randomised dosing regimen, as follows:

Dosing Regimen A: Continue fostamatinib 100 mg *bid*

Dosing Regimen B: Continue fostamatinib 150 mg *qd*

Dosing Regimen C: Continue fostamatinib 100 mg *qd*

Dosing Regimen D: Fostamatinib 100 mg *bid*

Dosing Regimen E: Continue fostamatinib 100 mg *bid* or fostamatinib 150 mg *qd*

Patients who have had their fostamatinib dose reduced to 100 mg *qd* will continue at this reduced dose in the extension study. Patients receiving dosing regimen C who discontinue from the study due to a requirement for dose reduction cannot enter the long-term extension study.

All treatment allocations will be managed using the IVRS/IWRS and the treatment allocation will not be revealed for these patients at the time of transfer to the extension study.

Safety monitoring

During the study, the AstraZeneca Physician and representatives, in conjunction with AstraZeneca Patient Safety, will closely monitor safety findings on an ongoing basis. In addition to this an independent SRC will be constituted to periodically review safety data. The SRC will be responsible for recommending appropriate action for any emerging safety issues. This is described in more detail in Section 12.4.

Figure 1 Study flow chart

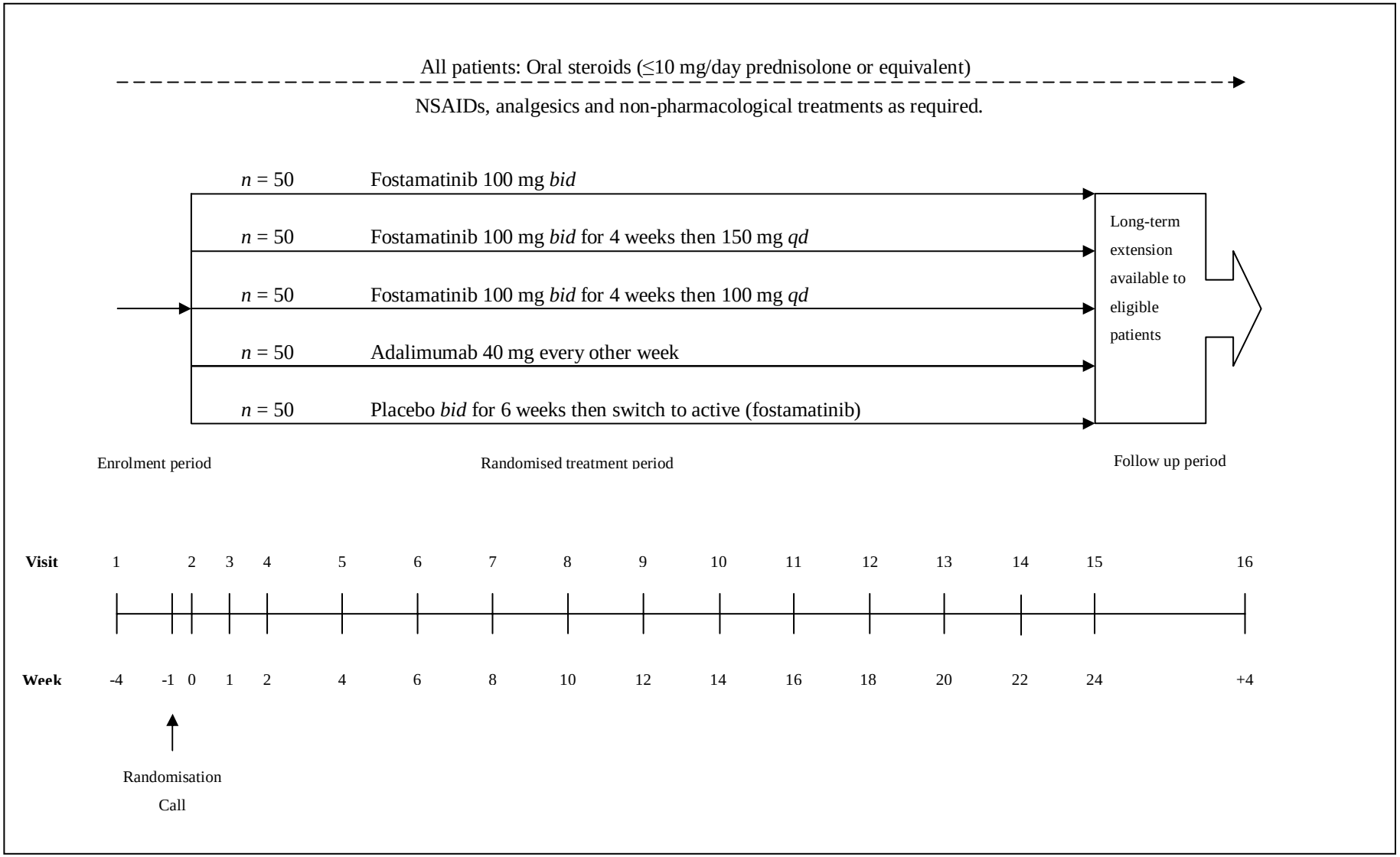

Table 2 Schedule of assessments

Assessments	**Randomised Treatment Period**															**Follow-up (unless entering OSKIRA-X)**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**(16)**	**Every 12 weeks[i]**
Week	**Screen**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24[g,h]**	**28**	
Obtain informed consent[a]	✓																
Demographic information	✓																
Medical and surgical history	✓																
Physical examination, height (V1 only) & weight	✓				✓		✓		✓						✓		
Radiological erosion status	✓																
Chest radiography	✓[b]																
Contraceptive history	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓[i]
Adverse events[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓[i]
Assess eligibility	✓																
Randomisation[d]	7-10 d prior to V2																
Confirm eligibility		✓[d]															
EFFICACY ASSESSMENTS																	
Swollen and tender joint counts[e]	✓	✓	✓	✓	✓	✓			✓			✓			✓		
Physician Global Assessment VAS[f]	✓	✓	✓	✓	✓	✓			✓			✓			✓		
HAQ-DI[f]	✓	✓	✓	✓	✓	✓			✓			✓			✓		
Patient Global Assessment VAS[f]	✓	✓	✓	✓	✓	✓			✓			✓			✓		
Patient Pain VAS[f]	✓	✓	✓	✓	✓	✓			✓			✓			✓		
SF-36[f]	✓	✓			✓				✓						✓		

Table 2 Schedule of assessments

Assessments	**Randomised Treatment Period**															**Follow-up (unless entering OSKIRA-X)**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**(16)**	**Every 12 weeks[i]**
Week	**Screen**	**0**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24[g,h]**	**28**	
LABS/SAFETY ASSESSMENTS																	
TB skin test (local)	✓																
Virology screen (HepB, HepC)	✓																
RF and anti-CCP	✓														✓		
Genetics sample		✓															
Biomarker sample[j]		✓				✓									✓		
Pregnancy test[k]	✓	✓[k]							✓						✓		
CRP	✓	✓	✓	✓	✓	✓			✓			✓			✓		
ESR (local)	✓[l]	✓	✓	✓	✓	✓			✓			✓			✓		
Total cholesterol, LDL, HDL, triglycerides, glucose[m]		✓							✓						✓		
Clinical chemistry[n]	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	
Haematology	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	
Urinalysis (local)	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓		✓	✓	
Pharmacokinetic blood samples[o]					✓										✓		
Blood pressure, pulse rate[p]	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓		✓	✓	
12-lead ECG[q]	✓								✓						✓		
Dispense oral investigational product		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Administer injected investigational product[r]		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			

[a] Informed consent should be obtained at Visit 1 or before, including optional consent to exploratory biomarker and/or exploratory genetic research.

[b] A chest X-ray, current or taken within the previous 3 months, which excludes active pulmonary tuberculosis or other pulmonary infection.
[c] Non-serious AEs and SAEs to be collected from time of informed consent (even if this is prior to Visit 1).
[d] Investigational product assignment/randomisation should be performed as soon as possible by the study centre after eligibility is determined based on Visit 1 assessments. The randomisation call should be made approximately 7-10 days prior to Visit 2, to allow for delivery of investigational products to the site. Eligibility must still be confirmed at Visit 2 prior to dispensing of investigational products, even though patients have already been randomised. If a patient fails to meet eligibility criteria at Visit 2, they must not be given investigational product and must be withdrawn.
[e] Joint assessor will be independent to the rest of the study team.
[f] Questionnaires must be completed in clinic by the patient before any investigations or discussions about their disease with the clinic staff.
[g] Patients who discontinue from investigational products prior to Week 24 (but do not withdraw consent) should return to the study site 24 weeks after randomisation to complete all Week 24 assessments.
[h] Patients who discontinue investigational products will, at discontinuation, have a withdrawal visit equivalent to the Week 24 assessments. This withdrawal visit will not include collection of a blood sample for exploratory biomarker research. Patients who discontinue investigational products before Week 24 should have a PK sample taken.
[i] All patients who discontinue investigational product prior to Week 24 (but do not withdraw consent) will be contacted every 12 weeks after the 4-week follow-up visit until the final contact at 24 weeks after their randomisation visit (Visit 2) in order to collect key safety outcomes data (see Section 5.8.3.1).
[j] Serum and plasma samples will be collected for exploratory biomarker profiling. Sampling is optional and subject to separate approval/consent.
[k] Women of childbearing potential only. At Visit 2 a urine pregnancy test should be performed to confirm inclusion.
[l] At Visit 1, this should be performed by a person independent of the study team without access to the other study assessments.
[m] Patients should be fasting prior to blood sampling (see Section 6.4.5).
[n] A finding of ALT or AST ≥3 x ULN or bilirubin ≥2 x ULN should prompt repeat testing of all liver function tests (preferably within 72 hours).
[o] Time of PK sample and time of previous dose to be recorded.
[p] Blood pressure and pulse rate, sitting after 10 minutes rest, 3 measurements at 2 to 5 minute intervals, automated machine.
[q] Three consecutive ECG recordings will be made.
[r] Administered by an unblinded person who will be independent of the on-site study team.

3.2 Rationale for study design, doses and control groups

Study design

This is a 24-week, randomised, double-blind, placebo-controlled (for 6 weeks), parallel group, multi-centre study. Three dosing regimens of fostamatinib are being assessed versus adalimumab or placebo: Regimen A 100 mg *bid*, Regimen B induction with 100 mg *bid* for the first 4 weeks followed by 150 mg *qd* maintenance thereafter and Regimen C induction with 100 mg *bid* for the first 4 weeks followed by 100 mg *qd* maintenance thereafter.

Randomisation minimises selection bias between the fostamatinib, adalimumab and placebo treatment groups. The parallel group design takes into account the progressive nature of the disease. Blinding of the treatment regimens throughout the 24-week study period minimises any bias that could be caused by knowledge of the treatment by either investigator or patient, which is especially important given that many of the efficacy and safety measures are subjective. Potential bias will be further minimised by identifying an experienced, blinded, independent joint assessor at each site. This person will perform the swollen and tender joint counts without access to any other study-related outcomes.

Inclusion of a placebo control allows changes over time to be assessed in relation to natural fluctuations in the disease. The study protocol switches placebo patients to active treatment at 6 weeks to ensure that patients with active disease are not maintained only on placebo for a prolonged period.

There are clear procedures within the protocol for fostamatinib dose reduction and discontinuation in the event of specific safety or tolerability issues.

Study population

The RA patient population selected for this study is a population of patients who are not currently receiving DMARDs (DMARD naive patients or patients who have had an inadequate response, or intolerance, to DMARDs). This population of RA patients would benefit from DMARD monotherapy with potentially fewer AEs than combination therapy. The trial medication (fostamatinib, adalimumab or placebo) will be administered as monotherapy, ie, without DMARDs.

The disease activity required for entry is typical of other monotherapy studies and should allow demonstration of a clinically meaningful treatment effect.

Patients diagnosed with ACR functional Class IV disease are excluded from this study (see Section 4.2) in order to exclude patients with such severe disease that it may impact on their ability to participate in the study or whose condition may confound the assessment of efficacy and safety of the investigational product. It should be noted that ACR Class IV is intended to be similar in severity to the original Steinbrocker or American Rheumatism Association functional Class IV definition, ie, it is intended to exclude patients with severe incapacitation, including those who are wheelchair or bed-bound not simply those with any degree of limitation to perform usual self-care, vocational and avocational activity.

In view of the immunomodulatory mechanism and safety signals identified to date, care has been taken to exclude patients likely to be at greater risk of serious infection (including patients with active or latent tuberculosis), hypertension, liver toxicity, neutropenia or pregnancy.

Selection of comparator

Adalimumab is an anti-TNFα agent that is widely available and has been widely studied. This treatment is being included as an active comparator in order to assess the relative efficacy of fostamatinib. Additionally, the bi-weekly dosing frequency of adalimumab, compared with the dosing frequency of other RA treatments, will reduce the number and frequency of study visits and decrease the injection burden on study centre personnel.

Selection of fostamatinib dose and treatment duration

The efficacy and safety dose response of fostamatinib are discussed in Section 1. The dosing regimens to be studied in this Phase IIb study are based on the results of the previous Phase II studies of fostamatinib in combination with methotrexate, C788-006 and C788-010. Study C788-006 defined a non-efficacious dose (50 mg *bid*) and a maximum well-tolerated dose (100 mg *bid*). Study C788-010 confirmed efficacy in treating the signs and symptoms of RA at the maximum well-tolerated dose (100 mg *bid*), as well as demonstrating that a second, lower dose (150 mg *qd*) was also efficacious, albeit with lower ACR response rates than demonstrated for 100 mg *bid*.

Three dosing regimens will be tested in this study: Dose A, Dose B and Dose C.

Dose A, 100 mg *bid*

Dose A is the maximum well-tolerated dose defined in Phase IIb which is expected to be efficacious with an acceptable tolerability profile.

Dose B, induction and maintenance: induction of response with 100 mg *bid* for 4 weeks followed by 150 mg *qd* maintenance

Dose B is a modification of the lower dose tested in Phase IIb (150 mg *qd*) which was generally better tolerated than Dose A, but was associated with lower efficacy. The modification is the addition of an induction regimen of 100 mg *bid* for 4 weeks. It is expected that this modification will result in greater efficacy whilst maintaining good tolerability. This expectation is based on the observation that the onset of action was generally rapid with statistically significantly greater ACR20 responses at 1 week following treatment with fostamatinib 100 mg *bid*. Furthermore, an analysis of the efficacy profile over time suggests that a similar level of efficacy is maintained in patients with dose reductions, which is also supported by the PK properties of fostamatinib.

Dose C, induction and maintenance: induction of response with 100 mg *bid* for 4 weeks followed by 100 mg *qd* maintenance

Similar to Dose B, Dose C includes an induction regimen of 100 mg *bid* for 4 weeks designed to achieve a clinically significant effect that can then be maintained by a lower dose. While previous Phase II clinical trials demonstrated that 50 mg *bid* had no greater efficacy than placebo, these studies did not include an induction regimen, and were conducted in patients taking a stable dose of methotrexate. It is anticipated that a maintenance dose of 100 mg *qd* will demonstrate greater efficacy with the inclusion of an induction regimen, while giving the best tolerability profile.

The treatment duration is relevant to the chronic nature of RA and the requirement for maintenance treatment.

Outcome variable selection

The study is designed to comply with the recommendations of the European regulatory authorities for studies in this indication (Committee for Proprietary Medicinal Products [CPMP]/EWP/556/95 Rev 1/Final).

The primary outcome variable (DAS28) is a standard outcome criterion for RA and has been accepted for regulatory purposes to demonstrate efficacy on signs and symptoms.

Visit frequency

Visits are scheduled every 2 weeks for the first 12 weeks of the study in order to provide the opportunity for frequent assessment of patient safety via recording of AEs and assessment of vital signs and laboratory parameters. After 12 weeks, although visits will occur every 2 weeks for administration and dispensing of investigational products, the frequency of safety assessments will be every 4 weeks.

The first study assessment at 1 week is scheduled in order to assess how rapidly fostamatinib demonstrates efficacy against the signs and symptoms of RA. Efficacy assessments will also be made at Weeks 2, 4, 6, 12, 18 and 24 to further characterize the onset of efficacy of fostamatinib.

Genetic and biomarker research

An objective of this study is to investigate the relationship between variations in the gene encoding UGT1A1 and the safety and tolerability of fostamatinib in the study population. Genotype at the *UGT1A1* locus is known to contribute to a spectrum of hyperbilirubinaemias, including Gilbert's syndrome (Strassburg et al 2008). Fostamatinib is an inhibitor of UGT1A1. Given this, *UGT1A1* genotype data will be used to aid interpretation of bilirubin levels throughout the fostamatinib clinical programme. The results of this research may be pooled with genetic data from other studies.

In addition, optional exploratory research will be performed into biomarkers and genes/genetic variation that may influence the disposition, tolerability, efficacy or safety of

fostamatinib and/or adalimumab and associated biomarkers, and susceptibility to, progression of, and prognosis of RA. Future exploratory analyses will be guided by emerging data from this and other studies with fostamatinib. The results of this exploratory research will not necessarily form part of the clinical study report (CSR) for this study but may be pooled with genetic data from other studies on RA patients to generate hypotheses for future studies. Please refer to Appendix D for further details.

4. PATIENT SELECTION CRITERIA

Investigators should maintain the pre-study screening log recording details of patients considered for inclusion in the study. Each patient enrolled should meet all of the inclusion criteria and none of the exclusion criteria. Under no circumstances can there be exceptions to this rule.

It is anticipated that patients will be recruited primarily from specialist rheumatology centres but other centres with access to the relevant patient population and appropriate expertise may participate.

4.1 Inclusion criteria

For inclusion in the study subjects must fulfil the following criteria:

1. Provision of informed consent, prior to any study-specific procedures.

   NB: Patients agreeing to participate in the optional exploratory biomarker and/or exploratory genetic research must provide a separate informed consent.

2. Male or female aged 18 and over.

   NB: Women of childbearing potential may be included only if using acceptable contraceptive methods (see Appendix H for definitions). Women of childbearing potential must have 2 negative pregnancy tests, at least 14 days apart, prior to receiving investigational products.

3. Diagnosis of RA, after the age of 16 according to the revised (1987) criteria of the American College of Rheumatology (see Appendix E for criteria) and one of the following:

   – diagnosis within 5 years prior to Visit 1 and inadequate response to treatment with a maximum of 2 the following DMARD therapies: methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, gold, penacillamine, minocycline, mycophenolate, cyclophosphamide, tacrolimus or doxycycline

   or

   – diagnosis within 5 years prior to Visit 1 and intolerance to DMARD therapy

or

- diagnosis within 2 years prior to Visit 1 and no previous use of DMARDs.

4. Active RA defined as:

   - ≥4 swollen joints and ≥4 tender/painful joints (from 28 joint count)

   and either:

   - ESR ≥28 mm/h, or
   - CRP ≥10 mg/L.

5. At least 2 of the following:

   - Documented history or current presence of positive rheumatoid factor (RF)
   - Radiographic erosion within 12 months prior to enrolment
   - Presence of serum anti-cyclic citrullinated peptide antibodies (anti-CCP).

4.2 Exclusion criteria

Subjects must not enter the study if any of the following exclusion criteria are fulfilled:

1. Females who are pregnant or lactating.

2. Any systemic inflammatory conditions (other than RA), connective tissue disease or chronic pain disorders that may interfere with the interpretation of the outcome data. Examples include psoriatic arthritis, reactive arthritis, gout, systemic lupus erythematosus (SLE), polymyalgia rheumatic and/or temporal arteritis, Lyme's disease, fibromyalgia and chronic fatigue syndromes.

3. American College of Rheumatology functional Class IV (see Appendix F) or wheelchair/bed-bound.

4. Uncontrolled or poorly controlled hypertension defined as ≥140 mmHg systolic and/or ≥90 mmHg diastolic at baseline (Visit 2) with or without current anti-hypertensive treatment.

   NB: If above these limits at Visit 1, anti-hypertensive treatment may be initiated according to local guidelines and patients may be considered eligible providing BP has been controlled before Visit 2, with the interval between screening (Visit 1) and baseline (Visit 2) not exceeding 4 weeks. If control of hypertension is not achieved within this period patients should be considered ineligible and not re-screened again.

Note that the mean of the 2nd and 3rd BP measurements should be used (see Section 6.4.8).

5. Absolute neutrophil count (ANC) <1500/mm^3 or 1.5 x 10^9/L. If a patient has ANC <1500/mm^3 or 1.5 x 10^9/L, but ANC >1200/mm^3 or 1.2 10^9/L, one re-test is allowed, at the investigator's discretion, within the 28-day period between Visit 1 and 2.

6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.2 x upper limit of normal (ULN), or bilirubin >1.2 x ULN. If a patient has AST or ALT >1.2 x ULN but <2 x ULN, one re-test is allowed, at the investigator's discretion, within the 28-day period between Visit 1 and 2.

   NB: Patients with documented Gilbert's Syndrome may be included at the discretion of the investigator where liver function tests are normal except for an elevation of unconjugated (indirect) bilirubin consistent with Gilbert's Syndrome, and where haemolysis has been excluded.

7. History of liver function abnormality requiring investigation, drug induced liver injury, chronic liver disease, excessive alcohol consumption or chronic alcohol induced disease.

8. Evidence of recent or significant CV disease defined as:

   – Any major CV event within the previous 6 months including myocardial infarction, unstable angina, cerebrovascular accident, pulmonary embolism, or heart failure New York Heart Association Class III or IV (see Appendix M).

9. Evidence of active or recent infection including:

   – Positive serological test for hepatitis B or hepatitis C (patients may be included if confirmed hepatitis C recombinant immunoblot assay negative or hepatitis C virus ribonucleic acid (RNA) negative [qualitative]), or patients with suspected human immunodeficiency virus (HIV).

   – Treatment with intravenous antibiotics within previous month prior to randomisation, oral antibiotics within 2 weeks prior to randomisation or current evidence of a clinically significant active infection.

10. Evidence of tuberculosis (TB) infection.

    – Patients should have a chest X-ray, current or taken within the previous 3 months, which excludes active pulmonary TB or other pulmonary infection.

    – Patients should have a negative TB skin test (negative means <5 mm induration).

- If the skin test is positive in an unvaccinated patient an appropriate prophylactic TB regimen must be documented and patients must have completed anti-TB treatment 12 months prior to randomisation.

- If the skin test is positive in a vaccinated patient, the patient may be included if the induration is <10 mm, the chest x-ray shows no signs of TB (as confirmed by a radiologist), and Quantiferon-TB Gold Test or T-SPOT.TB testing is negative or the patient has had a course of isoniazid (or comparable regimen).

11. Patients who have previously received treatment with a TNF-α antagonist (including etanercept, certolizumab, adalimumab, infliximab, golimumab) or anakinra.

12. Patients who have previously been treated with other biologic agents including rituximab, abatacept and tocilizumab.

13. Use of any DMARDs within 6 weeks prior to Visit 1, eg, methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, hydroxychloroquine, chloroquine, gold, penacillamine, minocycline, mycophenolate, cyclophosphamide, tacrolimus or doxycycline. Any patient that has received leflunomide within 12 weeks prior to randomisation must have completed a cholestyramine washout prior to study randomisation.

14. Intramuscular, intravenous or intra-articular steroid injection within 6 weeks prior to randomisation.

15. Patients requiring doses of oral steroids >10 mg/day prednisolone (or equivalent).

    NB: Patients on doses ≤10 mg/day are permitted but should have a stable dose for at least 6 weeks prior to randomisation.

16. Inability to comply with the local approved product information for adalimumab.

    NB: Where a local label is not available, then the label applicable to the supplied drug will apply.

17. Administration of a live vaccine in the 4 weeks prior to randomisation.

18. History of malignancy or neoplastic disease. Patients with a history of basal or squamous cell carcinoma of the skin that occurred >5 years ago from Visit 1 and was successfully treated are permitted.

19. Severely impaired renal function (estimated glomerular filtration rate ≤30 mL/min according to the Cockcroft-Gault formula).

20. Any other clinically significant disease or disorder, which in the opinion of the investigator (by its nature or by being inadequately controlled) might put the patient

at risk due to participation in the study, or may influence the results of the study, or the patient's ability to participate in the study.

21. Involvement in the planning and conduct of the study including involved staff at AstraZeneca, Rigel Pharmaceuticals, relevant Contract Research Organisations (CROs) and the investigational sites.

22. Previous randomisation in this study or patients who have received fostamatinib in a previous study.

23. Recent participation in a clinical study involving an investigational compound within the 12 weeks prior to randomisation or 5 half-lives of the investigational product (whichever is longer). Patients involved in non-drug methodology studies (either invasive or non-invasive) may be included without delay, at the discretion of the investigator.

24. Previous allogeneic bone marrow transplant.

25. Non-leukocyte depleted whole blood transfusion within 120 days of genetic sample collection.

5. STUDY CONDUCT

5.1 Restrictions during the study

NB: For concomitant medication restrictions, see Section 5.6, Table 5.

Pregnancy and conception

- All patients must be made fully aware of the information relating to the potential for reproductive toxicity as detailed in the informed consent form.
- Women of childbearing potential may be included only if acceptable contraception is in place for 3 months before trial entry, for the duration of the study and for 4 weeks after the last dose of fostamatinib (see Appendix H for definitions of childbearing potential and acceptable contraceptive methods). Due to the prescribing recommendations for adalimumab, women of childbearing potential are strongly recommended to continue to use adequate contraception to prevent pregnancy for at least 5 months after the last injection of adalimumab/placebo.
- Women of childbearing potential must have 2 negative pregnancy tests, at least 14 days apart, prior to receiving investigational products.
- Contraceptive history of women of childbearing potential must be checked throughout the study and patients should be made aware of the availability of

emergency “post-coital” contraception if there is an indication for it (eg, missing intra-uterine device threads or a late parenteral injection).

Other restrictions

- Patients should not donate blood at any time during the study or for 3 months following last treatment.
- Fostamatinib should not be taken with grapefruit juice or other food/drink known to inhibit CYP3A4.

5.2 Patient enrolment and randomisation

Randomisation to treatment groups will be managed centrally using IVRS or IWRS. For the purposes of this protocol, the term IVRS will be used to describe the use of either one of these systems. The IVRS will be used to allocate randomisation numbers and treatment groups.

The investigator will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.
2. Assign potential patient a unique enrolment number, beginning with “E#”, using an IVRS or an associated IWRS.
3. Determine patient eligibility. See Section 4.1 and Section 4.2.
4. Assign eligible patients a unique randomisation code (patient number) produced by the AstraZeneca Global Randomisation System using IVRS.

If a patient withdraws from participation in the study, then his/her enrolment or randomisation code cannot be reused.

5.2.1 Procedures for randomisation

After providing written informed consent, the patient will be assigned an enrolment number. The enrolment number (E-code) is a 7 digit code made up of centre number and patient number within that centre. All screened patients are allocated an E-code regardless of if they are randomised. Once allocated, this number will not be re-used.

Patient eligibility will be established before treatment randomisation. Patients will be randomised strictly sequentially, as they become eligible for randomisation. Patients will be randomised to receive 1 of the 3 dosing regimens of fostamatinib, adalimumab or matching placebo. At randomisation, the patients allocated to placebo will be assigned to switch to fostamatinib (100 mg fostamatinib *bid*; or 100 mg fostamatinib *bid* for 4 weeks, followed by fostamatinib 150 mg *qd* for the remaining 14 weeks up to Week 24) at Week 6.

The actual treatment given to patients will be determined by a randomisation scheme. The randomisation scheme will be generated by Biostatistics and produced by a computer software program that incorporates a standard procedure for generating random numbers. A central randomisation scheme will be produced, with codes released in blocks, so that the randomisation will be balanced within each country.

After eligibility is determined during the screening period, patients will be allocated to a treatment group using the IVRS. The study centre should contact the IVRS for randomisation after all screening results have been obtained. The randomisation call should be made approximately 7-10 days prior to Visit 2, to allow for delivery of investigational products to the site. Eligibility must still be confirmed at Visit 2 prior to dispensing of investigational products, even though patients have already been randomised. If a patient fails to meet eligibility criteria at Visit 2, they must not be given investigational product and must be withdrawn.

The IVRS will trigger the supply of investigational products to the study centre following the randomisation of the patient. The supply of investigational products will then be tailored to the rate of enrolment at the centre. Specific information concerning the use of this IVRS will be provided to the investigators. If a patient discontinues from the study, the randomisation number and corresponding patient kit will not be re-used, and the patient will not be allowed to re-enter the study.

5.3 Procedures for handling patients incorrectly enrolled or randomised

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule.

Patients who are incorrectly enrolled but are not yet randomised or initiated on treatment should be withdrawn from the study.

Where patients that do not meet the inclusion and/or exclusion criteria are enrolled in error, or incorrectly started on treatment, or where patients subsequently fail to meet the study criteria post-initiation, the Investigator should inform the AstraZeneca Global Study Delivery Team Physician immediately. If a patient fails to meet the eligibility criteria for BP at Visit 2 as outlined in exclusion criteria 4, the patient should be discontinued from the study prior to the dispensing of investigational product at that visit.

The AstraZeneca Global Study Delivery Team Physician or representative is to ensure all such decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The study treatment is double-blind for patients, investigators and study personnel and will remain so throughout the entire treatment period. The IVRS will be used to manage randomisation to treatment groups in a blinded manner. This includes those who transfer into the long-term extension study.

To ensure blinding of the treatments, the active and dose-matched placebo tablets will be identical in appearance and identical packaging and labelling will be used. Patients will receive the same number of tablets whichever randomised dose they receive. Since an exact placebo match for adalimumab is not available, each site will be required to appoint an unblinded administrator for the injection, who will be independent of the rest of the on-site study team and who will not otherwise be involved in the conduct of the study.

Where fostamatinib dose reduction is required, the original treatment allocation will remain blinded but patients will be aware of a reduction in the number of tablets and the switch to a reduced regimen. Patients on dose regimen C who meet the criteria for a dose reduction after Week 4 will need to be withdrawn since they are already taking fostamatinib 100 mg *qd* and no further dose reduction is available. This will entail unblinding of the patient via the IVRS. Patients receiving dosing regimen C who withdraw from the study due to a requirement for dose reduction cannot enter the long-term extension study.

Where necessary, SRC members may have access to unblinded data however no members of the Study team (at AstraZeneca or the CRO) will have access to unblinded data until after database lock is declared (see Section 12.4). The only exception to this is that personnel involved in the analysis of plasma concentrations for PK analysis may have access to treatment assignment information in order to exclude those samples taken from patients receiving placebo (for Week 4 PK sample only) or adalimumab from the analysis.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomisation for each randomised patient, will be available to the investigator(s) or pharmacists, and the personnel who are independent to the study evaluation at the Patient Safety Department, AstraZeneca from the IVRS. Routines for this will be described in the IVRS user manual that will be provided to each centre.

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomisation. The investigator documents and reports the action to AstraZeneca or its representative, without revealing the treatment given to the patient to the staff of AstraZeneca or its representative. Comprehensive instructions as to the methods for breaking the blind will be provided to the sites. Investigators are encouraged to discuss the patient's case with the AstraZeneca Physician or representative prior to breaking the blind.

AstraZeneca or its representative retains the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.5 Treatments

5.5.1 Identity of investigational products

Table 3 Investigational products

Investigational product	Dosage form and strength	Manufacturer
Fostamatinib oval, blue, film-coated tablets contain: fostamatinib, microcrystalline cellulose, sodium starch glycolate, povidone, magnesium stearate, starch and Opadry II Blue 85F99003.	Tablet 50 mg	
Adalimumab (Humira®) Injection	40 mg/ 0.8 ml (prefilled syringe)	
Placebo to fostamatinib oval, blue, film-coated tablets contain: microcrystalline cellulose, sodium starch glycolate, povidone, magnesium stearate, starch and Opadry II Blue 85F99003.	Tablet to match 50 mg	
Placebo to adalimumab	5 mL sterile sodium chloride 0.9% w/v ampoule (Mini-Plasco®) (packs containing 1 syringe and 1 ampoule)	

Investigational product (tablets) will be provided in blinded blisters. Fostamatinib dose reduction supply will be provided in bottles with a child resistant cap of either 50 mg or placebo.

The injectables will be provided as follows: the unblinded administrator will be required to prepare the syringes for each administration according to handling instructions provided. The manipulation required will be kept to a minimum but is necessary to facilitate blinding of the injection treatment arm.

Drug will be shipped to the site via the IVRS according to an individual patient randomisation. The site will not receive stock of drug prior to a patient being randomised.

5.5.2 Doses and treatment regimens

Table 4 Dosing regimens

Dosing regimen	Dose	Tablet taken morning	Tablet taken evening	Injection received every 2 weeks
A	100 mg twice daily	2 x 50 mg fostamatinib 1 x placebo to 50 mg	2 x 50 mg fostamatinib	Placebo
B	100 mg twice daily for first 4 weeks	2 x 50 mg fostamatinib 1 x placebo to 50 mg	2 x 50 mg fostamatinib	Placebo
	150 mg once daily from Week 5 to Week 24	3 x 50 mg fostamatinib	2 x placebo to 50 mg	
C	100 mg twice daily for first 4 weeks	2 x 50 mg fostamatinib 1 x placebo to 50 mg	2 x 50 mg fostamatinib	Placebo
	100 mg once daily from Week 5 to Week 24	2 x 50 mg fostamatinib 1 x placebo to 50 mg	2 x placebo to 50 mg	
D	Adalimumab 40 mg	3 x placebo to 50 mg	2 x placebo to 50 mg	Adalimumab 40 mg
E	Placebo twice daily up to Week 6	3 x placebo to 50 mg	2 x placebo to 50 mg	Placebo
	Switch to dosing regimen A or B at Week 6			
Fostamatinib dose reduction (A, B, or C*)	100 mg once daily	2 x 50 mg fostamatinib	None	Placebo
Fostamatinib dose reduction (D or E)	Placebo	2 x placebo to 50 mg	None	Adalimumab 40 mg (D) or placebo (E)

* Dose reduction for regimen C within the first 4 weeks of dosing ONLY.

Investigational product (tablets) will be self-administered, *bid* by mouth, once in the morning and once in the evening for 24 weeks. In the event that the investigator decides to reduce the dose due to AEs, dosing will be *qd* in the morning. Fostamatinib dose reduction is not available for patients on dosing regimen C after the first 4 weeks of dosing. Patients on dosing regimen C who require a dose reduction after Week 4 must be withdrawn from the study. Patients receiving dosing regimen C who withdraw from the study due to a requirement for dose reduction cannot enter the long-term extension study. At Visit 2

(Week 0) patients will be instructed to take their first dose of investigational product in the morning on the following day.

If a patient misses a scheduled dose, they are to continue to take their next dose as normal and should not take 2 doses at the same time.

Tablets may be taken with or without food. Tablets should not be taken with grapefruit juice or other food/drink known to inhibit CYP3A4. In the event of gastric upset it may be preferable to take the tablets with food.

Investigational product (injection) will be administered by study centre personnel at the study centre every other week. Injections will be given by an unblinded administrator, independent of the rest of the on-site study team and who will not otherwise be involved in the conduct of the study. Injections should be given after all other assessments have been performed (to avoid any bias due to possible injection site reactions).

5.5.3 Additional study drug

Patients will continue to take their usual prescribed concomitant medications, as allowed by the protocol, from their usual source.

5.5.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language and supplied in a multi-language format.

Each medication pack will be labelled with the Study Code and a unique identifier (Med ID). This will be programmed into the IVRS. At each visit, the IVRS will assign the correct pack for the allocated treatment type, treatment phase and visit and the Med ID will be linked to an individual patient. The Med ID assigned by the IVRS will then be linked to the protocol, randomisation code (patient number), site and patient E-Code.

Management of the expiry date will be within the IVRS and will be controlled by the use of triggers such as “do not dispense” dates which restrict the dispensing of expiring packs by a certain date linked to the expiry of that individual pack.

5.5.5 Storage

All investigational products should be kept in a secure place under appropriate storage conditions. The investigational product label specifies the appropriate storage conditions.

5.6 Concomitant and post-study treatments

Specific treatments allowed and restricted during the course of the study are described in Table 5. Other medication that is considered necessary for the patient’s safety and well-being may be given at the discretion of the investigator and recorded in the appropriate sections of

the electronic Case Report Form (eCRF). Investigators are encouraged to discuss the introduction of any restricted medications with the AstraZeneca Physician or representative.

Table 5 Concomitant treatments

Treatment	Restriction
DMARDS: eg, methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporine, hydroxychloroquine, chloroquine, gold, penacillamine, minocycline, mycophenolate, cyclophosphamide, tacrolimus, doxycycline.	Not permitted within 6 weeks prior to Visit 1 and throughout the study. Any patient that has received leflunomide within 12 weeks prior to randomisation must have completed a cholestyramine washout prior to study randomisation.
TNF-α antagonists (other than used as the investigational product) or anakinra	Not permitted. Patients who have previously received a TNF-α antagonist or anakinra are excluded from the study.
Other biologics	Not permitted. Patients who have previously been treated with other biologic agents including rituximab, abatacept and tocilizumab are excluded from the study.
NSAIDs	Permitted as medically indicated, including cyclooxygenase-2 inhibitors. Dose should remain stable from 4 weeks prior to randomisation. Any required changes to the dosing regimen should be avoided, where possible, within the 7 days prior to study visits in order to avoid confounding the efficacy assessments. On study visit days, NSAIDs should be taken at the usual time.
Analgesics	Permitted as required. If possible patients should avoid within the 12 hours before clinic assessments although paracetamol may be used as a rescue medication if necessary.
Oral corticosteroids	Permitted at doses ≤10 mg/day of prednisolone or equivalent. Dose should remain stable from 6 weeks prior to randomisation and where possible, throughout the entire study.
Parenteral steroids	If necessary, in order to control symptoms of RA, patients may have intramuscular, intravenous or intra-articular corticosteroid injections of up to 80 mg methyl prednisolone (or equivalent). However, no injections should be given within 8 weeks of primary outcome measures, ie, no injections will be given between Week 0 and Week 6 and between Week 16 and Week 24.

Table 5 Concomitant treatments

Treatment	Restriction
CYP3A4 inhibitors and inducers, CYP2C8 substrates, digoxin (P-glycoprotein substrate)	There is potential for fostamatinib to be affected by drug-drug interactions. The active metabolite of fostamatinib is metabolised by CYP3A4 and it is an *in vitro* inducer of cytochrome P450 isoenzyme 2C8 (CYP2C8). Fostamatinib, but not the active metabolite, is an *in vitro* inhibitor of P-glycoprotein. Restrictions on the co-administration of CYP3A4 inhibitors, inducers, CYP2C8 substrates and P-glycoprotein substrates (digoxin) are described in Appendix G.
Live vaccine	Not permitted.
Non-pharmacological treatments (eg, physical therapy)	Permitted freely.

End of study treatment

At the end of their participation in the study, patients will be treated according to local practices unless continuing into the long-term extension protocol.

5.7 Treatment compliance

The administration (dose, frequency and dates) of all concomitant medications (including new medications taken during the study and investigational products) should be recorded in the appropriate sections of the eCRF from Visit 1.

Patients will be asked to return their unused medication and all packaging (even if empty) to the study centre at each visit for reconciliation purposes. At each visit the investigator will check returned medication. The continued participation of patients who, in the opinion of the investigator, have failed to comply should be considered according to Section 5.8.

Any significant dose interruptions of investigational products should be discussed with the AstraZeneca representative and recorded in the eCRF.

5.7.1 Accountability

The investigational products provided for this study will be used only as directed in the study protocol.

The study personnel will account for all investigational products dispensed to and returned from the patient.

AstraZeneca personnel or its representative will account for all investigational products received at the site, unused investigational products and for appropriate destruction. Certificates of delivery, destruction or return should be signed.

5.8 Dose reduction, discontinuation of investigational products and withdrawal from study

5.8.1 Dose reduction

It is recognised that some AEs may require temporary withdrawal of investigational product (fostamatinib) and subsequent reduction of the dose. A reduced dosing regimen of fostamatinib 100 mg *qd* is available and should be considered under the following circumstances:

- A finding of an ALT, AST or bilirubin ≥3 x ULN. (NB: If the ALT or AST elevation is accompanied by an elevation of total bilirubin ≥2 x ULN discontinue investigational products.)
- ANC <1000/mm^3 or 1.0 x 10^9/L.
- Patient reports unacceptable GI intolerance (nausea, vomiting, diarrhoea) or dizziness. (Please refer to Appendix O 'Management of Diarrhoea - Guidance for Investigators', for guidance regarding management of diarrhoea.)
- Sustained increased BP (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) where attempts to manage such increases in BP by initiating or adjusting anti-hypertensive medication have been unsuccessful. An optional dose reduction at the discretion of the investigator may be done if BP exceeds 160 mmHg systolic and/or 100 mmHg diastolic (as defined in Appendix I). Note that the mean of the 2nd and 3rd BP measurements should be used (see Section 6.4.8).

Patients on regimen C who meet the criteria for a dose reduction after Week 4 will need to be withdrawn since they are already taking 100 mg *qd* and no further dose reduction is available. This will entail unblinding of the patient via the IVRS. Patients receiving dosing regimen C who withdraw from the study due to a requirement for dose reduction cannot enter the long-term extension study.

Dose reductions are not permitted for adalimumab injection, however due to the blinded nature of the study reduction of the placebo dose for patients on regimen D may occur (see Table 4).

Investigators are encouraged to discuss the patient's case with the AstraZeneca Physician or representative to agree upon appropriate action.

Where AST, ALT or bilirubin levels are found to rise 1.5 times above the patient's last result, investigators should consider proactive management such as repeat laboratory tests (see Section 6.4.5) and possible reduction of study drug dose or concomitant medication.

Randomised patients should be followed up as long as medically indicated.

Where dose reduction is required, the original treatment allocation will remain blinded.

Patients who have their dose reduced will remain on this dose for the remainder of the study and into the long-term extension, if applicable. Dose re-escalation is not permitted.

5.8.2 Discontinuation of investigational products

Patients **must** be discontinued from investigational product (both oral and injected) in the following situations:

- Patient decision. The patient is at any time free to discontinue investigational products, without prejudice to further treatment.
- Severe non-compliance to study protocol, including treatment compliance.
- Patient meets any of the following specific safety discontinuation criteria:
  - Any physical symptoms of hepatotoxicity.
  - AST or ALT or bilirubin rise to a value ≥5 x ULN at any time.
  - AST or ALT rises to a value ≥3 x ULN accompanied by an elevation of bilirubin ≥2 x ULN.
  - ALT or AST rises to ≥3 x ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
  - ANC <500/mm^3 or 0.5 x 10^9/L.
  - Persistent or recurrent GI intolerance or dizziness despite fostamatinib dose reduction.
  - Significant infection.
  - Cancer: any malignant lesion.
  - Severe uncontrolled hypertension (systolic ≥180 mmHg and/or diastolic ≥110 mmHg) on any occasion or
  - Persistent uncontrolled hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) despite the initiation or adjustment of anti-hypertensive medication(s) and fostamatinib dose reduction. If BP remains 160-179 mmHg systolic and/or 100-109 mmHg diastolic on two occasions within one week despite escalation of antihypertensive therapy and/or fostamatinib dose reduction (as defined in Appendix I).

    Note that the mean of the 2nd and 3rd BP measurements should be used (see Section 6.4.8).

Patients should be followed off investigational products until hypertension is resolved.

- Patients who, in the opinion of the investigator, cannot be adequately managed under the protocol-specified treatments, without imposing an unacceptable burden on the patient.
- Pregnancy in a female participant (see Section 13.3).
- Patient lost to follow-up despite diligent efforts to trace the patient.

Patients **may also** be discontinued from investigational product (both oral and injected) in the following situations:

- Adverse Event.
- Lack of efficacy. The patients may discontinue due to lack of efficacy at any time.

Note: In the event of borderline findings (or trends of uncertain significance) the investigator and AstraZeneca Physician or representative will discuss the findings, agree and document a course of action.

Details regarding withdrawal from the exploratory biomarker and/or exploratory genetic research components of the study are presented in Section 7.5.

5.8.3 Procedures for discontinuation of a patient from investigational products

There are no special procedures for withdrawal of investigational products. A patient who decides to discontinue investigational products will always be asked about the reason(s) and the presence of any AEs. If possible, they should be seen and assessed by an investigator(s).

Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); investigational products should be returned by the patient.

Patients who discontinue investigational products will be withdrawn, and will have a withdrawal visit equivalent to the Week 24 assessments. This withdrawal visit will not include collection of a blood sample for exploratory biomarker research. Patients who discontinue investigational products before Week 24 should have a PK sample taken at the withdrawal visit. Patients who decide not to participate in OSKIRA-X will also have a follow-up visit 4 weeks after the withdrawal visit.

All patients who discontinue from treatment prior to Week 24 (but do not withdraw consent) should return to the study site 24 weeks after randomisation to complete all Week 24 assessments (excluding blood sample for PK). These patients will also be contacted every 12 weeks after the 4-week follow-up visit in order to collect key safety outcomes (see Section 5.8.3.1).

Specific procedures for collecting detailed information on patients discontinuing due to abnormal liver function, GI side-effects, hypertension or significant infection will be provided to the site.

Patients who discontinue treatment during the study cannot be re-enrolled and will not be replaced.

Patients who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for the exploratory genetic and/or biomarker research.

5.8.3.1 Safety outcomes follow-up for patients who discontinue investigational product

All patients who discontinue investigational product prior to Week 24 (but do not withdraw consent) will be contacted every 12 weeks after the 4-week follow-up visit until the final contact at 24 weeks after their randomisation visit (Visit 2). At these 12-weekly contacts the following data will be collected and entered onto the clinical database:

- Survival status (including cause of death if applicable)
- Post-study SAEs (any events which fulfil the criteria for SAEs per Section 6.4.2), but with onset more than 28 days after discontinuing investigational product
  - These SAEs should be collected and recorded as for on-treatment SAEs, but do not need to be reported in an expedited manner to AstraZeneca as described in Section 6.4.4, unless considered to be a late onset adverse drug reaction to fostamatinib/placebo or to be related to a study procedure.
- Post-study serious infective events (events which fulfil the criteria for serious infective events per Section 6.4.3, but with onset more than 28 days after discontinuing investigational product)
- Post-study concomitant medications (including subsequent RA treatments).

Every effort should also be made to obtain follow-up information on AEs that were ongoing at the time of discontinuation of investigational product.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

A Web Based Data Capture (WBDC) system will be used for data collection and query handling.

An electronic device (ePRO system) will be used to collect patient reported outcome (PRO) questionnaires, Visual Analogue Scale (VAS) from the patients and VAS from the physician.

The investigator will ensure that data are recorded on the eCRF and ePRO system as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement (CSA). The investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrolment procedures

Each patient will undergo enrolment procedures (Visit 1) prior to randomisation. The following data will be collected at Visit 1:

- Demographics (including gender, date of birth, race, alcohol, nicotine use)
- Significant medical and surgical history (including RA history)
- Diagnosis of RA according to the revised (1987) criteria of the American College of Rheumatology (see Appendix E)
- Contraceptive history
- Concomitant medications
- Physical examination including height (cm) and weight (kg)
- Vital signs (resting pulse and BP)
- 12-lead electrocardiogram (ECG; 3 consecutive records)
- DAS28 and ACR Score components (see Section 6.3.1)
- Documentation of the presence/absence of radiological erosions (X-rays performed within 12 months of randomisation will be acceptable)
- Chest radiography status (an X-ray in the 3 months prior to enrolment)
- SF-36 questionnaire
- Virology screen (hepatitis C virus antibody, hepatitis B surface antigen)
- TB test
- Clinical chemistry and haematology
- Urinalysis

- Pregnancy test (women of childbearing potential)
- Rheumatoid factor
- Anti-CCP
- Adverse events.

6.2.2 Follow-up procedures

- Physical examination including weight (kg). This will be done at Week 24, rather than the follow-up visit, in order to ensure that any patients rolling into the long-term extension study have a physical examination at the end of the study.
- Concomitant medications
- Contraceptive history
- Vital signs (resting pulse and blood pressure)
- Clinical chemistry and haematology
- Urinalysis
- Adverse events.

6.3 Efficacy

6.3.1 Signs and symptoms: DAS28 and ACR score

The following assessments will be made at the time points indicated in Table 2 for the purposes of calculating the DAS28 and ACR response scores.

6.3.1.1 Joint assessments

Wherever possible, the same person should perform the joint assessment throughout the study (ie, for all patients at each study centre). This person will be independent to the rest of the study team, ie, will perform the swollen and tender joint counts without access to any other study-related outcomes in order to minimise any bias in the scoring of this outcome measure.

Standardised methodology training will be provided as necessary.

Each of the 28 joints will be evaluated for tenderness and swelling respectively, (prior to taking any required analgesic that day if possible). The 28 joints assessed for this measurement are the 8 proximal interphalangeal joints of the fingers, the interphalangeal joints of the thumbs, the 10 metacarpophalangeal (MCP) joints plus the wrists, elbows, shoulders and knees.

6.3.1.2 Patient's global assessment of disease activity: VAS

Patients will mark on a VAS their overall assessment of how their RA affects them, rating how they are managing from 0 (very well) to 100 (very poor). This is equivalent to the General Health (GH) component of the Disease Activity Score (DAS; see Appendix K).

6.3.1.3 Patient's assessment of pain: VAS

Patients will mark on a VAS the severity of pain that they have had because of their RA in the past week, ranging from 0 (no pain) to 100 (severe pain) (see Appendix K).

6.3.1.4 Physician's global assessment of disease activity: VAS

The physician's global disease assessment will be documented on a VAS, ranging from no arthritis activity (0) to extremely active arthritis (100) (see Appendix K).

6.3.1.5 Health Assessment Questionnaire Disability Index (HAQ-DI)

The physical function of the patient will be assessed using the HAQ-DI questionnaire. This is a widely used patient self-report tool which assesses the degree of difficulty a person has had in accomplishing tasks in 8 functional areas, over the previous week, taking into account any aids or help required. The 8 categories assessed by the HAQ-DI are (1) dressing and grooming, (2) rising, (3) eating, (4) walking, (5) hygiene, (6) reach, (7) grip and (8) common daily activities (see Appendix K).

6.3.1.6 Systemic Inflammation: CRP

A blood sample for CRP assessment will be taken and analysis will be conducted by a suitably qualified laboratory using validated methods.

6.3.1.7 Erythrocyte sedimentation rate

A whole blood sample (4 mL) will be collected for the ESR value (based on Westergren 1957) to be measured locally at individual study sites, using the kit supplied by the central laboratory (see separate Laboratory Manual). At Visit 1, this should be performed by a person independent of the study team without access to the other study assessments.

6.4 Safety

The investigator is responsible for ensuring that all personnel involved in the study are familiar with the content of this section.

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE

can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no investigational products have been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up) at any dose, that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Adverse events (non-serious AEs and SAEs) will be collected from the time of informed consent (even if this is prior to Visit 1), throughout the treatment period and until completion of the last on-treatment scheduled study visit (including the 28-day follow-up period).

Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study will be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca or delegate retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity

- Whether the AE is serious or not
- Investigator causality rating against the investigational products (fostamatinib and adalimumab) (yes or no)
- Action taken with regard to investigational products
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of AE.

The maximum intensity of an AE will be rated according to the following definition:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Causality collection

The investigator will assess causal relationship between investigational products and each AE, and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?", or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible). If a diagnosis is unknown, recording a list of signs and symptoms is necessary. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and ECGs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational products.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB: Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, please refer to Appendix N 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. There is currently no formal agreed definition of an RA disease flare. Where this occurs in the study, in the clinical judgement of the investigator, RA flare should be reported as an AE. However, the usual symptoms of RA (not a flare) should not be reported as AEs unless they fulfil the criteria for an SAE or result in discontinuation from the study.

Serious infective events

Serious infective events are defined as those infections fulfilling the criteria of a SAE, or other infection AEs requiring intravenous antibiotics.

Neutropenia

The AE term 'neutropenia' should only be reported for ANC <1500/mm^3 or <1.5 x 10^9/L and may or may not be associated with fever or concurrent infection.

Hypertension

If an AE of hypertension is reported, the investigator should ensure that a BP reading corresponding with the AE is provided.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational products, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca delegate within 1 day ie, immediately but **no later than the end of the next business day** of when he/she becomes aware of it.

The designated AstraZeneca delegate works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca delegate of any follow-up information on a previously reported SAE **within 1 calendar day** ie, immediately but **no later than the end of the next business day** of when he/she becomes aware of it.

The AstraZeneca delegate will advise the investigator/study site personnel how to proceed. Details on how SAE reporting will be carried out will be described in the specific Safety Handling Plan for the study.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca drug and the European Union Summary of Product Characteristics for adalimumab.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the times indicated in the Schedule of Assessments (Table 2).

The following laboratory variables will be measured:

Table 6 Laboratory variables

Clinical chemistry (serum)	Haematology (whole blood)	Urinalysis (local dipstick)
Creatinine	Haemoglobin	Protein
Potassium	Platelets	Glucose
Sodium	White blood cells	Blood
Total calcium	Neutrophils	
Albumin	Lymphocytes	
Total bilirubin[a,c]	Monocytes	
Alkaline phosphatase[b]	Eosinophils	
AST[c]	Basophils	
ALT[c]	Haematocrit	
Gamma-Glutamyl Transpeptidase	Red blood cells	
Creatine kinase[d]	MCV[g]	
Glucose[e]	MCH	
Lactate dehydrogenase[f]	MCHC	
Phosphate	RDW	
Total protein		

[a] Both unconjugated and conjugated bilirubin being routinely measured.
[b] If alkaline phosphatase is raised >3 x ULN then isoenzymes (liver and bone) should also be measured.
[c] A finding of ALT or AST ≥3 x ULN or bilirubin ≥2 x ULN should prompt repeat testing of all liver function tests (preferably within 72 hours). Where AST, ALT or bilirubin levels are found to rise 1.5 x above the patient's last result, investigators should consider proactive management such as repeat laboratory tests and possible reduction of study drug dose or concomitant medication.
[d] If creatine kinase is raised >500 IU/L then creatine kinase-MB isoenzyme should also be measured.
[e] Nonfasting glucose will be measured at Visit 1; fasting glucose will be measured at Visits 2, 12, and 24.
[f] If lactate dehydrogenase is raised >1.5 x ULN then LDH isoenzymes, a blood film to evaluate anisocytosis and form of erythrocytes, and reticulocytes should be measured at the next scheduled study visit.
[g] If MCV is <75 fl coupled with haemoglobin of <10.0 g/dL, then an additional sample should be collected at the next visit to determine iron levels (serum iron [µmol/L] and ferritin [ng/mL]).

In addition, the following variables will be analysed at the times indicated in the Schedule of Assessments (Table 2):

- CRP
- ESR (measured locally)
- Virology
- Serum HCG for pregnancy (women of childbearing potential only)
- Anti-CCP antibodies
- Rheumatoid factor (RF)
- Fasting lipids (total cholesterol, HDL, LDL-direct, LDL [calculated], triglycerides).

At visits where lipid parameters and fasting glucose are being measured, blood samples should be taken after a minimum 8-hour fast (no food or fluids, other than water) before sample collection. It is recommended that the study coordinator or designee contact the patient the day before blood collection to remind the patient of the requirement to fast. If a patient has not fasted appropriately, the blood should be collected and processed anyway and the fact that the sample was not fasted should be recorded on the appropriate eCRF module.

NB: In case a patient shows an AST **or** ALT ≥3x ULN **or** total bilirubin ≥ 2x ULN please refer to Appendix N 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

Details of all blood variable units and reference ranges can be found in the Laboratory Manual.

Blood samples will be analysed by the central laboratory provider. The central laboratory provider will also provide the materials for blood sampling. Instructions for the labelling, storage and shipment of the samples can be found in the Laboratory Manual. The central laboratory will provide up-to-date reference ranges throughout the study.

Pregnancy testing will usually be performed by the central laboratory using serum. To confirm inclusion at Visit 2, urine pregnancy testing may be conducted locally using urine testing kits provided by the central laboratory.

The investigator must assess all safety laboratory results.

Laboratory test abnormalities will be recorded throughout the study in the database of the central laboratory (see Section 6.4.3).

Criteria for discontinuation of patients due to clinical laboratory parameters are detailed in Section 5.8.

For blood volume see Section 7.1.

6.4.6 Physical examination

A physical examination will be performed by preferably the same medically qualified person at the times indicated in the Schedule of Assessments (Table 2). This should include assessment of the following: general appearance, skin, head, neck, throat, lymph nodes, thyroid, musculoskeletal/extremities, neurological, CV, respiratory and abdomen.

Body weight will also be measured.

Height should be measured at Visit 1 only.

6.4.7 Resting 12-lead ECG

Digital ECG data will be collected at the times indicated in the Schedule of Assessments (Table 2).

Patients should rest for at least 10 minutes in a supine position before ECG evaluations. (Note: a sitting rest followed by a supine recording will induce QT-changes that are caused by changes in body position and haemodynamic conditions). Three consecutive recordings will be made.

The original ECG traces and variables must be stored in the patients' medical record as source data. The investigator should evaluate the ECG from a clinical perspective and the result (whether the ECG result is normal or abnormal) should be recorded on the appropriate eCRF module.

If the investigator finds any clinically relevant abnormalities, these should be reported as AEs/SAEs as appropriate (see Section 6.4.3).

6.4.8 Vital signs

Vital signs will be assessed at the times indicated in the Schedule of Assessments (Table 2).

Blood pressure and pulse rate measurement will be standardised as follows:

- An automated BP machine will be used.
- Measurements should be taken at approximately the same time of the day at each visit (±2 hours).
- Blood pressure and pulse rate will be measured in the sitting position following at least 10 minutes rest.
- The appropriate cuff size for the patient should be used and the cuff positioned level with the heart.
- Three separate measurements will be taken with a 2 to 5 minute interval between the measurements; results should be printed at the time of

measurement and retained in patient files (if for any reason results cannot be printed all three should be written in the patient files). All 3 measurements will be recorded on the database.

- The mean of the 2nd and 3rd measurements will be calculated and used for patient management decisions and for study reporting.

- The investigator must review BP findings during each visit regardless of which member of the site personnel is responsible for performing the measurements.

See Section 6.4.3 for the appropriate reporting of any clinically relevant abnormalities as AEs/SAEs.

6.5 Patient reported outcomes (PRO)

6.5.1 Patient's global assessment of disease activity: VAS

For details, refer to Section 6.3.1.2. This forms part of the primary efficacy variable.

6.5.2 Patient's assessment of pain: VAS

For details, refer to Section 6.3.1.3. This forms part of the secondary ACR efficacy variables.

6.5.3 Health Assessment Questionnaire Disability Index (HAQ-DI)

For details, refer to Section 6.3.1.5. This forms part of the secondary ACR efficacy variables.

6.5.4 Short Form 36 (SF-36) questionnaire

Patients will complete the SF-36 v2, standard version, a generic, health survey consisting of 36 questions (Appendix L), yielding 8 health-related quality of life (HRQoL) domains (physical functioning, role-physical, bodily pain, general health, vitality, social function, role-emotional, mental health) as well as a psychometrically based physical component score (PCS) and mental component score (MCS).

6.5.5 Administration of PRO questionnaires

The PROs will be assessed in this study according to the schedule described in Table 2.

These will be completed by the patient in the clinic using an electronic device. Assessment and analysis of these data will be performed centrally and do not require the investigator to interpret any data.

Each centre should designate responsibility for the administration and compliance monitoring of the ePROs to a specific individual (eg, a research nurse). Relevant training in administration of the ePROs will be provided. It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection (Fallowfield et al 1987). The date of completion of each ePRO will be recorded. The instructions for completion of the questionnaires are as follows:

- Questionnaires must be completed in clinic by the patient **before** any investigations or discussions about their disease with the clinic staff.
- Patients should be provided with a suitable, private place to complete the questionnaire alone (ie, without assistance from clinic staff, relative or friend).
- If a patient is unable to complete the questionnaire unaided, due to physical disability or inability to read the questionnaires, the designated clinic staff member will read the questions *verbatim* to the patient and record the answers, without interpretation. (Training will be provided in interviewing techniques). Interviews will be captured on the ePRO device.
- Any reason for non-completion of questionnaires will be recorded on the ePRO device.

Questionnaires will be administered in those countries where there is a validated translation available.

6.6 Pharmacokinetics

6.6.1 Collection of samples

Blood samples (3 mL) for determination of R406 and/or R788 and metabolite concentrations in plasma will be taken by venepuncture at the times presented in the study plan (Table 2).

On clinic days, patients should take their oral dose of investigational product at home at the usual time. Samples can be taken at any time in relation to the administration of investigational products. The time of sample and time of last dose will be documented in the eCRF.

In the event of premature discontinuation of investigational products, a PK sample should be taken, if possible, and as soon as possible, with date and time of sample and time of dose prior to this sample recorded.

Wherever possible PK blood samples will be taken at the same time as blood is drawn for other analyses to limit repeated venepuncture.

Full instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

For blood volume see Section 7.1.

6.6.2 Determination of drug concentration

The total concentrations of the active metabolite R406 and/or R788 will be determined by a suitably qualified laboratory using validated methods. Pharmacokinetics analyses will only be performed on the samples collected from patients who actually received fostamatinib, not those receiving adalimumab.

Samples may also be used to assess performance of the bioanalytical methods in order to add confidence to the results of the analysis and for exploratory analysis of fostamatinib metabolites, the results of which will not be reported in the CSR. The results of incurred sample reanalysis will be reported in a bioanalytical report to be appended to the CSR. Any metabolite investigation may be reported in a separate report.

Pharmacokinetic analyses will be specified in a Pharmacokinetic Analysis Plan prior to analysing the data. The resulting data will be reported in a separate report. Additional analysis may be undertaken where these data are combined with data from both healthy volunteers and patient studies. The resulting analysis will be reported in a separate report.

6.7 Pharmacogenetics

6.7.1 Collection of pharmacogenetic samples

The blood sample for genetic research will be obtained from patients at Visit 2. Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at Visit 2, it may be taken at any visit until the last study visit. Only 1 sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Please refer to Appendix D for further details.

For blood volume see Section 7.1.

6.7.2 Determination of *UGT1A1* genotype

UGT1A1 genotype will be determined by a suitably qualified laboratory using validated methods.

Analysis of *UGT1A1* genotype will be specified in the Statistical Analysis Plan (SAP) prior to analysing the data. The resulting data will be reported in the CSR.

6.8 Exploratory Biomarkers

6.8.1 Collection of biomarker samples

Where consent is given, blood samples for exploratory biomarker research will be taken by venepuncture at the times presented in the study plan (Table 2).

Two samples will be collected: 10 mL (to obtain 5 mL serum) and 10 mL (to obtain 5 mL plasma).

The date of the sample will be documented in the eCRF.

Please refer to Appendix D for further details.

Samples will be handled and obtained in accordance with the instructions provided in the Laboratory Manual.

6.8.2 Determination of biomarkers

The samples will be archived for possible future exploratory analyses of inflammatory or other markers that may be important to RA and/or its treatment. Results from this research will be reported separately from the CSR.

6.9 Health economics

Healthcare resource utilisation will not be collected within the trial. Separately from this trial an economic model may be constructed incorporating clinical endpoint data from the trial to provide estimates of cost-effectiveness for different countries.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 7 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
ESR		4	9	36
Virology		4	1	4
Pharmacokinetic		3	2	6
Pharmacogenetic		10	1	10
Exploratory biomarker		20	3	60
Safety	Clinical chemistry (inc CRP and rheumatoid factor and pregnancy)	8.5 approx	13	110.5
	Haematology	2	13	26
Total with PK and optional biomarker profiling				252.5

It should also be noted that additional samples may be required to follow safety findings (eg, liver function abnormalities or raised LDH characterisation).

7.2 Handling, storage and destruction of biological samples

Sample handling is described in more detail in a separate Laboratory Manual. The samples will be used up or disposed of after analyses or retained for future use as described here.

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Samples for investigation of long-term stability and/or metabolite analysis will be retained by AstraZeneca or nominated representative for a maximum of 1 year following the finalisation of the CSR. The results from any additional investigations will be reported separately.

Samples will be disposed of after the CSR has been finalised, except key samples retained for future analysis (see Section 7.2).

7.2.2 Pharmacogenetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years from the date of the last subject's last visit (LSLV), after which they will be destroyed. DNA is a finite resource that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples, irrespective of the type of coding used, the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (AstraZeneca employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the subject enrolment/randomisation code and the DNA number will be maintained and stored in a secure environment, with restricted access WITHIN the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent when the subject has requested disposal/destruction of collected samples not yet analysed.

7.2.3 Biomarker samples

Samples from this exploratory biomarker research may be kept for up to 15 years after LSLV. At that time, all remaining samples and preparations derived from these samples, collected and stored by the study sponsor as part of this biomarker research, will be destroyed.

7.3 Labelling and shipment of biohazard samples

The investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca or its representative and appropriate labelling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle. The investigator at each centre keeps full traceability of collected biological samples from the patients while in storage at the centre until shipment and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed.

AstraZeneca or its representative keeps oversight of the entire life cycle through internal procedures, monitoring of study sites until samples are used/disposed or transferred for long-term storage, while AstraZeneca performs auditing as applicable of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed and the action documented. If samples are already analysed, AstraZeneca or its representative is not obliged to destroy the results of this research.

As collection of the biological samples is an optional part of the study, then the patient may continue in the study.

The investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca or its representative.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the patient and AstraZeneca or its representative are informed about the sample disposal.

AstraZeneca or its representative ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

7.5.1 Withdrawal of informed consent for optional exploratory genetic research

A single DNA sample will be collected for both *UGT1A1* genetic analysis and optional exploratory genetic research.

A patient can withdraw consent to the use of their DNA sample for exploratory genetic research. If this occurs, AstraZeneca or its representative will ensure that the patients DNA sample is not used for exploratory genetic research. This action will be documented. If the patient's DNA sample has already undergone exploratory genetic research, AstraZeneca or its representative is not obliged to destroy the results of this research, but no further exploratory genetic research will be conducted.

As the exploratory genetic research is an optional part of the study, then the patient may continue in the study.

The investigator ensures patients' withdrawal of informed consent to the use of donated samples for exploratory genetic research is notified immediately to AstraZeneca or its representative.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

8.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician (or representative) or an investigator might know a subject's identity and also have access to his or her genetic data. Also Regulatory

authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

8.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable Ethics Committee and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca or its representative before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca or its representative should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca or its representative will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca or its representative will provide Regulatory Authorities, Ethics Committees and investigators with safety updates/reports according to local requirements.

For the US and Canada and certain other countries, each investigator is responsible for providing the Ethics Committees with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational products. AstraZeneca or its representative will provide this information to the investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue investigational products and/or withdraw from the study at any time.

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed Informed Consent Forms is stored in the Investigator's Study File.
- Ensure a copy of the signed Informed Consent Form is given to the patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.
- Ensures that separate consent is given for exploratory biomarker and/or exploratory genetic research and that patients are aware that exploratory biomarker and exploratory genetic research are optional.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International co-ordinating Investigator, National Co-ordinating Investigator, investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment should be approved by each Ethics Committee and if applicable, also the national regulatory authority, before implementation. Local requirements should be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each investigator. For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee should approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification (SDV). The purpose of an audit or inspection is to systematically and independently examine all

study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP, guidelines of the ICH and any applicable regulatory requirements. The investigator will contact AstraZeneca or its representative immediately if contacted by a regulatory agency about an inspection at the centre.

9. STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities.
- Determine availability of appropriate patients for the study.
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence and the responsibilities of AstraZeneca or its representatives. This will be documented in a CSA between AstraZeneca and the investigator.

9.2 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC and ePRO systems utilised.

The investigator will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

The investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.3 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in

accordance with the Laboratory Manual and that investigational product accountability checks are being performed.

- Perform SDV (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts).

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.3.1 Source data

Refer to the CSA for location of source data.

9.4 Study agreements

The investigator at each centre should comply with all the terms, conditions and obligations of the CSA for this study. In the event of any inconsistency between this Clinical Study Protocol and the CSA, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the CSA shall prevail.

Agreements between AstraZeneca or its representative and the investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.4.1 Archiving of study documents

The investigator follows the principles outlined in the CSA.

9.5 Study timetable and end of study

The end of the study is defined as "the last visit of the last patient undergoing the study".

The study is expected to start in and to end by .

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if the centre is not meeting plans for recruitment of patients. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with fostamatinib.

10. DATA MANAGEMENT BY ASTRAZENECA OR DELEGATE

Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When the investigator has signed the eCRF electronically as per eCRF instructions, then the patient's data will be locked.

10.1 Electronic case report forms

The eCRF and the protocol are both confidential. The eCRF will be created by the CRO and programmed into the WBDC system. All sites will need internet access to access the eCRFs and will only have access to data for patients at their own sites. Data Management and other co-ordinator teams will have access to data at all sites.

AstraZeneca or its representative will arrange access to the eCRFs. All eCRFs are to be completed by an authorized member of the investigational staff and reviewed and signed by the investigator. All entries, corrections and alterations are to be made by the responsible investigator or an authorized member of the investigational staff. All eCRFs are to be completed in a manner that ensures accurate interpretation of data.

It is each investigator's responsibility to ensure that all discontinued orders or changes in the study or other medications entered on the patient's eCRF correspond to the entries on the patient's medical records.

The eCRFs for any subject leaving the study should be completed at the time the investigational products are terminated for whatever reason.

Electronic case report forms must accurately reflect data contained in patients' records (eg, source documents).

10.2 Dataflow

After data is entered into the eCRF by the site, autoqueries that are generated by the WBDC system should be addressed by the site. At the monitoring visit, the Study Monitor must perform the SDV of the required fields on completed forms and if there are no open queries, freeze the form. Data Management will run manual consistency checks outside of the WBDC system and will raise manual queries for sites to address; if the form is frozen, Data Management will unfreeze to allow sites to amend data. The same process is to be followed by any other groups creating manual queries in the WBDC system (eg, for SAE reconciliation). Once all data is entered, SDV completed on required fields, manual queries and electronic data reconciliation completed and all queries closed, then the casebook can be signed. Once the casebook is signed, Data Management will then lock the casebook so that no amendments can be made.

10.3 Database lock

Once all patient eCRFs are locked, the final data transfer can be provided for statistical analysis. A database lock checklist will also be completed by Data Management and the programmer to confirm all applicable quality control checks were confirmed.

10.4 Coding

All AEs and Medical Histories recorded in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and all medications coded using AstraZeneca's Drug Dictionary. The coding will occur outside of the WBDC system and will be merged with the clinical datasets sent to statistics.

10.5 Investigator site file

At the beginning of the study, an investigator's study file will be established at the study centre. The investigator/institution is responsible for maintaining the study documents as specified in the guideline for ICH GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) and as required by the applicable regulatory requirement(s). The investigator/institution must take measures to prevent accidental or premature destruction of these documents.

10.6 SAE reconciliation

Prior to database lock, the CRO will perform SAE reconciliation between the CRO and clinical study database and the AstraZeneca Clinical Patient Safety database.

10.7 Biological samples

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca or its representative.

10.8 Genetic data

Any genotype data generated in this study will be stored in the AstraZeneca genotyping LIMS database, or other appropriate secure system within AstraZeneca and/or third party contracted to work with AstraZeneca to analyse samples. The results from this genetic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Genotype data will be transferred to the clinical database, and merged with the clinical data from the main study, prior to the statistical analysis and reporting of the study. In addition, some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database. Data management will be performed by AstraZeneca or its representative.

11. EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR DELEGATE

A SAP will be finalised prior to unblinding of the data.

A summary of the study objectives and their associated outcome variables are presented in Table 8. The primary time point for interpretation of all efficacy endpoints is Week 24 unless otherwise stated.

Table 8 Objectives and outcome variables

Objective	Variables
Primary	
To evaluate the efficacy at Week 6 of 3 different dose regimens of fostamatinib on the signs and symptoms of RA, compared with placebo in patients with active RA when used as monotherapy (ie, without any background DMARDs).	DAS28 score at Week 6
To evaluate whether the efficacy on the signs and symptoms of RA at Week 24 of 3 oral dosing regimens of fostamatinib is non-inferior to that of adalimumab in patients with active RA when used as monotherapy (ie, without any background DMARDs).	DAS28 score at Week 24
Secondary	
To further assess the efficacy of fostamatinib measured by DAS28, DAS28 response criteria, ACR20, ACR50, ACR70, ACR-N and the individual components of the ACR score.	DAS28 score, DAS28 European League Against Rheumatism (EULAR) response criteria, DAS low disease activity, DAS28 remission, clinically important change in DAS28 score, ACR20, ACR50, ACR70, ACR-N, individual components of ACR (swollen joint count, tender joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function [as measured by the HAQ-DI], CRP)
To assess physical function status of patients after administration of fostamatinib using the HAQ-DI.	HAQ-DI score; HAQ-DI response, individual dimensions of HAQ-DI
To investigate the effects of fostamatinib on HRQoL.	SF-36 – PCS, MCS, 8 individual domain scores

Table 8 Objectives and outcome variables

Objective	Variables
Safety	
To evaluate the safety and tolerability of fostamatinib in patients with active RA.	AEs Vital signs Laboratory safety assessments ECG abnormalities Weight Physical examination
To investigate the relationship between variations in the gene *UGT1A1* and the safety and tolerability of fostamatinib in the study population.	*UGT1A1* genotype
Exploratory	
To investigate the PK of R406 (the active metabolite of fostamatinib) and/or the PK of R788 or other metabolites and to investigate the relationship between systemic exposure to these metabolites and AEs, safety parameters and efficacy outcomes (may be reported separately).	Plasma R406 and/or R788 or other metabolites concentrations, oral clearance and area under plasma concentration-time curve during the dosing interval at steady-state Only limited PK data will be available due to sparse sampling (Weeks 4 and 24).
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib and/or adalimumab; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers. This may be described in a separate report.	DNA from whole blood
To investigate systemic biomarker profiles in RA patients.	Serum and plasma biomarkers

11.1 Calculation or derivation of efficacy variables

Baseline will be determined based on the evaluable assessment that is closest to and precedes first dose. Assessments performed at Visit 2 will be included in the calculations of baseline, unless the assessment is planned to be taken after first dose of investigational products.

For patients who withdraw prematurely for whatever reason, baseline values of the four components from which DAS28-CRP is derived (see Section 11.1.1) and all other efficacy endpoints will be imputed at all subsequent visits after the date of withdrawal. This approach

will ensure that patients are still included in all analyses but they will have no improvement from baseline.

The baseline imputation method will also be used to substitute all efficacy data at all visits subsequent to those events listed below, to ensure that patients have no improvement from baseline at any visit after these events.

1. Any DMARD initiated

2. Parenteral steroids received (see Section 5.6), non-response imputed for 8 weeks following this event only.

For patients with no post-baseline efficacy data, the baseline imputation approach will also be used to create all post-baseline scheduled time points.

If, following application of this non-response imputation, any unexplained missing data occur at a visit (ie, not missing due to withdrawal), the last available non-missing value post-baseline will be carried forward to impute this missing value.

11.1.1 Clinical response: DAS28

The DAS28 score will be derived using the following formula:

$$DAS28\text{-}CRP = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*GH + 0.96$$

Where:

- TJC28 = 28 joint count for tenderness
- SJC28 = 28 joint count for swelling
- Ln(CRP) = natural logarithm of CRP
- GH = patients global assessment on VAS of 100 mm (see Section 6.3.1.2).

Change from baseline in DAS28 score will be calculated at each visit.

Improvement in DAS28 at each post-baseline scheduled assessment will also be categorised using the EULAR response criteria (see Table 9).

Table 9 DAS28 EULAR response

Baseline DAS	DAS28 Improvement >1.2	DAS28 Improvement >0.6 -1.2	DAS28 Improvement ≤0.6
≤3.2	Good Response	Moderate response	No Response
>3.2-5.1	Moderate response	Moderate response	No Response
>5.1	Moderate response	No Response	No Response

Low disease activity is defined as a DAS28 score of less than 3.2. DAS28 remission is defined as a DAS28 score of less than 2.6. A clinically important change in DAS28 score is defined as an improvement in DAS28 score of at least 1.2.

DAS28-ESR will also be calculated, but the primary interpretation of DAS28 will be based on DAS28-CRP:

DAS28-ESR = $0.56*\sqrt{}$ (TJC28) + $0.28*\sqrt{}$ (SJC28) + 0.70*ln(ESR) + 0.014*GH

11.1.2 ACR20, 50, 70

The proportion of patients who achieved ACR20 will be calculated at each post-baseline scheduled assessment.

The percentage change from baseline of the individual components will be calculated at each visit in order to determine the clinical response against ACR criteria.

Note that if a patient has been included on the basis of ESR alone (ie, without meeting the alternative CRP inclusion criterion of ≥10 mg/L) the percentage change in ESR will be used for determination of ACR response in that patient. Otherwise the percentage change in CRP will be used for determining ACR response.

Clinical response: ACR Criteria

A patient has an ACR20 response if all of the following occur:

- A ≥20% improvement in the swollen joint count (28 joints)
- A ≥20% improvement in the tender joint count (28 joints)
- A ≥20% improvement in at least 3 of the following 5 assessments:
  - Patient's assessment of pain
  - Patient's global assessment of disease activity
  - Physician's global assessment of disease activity

- Patient's assessment of physical function, as measured by the HAQ-DI
- Acute phase reactant (CRP or ESR depending on entry criterion).

As the ACR20 is a composite endpoint, imputations will be made at the individual component level prior to calculating the response criteria.

In a similar way, patients will be considered to have had an ACR50 or ACR70 response if a 50% or 70% improvement from baseline (respectively) rather than 20% was observed in the criteria specified above for ACR20.

11.1.3 ACR-N

ACR-N is defined as the smallest percentage improvement from baseline of the following 3 values:

- Tender joint count
- Swollen joint count
- Median of the values for percentage improvement in the following 5 measurements:
  - Patient's assessment of pain
  - Physician's global assessment of disease activity
  - Patient's global assessment of disease activity
  - Patient's assessment of physical function, as measured by the HAQ-DI
  - CRP or ESR depending on entry criterion.

If symptoms are worsening, the ACR-N value may be negative, with a lower bound of -100.

11.1.4 Acute Phase Reactants; systemic inflammation; ESR and CRP

The change from baseline and percentage change from baseline in the ESR and CRP values will be calculated for each patient at each scheduled assessment post-baseline. Note that if a patient has been included on the basis of ESR alone (ie, without meeting the alternative CRP inclusion criterion of ≥10 mg/L) the percentage change in ESR will be used for determination of ACR response in that patient. Otherwise the percentage change in CRP will be used for determining ACR response.

11.1.5 Other ACR components

The change from baseline and percentage change from baseline in the physician's global assessment of disease activity VAS scores will be calculated for each patient at each scheduled assessment post-baseline.

The change from baseline and percentage change from baseline in the swollen joint count and the tender joint count will be calculated for each patient at each scheduled assessment post-baseline.

The percentage change from baseline in the above scores will be used to determine the patients' response against the ACR criteria (Section 11.1.2).

11.2 Calculation or derivation of safety variables

Baseline will be determined based on the evaluable assessment that is closest to and precedes first dose. Assessments performed at Visit 2 will be included in the calculations of baseline, unless the assessment is planned to be taken after first dose of investigational products. For the group randomised to placebo for the first 6 weeks followed by either fostamatinib 100 mg *bid* up to Week 24 or fostamatinib 100 mg *bid* for 4 week, followed by 150 mg *qd* up to Week 24, the baseline for all assessments after Week 6 will be based on the evaluable assessment that is closest to and precedes the first active dose.

Exposure will be calculated in order to assess the rates of AEs and other safety events of interest relative to the total person-years at risk. For each patient the time at risk is defined as time from first dose to the earliest of the end of the period of interest or withdrawal from the study.

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and discontinuations due to adverse events (DAEs). Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of laboratory, vital signs and ECG data will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention, dose reduction or significant additional treatment.

11.3 Calculation or derivation of patient reported outcome variables

11.3.1 Health Assessment Questionnaire Disability Index (HAQ-DI)

The 8 categories assessed by the HAQ-DI are (1) dressing and grooming, (2) rising, (3) eating, (4) walking, (5) hygiene, (6) reach, (7) grip and (8) common daily activities. For each of these categories, patients report the amount of difficulty they have in performing 2 or 3 specific activities. There are 4 possible responses for the HAQ-DI questions: without ANY difficulty (0), with SOME difficulty (1), with MUCH difficulty (2) and UNABLE to do (3).

The highest score for any component question for each of the 8 categories determines the score for that category. The category scores are adjusted based upon the patient's use of an aid, device or assistance for that category. The HAQ-DI is then calculated by summing the category scores and dividing by the number of categories completed. Each category must

have at least 1 question completed. If fewer than 6 categories have been completed, then the HAQ-DI cannot be computed. The HAQ-DI scores between 0-3, with higher score indicating greater disability.

The change from baseline and percentage change from baseline in HAQ-DI score will be calculated at each scheduled assessment post-baseline. The percentage change from baseline in HAQ-DI score will be used to determine the patients' response against the ACR criteria (Section 11.1.2).

A HAQ-DI response is defined as a reduction from baseline in HAQ-DI score greater than 0.22 (Wells et al 1993).

Change from baseline will also be calculated for the individual categories of the HAQ-DI.

11.3.2 Patient's global assessment of disease activity on a VAS

The change from baseline and percentage change from baseline in disease activity VAS scores will be calculated for each patient at each scheduled assessment post-baseline. The percentage change from baseline in VAS score will be used to determine the patients' response against the ACR criteria (Section 11.1.2).

11.3.3 Patient's assessment of pain on a VAS

The change from baseline and percentage change from baseline in pain VAS score will be calculated for each patient at each scheduled assessment post-baseline. The percentage change from baseline in VAS score will be used to determine the patients' response against the ACR criteria (Section 11.1.2).

11.3.4 Short Form 36 (SF-36) questionnaire

The SF-36 uses norm-based scoring, involving a linear T-score transformation method. SF-36 mean scores are based on 1998 US population scores, with a mean of 50 and an SD of 10. A higher score represents a better Quality of Life.

Scoring of the SF-36 will be conducted as per the SF-36 Health Survey Manual and Interpretation Guide (Ware et al 2007). The 8 domains plus 2 overall summary scores, (the physical component score and the mental health component score), will be derived at each visit. Change from baseline in the scores will be calculated at each scheduled assessment post-baseline.

If less than 50% of the items in 1 scale are missing, the mean scores for the completed items will be used for imputation. If 50% or more of the items in 1 scale are missing, that subscale will be treated as missing.

11.4 Calculation or derivation of pharmacokinetic variables

The population PK and PK/PD analysis will be undertaken either by, or on behalf of AstraZeneca R&D, UK. Details of the analysis to be undertaken will be documented in a PK

analysis plan prior to database lock. The results of this analysis may be reported in a separate PK/PD report.

Drug concentration measurements will be presented descriptively and, if possible, PK will be evaluated by non-linear mixed effect modelling.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

A SAP will be prepared prior to unblinding of the data. Details of all analyses, including sensitivity analyses, will be fully documented in the SAP.

Once there are sufficient numbers of patients for the analysis (approximately 250 patients who have received randomised treatment and who have completed either this study or sub-study), there will be a database lock. This will only include those patients who have been randomised to either this study or the sub-study and have completed the study. If recruitment in the sub-study is not complete, patients ongoing in the sub-study will continue and their data will not be locked. At this stage, those patients who have had their data locked will be unblinded for the purposes of analysis. Sub-study patients who are ongoing in the study will not be unblinded.

Once recruitment in the sub-study is complete and all patients have completed the study, a second database lock will take place, to lock the additional sub-study patients. After the first database lock, the analyses specified in the main study SAP will be carried out on the set of completed unblinded patient data from the main and sub-study.

The analyses to be performed after the second database lock, will include an updated analysis of the primary objectives for this study. Further analyses will be described in the sub-study protocol and SAP.

If all sub-study patients are recruited before the main study recruitment completes, then the sub-study results will be included in the main study report. If the sub-study recruitment completes after the main study recruitment, then the sub-study results, including the analyses and summaries of additional main study data, will form an addendum to the main study report.

12.1 Description of analysis sets

The following analysis sets will be used in this study:

12.1.1 Full analysis set

The full analysis set will be used as the primary population for reporting efficacy and safety data. This comprises all patients randomised into the study who receive at least 1 dose of investigational product, and will be analysed according to randomised treatment (intention-to-treat principle). Any major deviations from randomised treatment will be listed and considered when interpreting the safety data.

12.2 Methods of statistical analyses

In the statistical analysis of data from this study, each dose regimen of fostamatinib will be compared separately to placebo and to adalimumab.

All efficacy endpoints will be tested at a 2-sided significance level of 10% for each dose regimen versus placebo, as this is a dose finding Phase II study.

Since adalimumab is an active comparator a non-inferiority margin of 0.6 in the change from baseline in DAS28-CRP has been chosen to evaluate the efficacy of fostamatinib compared to adalimumab.

Where confidence intervals (CIs) are presented for treatment comparisons these will be presented as 90% CIs. Where CIs are presented for the second primary objective comparing fostamatinib versus adalimumab on DAS28-CRP at 24 weeks, these will also be presented as 80% CIs, to allow assessment of non-inferiority by comparing the lower confidence limit with the non-inferiority margin of 0.6 in the change from baseline in DAS28-CRP.

Since this is a Phase II trial, no adjustments will be made for multiplicity. However, when assessing the primary objectives, the number of treatment groups and the correlations between comparisons will be informally considered. The interpretation of the secondary endpoints will take into account whether the associated primary objective (ie, comparison vs placebo or comparison vs adalimumab) has been met.

12.2.1 General considerations

The treatment comparisons and the time points they apply to are detailed below.

0-4 weeks

Since the 3 fostamatinib dosing regimens are identical for the first 4 weeks of dosing, all analyses comparing the efficacy of fostamatinib versus either placebo or adalimumab up to and including Week 4 will be performed using pooled data from the 3 dosing regimens.

Week 6

Each dosing regimen of fostamatinib will be compared to both placebo and adalimumab at 6 weeks.

8-24 weeks

Each dosing regimen of fostamatinib will be compared to adalimumab at each time point between Week 8 and Week 24. After Week 6 there will be no further comparisons with placebo as all patients will be on active treatment.

Sensitivity analysis

After Week 6, the patients receiving placebo (Dosing Regimen E) switch to either fostamatinib 100 mg *bid* (same as Dosing Regimen A) up to Week 24 or 150 mg *bid* for 4 weeks, followed by 100 mg *qd* (same as Dosing Regimen B) up to Week 24. As these new 18 week treatment regimens are the same as existing treatment regimens, the Week 18 data from Dosing Regimens A and B respectively will be pooled with the corresponding Week 24 data from Dosing Regimen E and compared to the Week 18 data from Dosing Regimen D (adalimumab).

Derivations and definitions of endpoints are specified in Section 11.

Summaries of the data will be produced using graphs and standard summary statistics.

12.2.2 Efficacy data

12.2.2.1 Primary efficacy variable

The primary efficacy variables of this trial are:

- DAS28 score at Week 6.
- DAS28 score at Week 24.

The primary endpoints will be analysed using an analysis of covariance (ANCOVA) model on the change from baseline, including terms for baseline as a continuous covariate and treatment, DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country as factors. Results will be presented in terms of the adjusted means for each treatment group, and estimates of treatment difference, associated CI and p-value for each treatment comparison (see Section 12.2.1 for applicable treatment comparisons). Model assumptions will be checked and if not met, appropriate data transformations may be applied or non-parametric approaches will be considered.

In order to examine the sensitivity of the conclusions to key covariates, an additional exploratory ANCOVA may also be performed including terms for duration of disease and rheumatoid factor in addition to baseline DAS28 score, treatment, DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country. If the 2 analyses yield different conclusions, the consequences of the covariate adjustment will be explored. In addition, other subgroups may be explored including baseline demographic characteristics, RA severity and previous RA treatments; further details will be specified in the SAP.

12.2.2.2 Secondary efficacy variables

ACR20, 50, 70

The analysis of ACR20, ACR50 and ACR70 at each time point will be performed using a test of treatment difference in proportion of responders with a Mantel-Haenszel approach stratified by DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country. The results of

the analyses will be presented as the adjusted difference in the proportion of patients who achieve ACR20, ACR50 and ACR70 at each time point, together with the associated 95% CI and 2-sided p-value for each treatment comparison (see Section 12.2.1 for applicable treatment comparisons).

The 7 individual ACR components are swollen joint count, tender joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, HAQ-DI score and acute phase reactant (CRP or ESR depending on entry criterion). The individual ACR components at each time point will be analysed using an ANCOVA model on the change from baseline, including terms for baseline as a continuous covariate and treatment, DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country as factors. CRP and ESR will be log-transformed prior to analysis. Results will be presented in terms of the adjusted means for each treatment group, and estimates of treatment difference, associated CI and p-value for each treatment comparison (see Section 12.2.1). Model assumptions will be checked and if not met, appropriate data transformations may be applied or non-parametric approaches will be considered.

ACR-N response at each time point will be analysed using a non-parametric method. The treatment difference between each dose of fostamatinib and either placebo or adalimumab (see Section 12.2.1), the associated CIs and p-values will be estimated using the van Elteren test stratified by DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country.

DAS28 Response

The DAS28 EULAR response at each time point will be analysed using a proportional odds model including treatment, DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country as factors. The proportion of patients achieving each level of response, the odds ratio, associated CI and p-value will be presented for each treatment comparison (see Section 12.2.1).

The proportion of patients classified as having achieved low-disease activity, DAS28 remission and a clinically important change in DAS28 score at each time point will each be analysed using logistic regression including treatment, DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country as factors (see Section 11.1.1).

HAQ-DI

In addition to the analysis of HAQ-DI scores (individual ACR component) described above, the proportion of patients classified as HAQ responders at each time point will be analysed using logistic regression including treatment, DMARD naivety (DMARD naive vs DMARD-IR/intolerant) and country as factors. Individual dimensions of the HAQ-DI will be also be analysed at the primary time point only for each treatment comparison using the ANCOVA model described for individual ACR components above.

SF-36

The SF-36 (including the 8 sub-scores and the physical component score and mental component score) will be summarised in terms of change from baseline over time. The physical component score and the mental component score will be analysed at each time point using the ANCOVA model described for individual ACR components above.

12.2.3 Safety data

Safety and tolerability will be assessed in terms of AEs, laboratory data, body weight, vital signs, ECG data and physical examination. Appropriate summaries of these data will be presented by dosing regimen and time period (up to Week 6 assessment and post-Week 6 assessment).

Adverse events will be classified according to the terminology of MedDRA and rates per 100 patient-years exposure (see Section 11.2) will be summarised by preferred term and system organ class. Additional summaries of AEs will be presented which includes summaries by causality and maximum intensity. Summary tables of grouped MedDRA preferred terms or other safety events of interest will also be produced (eg, infection, serious infective events), these will be specified in the SAP. Summaries of safety data of particular interest by variations in the gene *UGT1A1* will also be specified in the SAP.

Changes over time in laboratory data, body weight, vital signs and ECG data will be summarised for each treatment group using standard summary statistics. Out of range laboratory data will also be presented. AEs (and elevated laboratory measurements) of interest will be investigated for any temporal effects using appropriate graphical (and tabular) summaries.

The frequency of abnormal physical examination or ECG will also be summarised for each treatment group.

12.2.4 Other data

Baseline demographic data, medical and surgical histories will be summarised using standard summary statistics.

Concomitant medications will be summarised and classified according to the current version of the AstraZeneca Drug Dictionary.

Compliance rates for patient questionnaires will be summarised.

12.2.5 Interim analyses

No formal interim analyses are planned for this study.

12.3 Determination of sample size

The sample size for this study was selected to be consistent with the research hypothesis as described in Section 1.2.

Patients will be randomised equally to each of the 5 dosing regimens as described in Section 3.1.

Since this is a Phase II trial, no adjustments will be made for multiplicity.

Data from the previous Phase II study (C788-010) showed mean change from baseline in DAS28-CRP at Week 6 of 1.3 and 1.6 for the fostamatinib + methotrexate groups (150 mg *qd* and 100 mg *bid*, respectively) and 0.9 for the placebo + methotrexate group, with a standard deviation (SD) of approximately 1.25. Therefore a difference of 0.7 in the mean change from baseline in DAS28-CRP at Week 6 has been used for the sample size calculations, assuming a SD of 1.25. A sample size of approximately 50 in each arm provides at least 85% power to detect a difference (between fostamatinib and placebo) in the mean change from baseline in DAS28-CRP of 0.7 at Week 6, assuming a SD of 1.25.

For the comparisons with adalimumab, a non-inferiority margin of 0.6 in the mean change from baseline in DAS28-CRP has been chosen, and a zero difference in the mean change from baseline in DAS28-CRP between the fostamatinib dose regimens and adalimumab has been assumed. A sample size of approximately 50 in each arm provides approximately 85% power to confirm non-inferiority between fostamatinib and adalimumab using these assumptions, and a SD of 1.25.

Since up to 90 patients will be randomised to either Dosing Group A, D or E, in the sub-study, the actual numbers in each group will vary, with there being fewer patients in dosing groups B and C. As it is not known how many of the sub-study patients will be recruited prior to the database lock for this study, the degree of imbalance between the groups is unknown. However, the power for the comparison between the highest dose of fostamatinib and both placebo and adalimumab cannot be reduced as these are the 3 groups included in the sub-study. Hence it is considered that this study is adequately powered for its primary objectives.

Since patients are randomised prior to their second visit, it is expected that 10% to 15% of patients may fail an exclusion criterion (eg, raised blood pressure), therefore approximately 370 patients will be randomised, in order that approximately 250 patients (approximately 50 patients in each of the 5 dose regimens) will receive their randomised treatment in the main study. Ninety patients will receive randomised treatment in the sub-study.

12.4 Safety Review Committee

An independent SRC will be constituted to review accumulating safety data on an ongoing basis. Where necessary, SRC members may have access to unblinded safety data however no members of the study team (at AstraZeneca or the CRO) will have access to unblinded data until after database lock is declared. The SRC will be governed by a specific SRC charter which is summarized in Appendix J.

In addition, a blinded CV adjudication committee will review pre-defined CV events. This is independent of the SRC. The CV adjudication committee will be governed by a specific

charter which is summarized in Appendix P. The CV adjudication reports will be provided to the SRC.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.

In the case of a medical emergency the investigator may contact the 24-hour Urgent Medical Contact at

Name	Role in the study	Address & telephone number
-	24-hour emergency cover at	

13.2 Overdose

For the purposes of this study, exceeding the dosage requirements specified in this clinical study protocol represents an overdose.

Adalimumab doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

There is limited human experience regarding the use of fostamatinib. In case of overdose, monitoring of cardiac, hepatic and haematological effects is essential and appropriate standard support therapy should be initiated where appropriate (for further information refer to the IB).

- An overdose with associated AEs/SAEs is recorded as the AE/SAE diagnosis/symptoms on the relevant AE/SAE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca investigational product occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within 1 day**, ie, immediately but no later than **the end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca or its representative.

13.3.1 Maternal exposure

If a patient becomes pregnant during the course of the study, investigational products should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational products under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives **within 1 day** ie, immediately but no later than the **end of the next business day** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4, and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Details of the pregnancy and outcome will be recorded locally at individual study centres.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

13.3.2 Paternal exposure

There are no restrictions for male patients participating in the study who wish to father a child or donate sperm. This is based on the findings of a study in healthy male volunteers where it was found that extremely low amounts of fostamatinib are present in human semen. In addition, no effects have been observed on male fertility or spermatogenesis in pre-clinical studies and fostamatinib was not mutagenic or clastogenic in genotoxicity studies.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented.

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Clinical Study Protocol Appendix B

Drug Substance	Fostamatinib
Study Code	D4300C00004
Edition Number	1
Date	

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Cat A pathogens are eg, Ebola, Lassa fever virus

- are to be packed and shipped in accordance with IATA Instruction 602

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Cat B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Cat B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Clinical Study Protocol Appendix D

Drug Substance	Fostamatinib
Study Code	D4300C00004
Appendix Edition Number	2
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Appendix D
Pharmacogenetics and Exploratory Genetic and Biomarker Research

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
CSR	Clinical study report
DNA	Deoxyribonucleic acid
LIMS	Laboratory information management system
MTX	Methotrexate
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1
PGx	Pharmacogenetics
RA	Rheumatoid arthritis
SRC	Safety review committee

1. BACKGROUND AND RATIONALE

AstraZeneca intends to perform genetic and biomarker research in the fostamatinib clinical development programme to explore how genetic variations may affect, or biomarkers may be affected by the clinical parameters associated with fostamatinib and/or adalimumab. This section describes rationale for inclusion of genetic and biomarker sampling in the fostamatinib programme, and in particular in *(OSKIRA-4): A Phase IIB, Multi-Centre, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study of the Efficacy and Safety of Fostamatinib Disodium Monotherapy Compared with Adalimumab Monotherapy in Patients with Active Rheumatoid Arthritis*, which we will call "the main study" in the rest of this document.

1.1 Genetic analysis of *UGT1A1*

A safety objective of the main study is to investigate the relationship between variations in the gene encoding UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) and the safety and tolerability of fostamatinib in the study population. Genotype at the *UGT1A1* locus is known to contribute to a spectrum of hyperbilirubinemias, including Gilbert's syndrome (Strassburg et al 2008). Fostamatinib is a potent inhibitor of UGT1A1. Considering these facts, *UGT1A1* genotype data will be used to aid interpretation of potential changes in the serum levels of bilirubin throughout the fostamatinib clinical programme. This pharmacogenetic (PGx) investigation will be referred to as "genetic analysis of *UGT1A1*".

1.1.1 UGT1A1 and hyperbilirubinemia

UGT1A1 has an important metabolic role in the liver, where it is involved in the metabolism of a range of endogenous compounds and xenobiotics. Importantly, UGT1A1 is the sole enzyme responsible for bilirubin metabolism. Defects in the gene encoding UGT1A1 contribute to a spectrum of hyperbilirubinaemias ranging from the common and mild (eg, Gilbert's syndrome), through to the rare, very severe Crigler-Najjar Syndrome Type I (Strassburg et al 2008).

Estimates of the prevalence of Gilbert's syndrome vary from 5 to 9% in Caucasoid populations (Strassburg et al 2008). However a lack of overt symptoms means a large number of individuals remain subclinical, and are not diagnosed.

1.1.2 *UGT1A1* polymorphisms

Genetic polymorphisms in the gene *UGT1A1* are associated with hyperbilirubinemias. Crigler-Najjar syndromes type I and II are associated with around 60 rare mutations, few of which are at >1% in general population (Strassburg et al 2008). Gilbert's syndrome is associated with a dinucleotide "TA" repeat in the TATA box of the genes' promoter. Variations give rise to 4 different alleles (UGT1A1*1, *28, *36 and *37), with a longer number of repeats giving lower UGT1A1 expression (Table 1). The paradigm linking variability in the *UGT1A1* gene, with alterations in UGT1A1 protein function or expression,

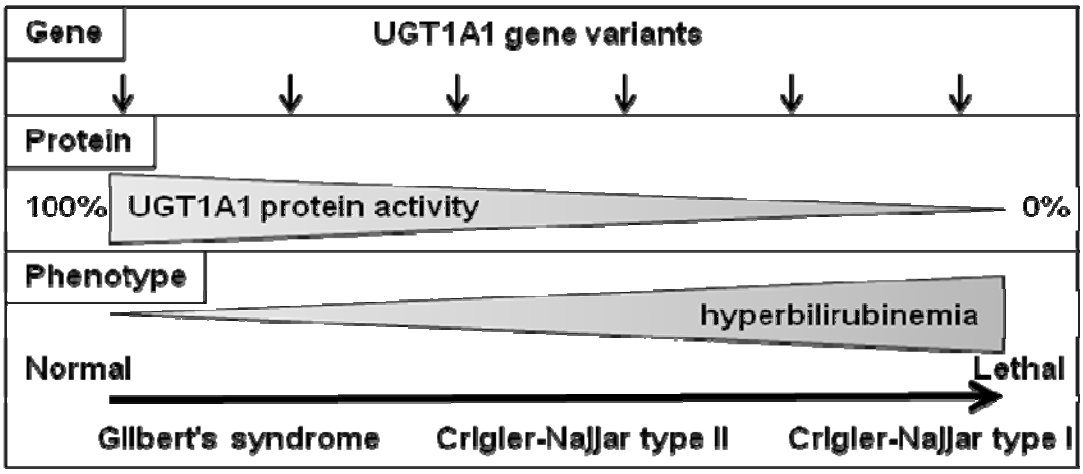
impacting bilirubin metabolism, and leading to a spectrum of hyperbilirubinemias, is described in Figure 1.

Table 1 Key *UGT1A1* polymorphisms

UGT1A1 Allele	Allele Details	Reported Effect	Minor Allele Frequency [a]				
			Ca[b]	His[c]	Indian	Af/AfAm[d]	Asian[e]
*1[f]	promoter "TAx6"; R71R	None	-		-	-	-
*28	promoter "TAx7"	Reduced activity[g]	0.26-0.36	0.36	0.38-0.40	0.20-0.56	0.09-0.16
*36	promoter "TAx5"	Increased activity[h]	<0.01	NR[i]	NRi	0.03-0.10	<0.01
*37	promoter "TAx8"	Severely decreased activity[h]	<0.01	NR[i]	NRi	0.02-0.07	<0.01
*6	R71G	Reduced activity[j]	<0.01	NR[i]	0.05	<0.01	0.13-0.23

[a] Minor allele frequencies have been estimated from public databases and literature reports (Akaba et al 1998, Beutler et al 1998, Farheen et al 2006, Hall et al 1999, Kaniwa et al 2005, NCBII, Premawardhena et al 2003)
[b] Caucasian populations, include Scandinavian, Eastern and Western European countries and the USA
[c] Hispanic
[d] African/African American
[e] Asian populations include Chinese, Japanese and Korean
[f] *UGT1A1*1* is the common or "wild type" allele
[g] Bosma et al 1995
[h] Beutler et al 1998
[i] Not reported to date
[j] Yamamoto et al 1998

Figure 1 Paradigm of *UGT1A1* gene variation and hyperbilirubinemia



Adapted from Strassburg et al 2008.

UGT1A1*28 is of major significance as it is common in many populations, including Caucasians. UGT1A1*6 is a coding polymorphism common only in Asian populations (Table 1). Both alleles have been shown to reduce UGT1A1 protein activity by up to 70%, and are strongly associated with Gilbert's syndrome (Bosma et al 1995, Yamamoto et al 1998). Furthermore, both alleles have been associated with increased risk of adverse outcome and severe toxicity during irinotecan treatment (Iyer et al 2002).

In addition to the described key polymorphisms in *UGT1A1* (Table 1), there are a large number of other polymorphisms in the gene which may play a role in the baseline levels of serum bilirubin in humans (Strassburg et al 2008).

1.1.3 Utility of *UGT1A1* genetic analysis

Fostamatinib is a potent inhibitor of UGT1A1. Inhibition of UGT1A1 effectively reduces the ability of UGT1A1 to metabolise bilirubin, and may contribute to an increase in serum bilirubin levels in some individuals. Raised bilirubin levels may present as jaundice, one of the clinical features of Gilbert's syndrome. Given the evidence linking polymorphisms in *UGT1A1* with Gilbert's syndrome, and the high frequency of these polymorphisms in the populations being sampled in the main study (Table 1), *UGT1A1* genetic analysis is a key safety objective for this study and programme.

Information from the genetic analysis of *UGT1A1* will allow exploration of factors contributing to observations of raised bilirubin in response to the study drug. The analysis may allow differentiation of individual cases of raised bilirubin where there is an underlying predisposition (in those individuals carrying *UGT1A1* polymorphisms) from cases where other factors predominate. It is intended that genetic analysis of *UGT1A1* will be performed in the whole study population upon completion of the main study; however exceptional circumstances may initiate early analysis. For instance an emerging signal identified by the safety review committee (SRC) could result in the genetic analysis of *UGT1A1* in a patient

sub-group (or an individual) being important to exclude known causalities. In this rare instance *UGT1A1* genotype data would be returned to the SRC to aid decision making. AstraZeneca does not intend to routinely return *UGT1A1* genotype data to individuals or their primary care physicians as the information about *UGT1A1* genotype status is not considered informative for the long term management of rheumatoid arthritis and the genotype data alone is inadequate to make a clinical diagnosis of Gilbert's syndrome.

Given the frequency with which the causative alleles are expected in the populations included in the main study, the genetic analysis of *UGT1A1* will give confidence in treating a full demographic of RA patients, whose lives may benefit from fostamatinib.

In order to facilitate these aims, collection of DNA from a full, unbiased cohort is important. It is for these reasons that genetic analysis of *UGT1A1* has been included in the main study.

1.2 Exploratory genetic and biomarker research

Collection of DNA and biomarker samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to individual guided treatment strategies. Future research may suggest other biomarkers, genes or gene categories as candidates for influencing not only response to fostamatinib and/or adalimumab but also susceptibility to rheumatoid arthritis (RA) for which fostamatinib may be evaluated. Thus, this optional exploratory research may involve study of additional un-named biomarkers, genes or gene categories, but only as related to RA and fostamatinib and/or adalimumab. This optional exploratory genetic and biomarker research will be referred to as "exploratory research".

2. GENETIC AND BIOMARKER RESEARCH OBJECTIVES

2.1 Genetic analysis of UGT1A1

To investigate the relationship between variations in the gene encoding UDP glucuronosyltransferase 1 family, polypeptide A1 (*UGT1A1*) and the safety and tolerability of fostamatinib in the study population. This is a part of the main study.

2.2 Exploratory genetic and biomarker research

To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, absorption, distribution, metabolism and excretion, safety, tolerability and efficacy) to fostamatinib and/or adalimumab; and/or susceptibility to, progression of and prognosis of RA; and/or associated biomarkers. This may be described in a separate report.

To investigate systemic biomarker profiles in RA patients. This may be described in a separate report. Biomarkers of interest may include cellular and soluble biomarkers in plasma and/or serum, such as cytokines and other markers of inflammation that may change as a result of treatment with fostamatinib, as well as proteins that may be indicative of disease severity and progression.

3. GENETIC AND BIOMARKER RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic and biomarker research population

3.1.1 Study selection record

3.1.1.1 Genetic analysis of UGT1A1

DNA sample collection for genetic analysis of *UGT1A1* is part of the main study, is described within the scope of the informed consent for the main study, and will be reported in the CSR.

3.1.1.2 Exploratory genetic and biomarker research

All subjects will be asked to participate in this exploratory research. Participation in the exploratory research is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this exploratory research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the exploratory genetic and/or biomarker sampling and analyses.

3.1.3 Exclusion criteria

Exclusion criteria from exploratory genetics research are as described in Section 4.2 of the Clinical Study Protocol.

3.1.4 Discontinuation of subjects from this exploratory research

Specific reasons for discontinuing a subject from this exploratory research are:

Withdrawal of consent for exploratory research: Subjects may withdraw from this exploratory research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 7.5 of the main Clinical Study Protocol.

3.2 Collection of samples for exploratory research

For blood volume, see Section 7.1 of the Clinical Study Protocol.

3.2.1 Genetic research samples

A single blood sample for DNA will be collected for both *UGT1A1* genetic analysis and optional exploratory genetic research. For those subjects who consent to participate in the exploratory research no additional blood samples will be taken for DNA. If consent for optional exploratory research is granted by the individual, any exploratory genetic research

will be undertaken using the DNA sample collected for the *UGT1A1* genetic analysis. For further information, see Section 6.7.1 of the Clinical Study Protocol.

3.2.2 Exploratory biomarker research samples

The blood samples for exploratory biomarker research will be obtained from the subjects at Visit 2, Visit 6 and Visit 15. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

3.3 Coding and storage of DNA and biomarker samples

The processes adopted for the coding and storage of samples for genetic and biomarker analyses are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA and biomarker samples are finite resources that may be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For details on coding of genetic samples, see Section 7.2.2 of the Clinical Study Protocol.

4. ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including the exploratory research component, are outlined in Section 8 of the main Clinical Study Protocol.

4.1 Informed consent

4.1.1 Genetic analysis of UGT1A1

DNA sample collection for genetic analysis of *UGT1A1* is part of the main study, is described within the scope of the informed consent for the main study, and will be reported in the CSR.

4.1.2 Exploratory genetic and biomarker research

The exploratory genetic and biomarker research components of this study are optional and the subject may participate in other components of the main study without participating in the exploratory genetic and/or biomarker research components. To participate in the exploratory genetic and/or biomarker research components of the study the subject must sign and date both the consent form for the main study and the appropriate exploratory research component of the study (there will be one form with separate consents for the exploratory genetic and biomarker research). Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely discontinue from the exploratory genetic and/or biomarker research aspect of the study at any time.

4.2 Subject data protection

For details on subject data protection, see Section 8.2 of the Clinical Study Protocol.

5. DATA MANAGEMENT

For details on genetic data management, see Sections 10.7 and 10.8 of the Clinical Study Protocol.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the exploratory research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

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Appendix E
American College of Rheumatology 1987 Revised Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis

AMERICAN COLLEGE OF RHEUMATOLOGY 1987 REVISED CRITERIA FOR THE CLASSIFICATION OF ACUTE ARTHRITIS OF RHEUMATOID ARTHRITIS

Criterion		Definition
1.	Morning stiffness	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement.
2.	Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling of fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3.	Arthritis of hand joints	At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint.
4.	Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry).
5.	Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6.	Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result had been positive in <5% of normal control patients.
7.	Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify).

* For classification purposes, a patient shall be said to have rheumatoid arthritis if he/she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made.

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Appendix F
Functional Class

AMERICAN COLLEGE OF RHEUMATOLOGY REVISED CRITERIA FOR CLASSIFICATION OF FUNCTIONAL STATUS IN RHEUMATOID ARTHRITIS

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

* Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age-and-sex specific.

Appendix G
Disallowed Medications and Medications to be Administered with Caution

DISALLOWED MEDICATIONS AND MEDICATIONS TO BE ADMINISTERED WITH CAUTION

There is potential for fostamatinib to be affected by drug-drug interactions. The active metabolite of fostamatinib is metabolised by CYP3A4 and it is an *in vitro* inducer of CYP2C8.

In the presence of a CYP3A4 inhibitor, fostamatinib systemic exposures may increase. Whereas, in the presence of a CYP3A4 inducer, fostamatinib concentrations may decrease, possibly to sub-therapeutic concentrations.

The active metabolite of fostamatinib is an *in vitro* inducer of CYP2C8 and further studies are planned to investigate this further. In the meantime, caution is recommended with co-administration of CYP2C8 substrates as, in the presence of fostamatinib, concentrations of the co-administered drug may decrease.

Fostamatinib, but not the active moiety R406, is an *in vitro* inhibitor of P-glycoprotein (P-gp). Fostamatinib is rapidly converted to R406 pre-systemically (in the gut) so systemic inhibition of P-gp is not expected to occur. It is theoretically possible that, through inhibition of intestinal P-gp leading to increased absorption, the circulating plasma levels of P-gp substrates (including digoxin which has a narrow therapeutic index) may be increased if co-administered in patients receiving fostamatinib. Until the clinical significance of this finding has been investigated, caution is recommended with the co-administration of digoxin for patients in the study. For patients requiring initiation of digoxin during the study, or who are already receiving treatment with digoxin, monitoring of digoxin levels is recommended in accordance with local practice and any adjustments to the digoxin dosage should be carried out accordingly. Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

Strong inhibitors of CYP3A4 should <u>not</u> be co-administered with fostamatinib.

Caution should be applied when co-administration of weak or moderate CYP3A4 inhibitors, CYP3A4 inducers, CYP2C8 substrates, or digoxin is indicated.

This is not an exhaustive list. In addition, any other drugs should be avoided at the Investigator's discretion if in their opinion the co-administration with fostamatinib may increase the risk of a clinically significant drug interaction.

CYP3A Inhibitors

Strong

- Clarithromycin.
- Telithromycin.

- Ketoconazole.
- Itraconazole.
- Fluvoxamine.
- Nefazodone.
- Ritonavir.
- Indinavir.
- Nelfinavir.
- Saquinavir.
- Atazanavir.

Moderate

- Amiodarone.
- Aprepitant.
- Erythromycin.
- Troleandomycin.
- Fluconazole.
- Imatinib.
- Verapamil.
- Diltiazem.
- Amprenavir.
- Fosamprenavir.
- Grapefruit juice.
- Seville oranges.
- Star fruit.

Weak

- Cimetidine.

CYP3A Inducers

- Barbiturates.
- Efavirenz.
- Nevaripine.
- Pioglitazone.
- Rifampin.
- Rifabutin.
- Carbamazepine.
- Phenytoin.
- Modafinil.
- St. John's Wort.

CYP2C8 Substrates

The main CYP2C8 substrates where caution is needed are:

- Rosiglitazone.
- Repaglinide.
- Pioglitazone.

P-gp Substrates

- Digoxin.
  - if a patient requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

Appendix H
Definition of Women of Child Bearing Potential and Acceptable Contraceptive Methods

DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL

Women of Child Bearing Potential (WoCBP) - Women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation.

Women NOT of Childbearing Potential - Women who are permanently or surgically sterilized or postmenopausal (definitions below):

- **Permanent sterilisation** includes hysterectomy and/or bilateral oopherectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. (The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts). Women who have undergone tubal occlusion should be managed on trials as if they are of WoCBP (eg, undergo pregnancy testing etc as required by the study protocol).

- Women will be considered **postmenopausal** if they are amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

  – Women under 50 years old will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range.

  – Women over 50 years of age will be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments.

ACCEPTABLE CONTRACEPTION METHODS

Highly effective method of birth control is defined in Note 3 in ICH Guidance M3 (Non-clinical Safety Studies for the conduct of Human Clinical trials for Pharmaceuticals) as one that results in a low failure rate (eg, less than 1 percent per year) when used consistently and correctly.

The following methods of highly effective contraception are considered acceptable by AstraZeneca for clinical trials with fostamatinib disodium. Note that women should have been stable on their chosen method of birth control for a minimum of 3 months before entering the trial. Generic names and examples of trade names are given. As trade names may vary, investigators should check the generic name of any contraception to ensure suitability.

Acceptable contraception methods are:

- Total sexual abstinence (abstinence must be for the total duration of the trial and the follow-up period)
- Vasectomised sexual partner plus male condom (with participant assurance that partner received post-vasectomy confirmation of azoospermia)
- Tubal occlusion plus male condom
- Intra-uterine Device (IUD) - provided coils are copper-banded, plus male condom
- Intra-uterine system (IUS) Levonorgestrel Intra Uterine System (e.g, Mirena), plus male condom
- Medroxyprogesterone injections (Depo-Provera) plus male condom
- Etonogestrel implants (eg, Implanon, Norplan) plus male condom
- Normal and low dose combined oral contraceptive pills, plus male condom
- Norelgestromin / ethinylestradiol transdermal system plus male condom
- Intravaginal device (eg ethinylestradiol and etonogestrel) plus male condom
- Cerazette (desogestrel) plus male condom. Cerazette is currently the only highly efficacious progesterone based pill

UNACCEPTABLE CONTRACEPTION METHODS

The following methods are considered not to be highly effective and are therefore **not acceptable contraceptive methods** in AstraZeneca clinical trials:

- Triphasic combined oral contraceptives (COCs)
- All progesterone only pills except, Cerazette
- All barrier methods, if intended to be used alone
- Non-copper containing Intra-Uterine Devices (IUDs)
- Fertility awareness methods
- Coitus interruptus

Appendix I
Management of Hypertension

1. MANAGEMENT OF ELEVATED BLOOD PRESSURE

As treatment with fostamatinib may be associated with hypertensive responses in some patients, blood pressure (BP) needs to be carefully monitored and managed throughout the study. Elevated BP (hypertension) is generally defined as a persistent BP ≥140 mmHg systolic and/or ≥90 mmHg diastolic. Goal blood pressure for some patients may need to take into account other comorbidities: in patients with diabetes or chronic kidney disease the decision to treat may be taken at lower BP levels in accordance with local guidelines. A similar action at the Investigator's discretion may apply to significant relative BP elevations (i.e. >20/10 mmHg) that are still within "normal range", i.e. < 140/90 mmHg.

BP determination methodologies are detailed in Section 6.4.8 of the Protocol.

Given the similarities between fostamatinib and other tyrosine kinase agents, the reported hypertensive effects may be related to a secondary inhibition of vascular endothelial growth factor (VEGF). The probable mechanism of the hypertension related to drugs that interfere with VEGF is peripheral vasoconstriction, and therefore the first-line drug of choice is usually a dihydropyridine calcium channel blocker (CCB) such as amlodipine or felodipine as such agents act as direct vasodilators. Non-dihydropyridine CCBs, e.g. verapamil and diltiazem, should generally be avoided because of their lower anti-hypertensive efficacy, the risk for adverse events if combined with beta-blockers (BBs) and possible drug-drug interactions with fostamatinib. It is anticipated that combination antihypertensive treatment will be needed. CCB – BB combinations, CCB – angiotensin II receptor blocker (ARB) and CCB - angiotensin converting enzyme inhibitor (ACEI) combinations may be considered. All these agents/combinations may be combined with diuretics (see Table 1).

Study drug discontinuation criteria are severe hypertension, i.e. BP ≥180 mmHg systolic and/or ≥110 mmHg diastolic recorded at any visit or a hypertensive complication (aggravation of angina pectoris, TIA).

1.1 General principles

- Apart from our specific recommendation on CCBs as the first-line medication, Investigators are expected to manage elevated blood pressure in accordance with local guidelines.
- Anti-hypertensive therapy during the study may require periodic adjustment – dose escalation or combination treatment, usually the addition of a drug (s) from another class.
- Add-on strategies may be preferable to dose escalation as this approach may mitigate dose-related side-effects

- Combination therapy is preferred to switching between single-drug therapies because rational combinations are more likely to act on multiple mechanisms of BP elevation and may help to counteract dose related side-effects of single drugs.

- There are no limits to the number of drugs in a combination regimen. In fact, at least 15-20% of hypertensive patients usually require a combination of 3 and more drugs. However, to limit the total number of tablets and improve patient compliance one may consider using fixed-dose combinations (see Table 1).

- Step-wise adjustment of anti-hypertensive therapy is expected to control BP (below 140/90 mmHg) in the majority of patients. However, if BP persistently remains ≥140 mmHg systolic and/or ≥90 mmHg diastolic (more than 8 weeks) despite repeated therapy adjustments, the dose of blinded study medication should be reduced to 100 mg once daily. If BP is still uncontrolled after 4 weeks despite the reduced dose, study medication should be discontinued. These patients will be followed up until hypertension resolved. Note, that resolution of the hypertensive response to study drug may require parallel reduction or discontinuation of the antihypertensive regimen. A similar line of action may be taken following discontinuation of NSAIDs since the patient's BP may decrease off NSAID.

- Blood pressure in the range 160-179 mmHg systolic and/or 100-109 mmHg diastolic requires prompt escalation of anti-hypertensive therapy, with or without reduction of blinded study medication dose, to reduce the BP below that level within hours rather than days. An extra visit to assess BP should be scheduled within one week, and if the BP is still in the above specified range at the repeated assessment, study medication should be discontinued and the patient followed-up.

- Severe hypertension, i.e. BP ≥180 mmHg systolic and/or ≥110 mmHg diastolic recorded at any visit or a hypertensive complication (aggravation of angina pectoris, TIA) should prompt immediate study drug discontinuation and close clinical follow-up until the patient is clinically stabilized.

- Apart from careful monitoring and management of blood pressure, addressing other preexistent cardiovascular risk factors is no less important. Investigators should encourage lifestyle modification including cessation of cigarette smoking, dietary sodium restriction, body weight reduction in overweight and especially in abdominal obesity, and increase in physical activity if appropriate. Of special importance are tight glycemic control in diabetic patients and lipid lowering therapy as required.

- More information on blood pressure management in patients receiving inhibitors of vascular endothelial growth factor may be found in Maitland ML et al 2010, as a part of recent National Cancer Institute Guidelines (see reference in Section 1.6).

1.2 Before randomization

All patients are screened at Visit 1. All patients should have their BP below 140/90 mmHg, irrespective whether or not on current anti-hypertensive treatment. If the BP is elevated and if the patient otherwise meets all enrollment criteria, the investigator may initiate treatment with dihydropyridine CCB in untreated patients, and add such drug to those already on anti-hypertensive therapy. If the therapy already includes dihydropyridine CCB, escalate the dose and/or add beta-blocker (BB), **or** angiotensin converting enzyme inhibitor (ACEI), **or** angiotensin receptor blocker (ARB). If BP control is achieved, i.e. BP is below 140/90 mmHg at Visit 2 (baseline) with the interval between these 2 visits not exceeding 4 weeks, the patient may be considered eligible. Conversely, if BP control is not achieved within this period the patient should be considered ineligible and not re-screened again. Note that the mean of the 2nd and 3rd BP measurements should be used (see Section 6.4.8 of the protocol).

1.3 After randomization

Both previously normal and controlled hypertension patients may experience elevated blood pressure while on study treatment. If BP is ≥140 mmHg systolic and/or ≥90 mmHg diastolic at any Visit, anti-hypertensive therapy needs to be adjusted by further dose up-titration or by adding an agent from another class of drugs as outlined in the above-mentioned general principles. The choice of second drug to be combined with a dihydropyridine CCB is often determined by compelling indications. For example, in patients with coronary heart disease the second drug is often a beta-blocker or its combination with a diuretic, in diabetics and patients with renal disease it would be ACEI or ARB, or their combinations. It should be noted, however, that in patients receiving non-steroidal anti-inflammatory drugs (NSAIDs) a combination of ACEI or ARB with a diuretic should be used with caution because of the risk for renal dysfunction.

1.4 Recommendations on specific anti-hypertensive drugs

Main classes of commonly used oral anti-hypertensive drugs including fixed-dose combinations are listed in Table 1. The preference is given to agents suitable for once daily use. If none of the specific drugs listed there is available in your country please discuss with AstraZeneca Study Physician to find an alternative drug.

Table 1

Drug class	Generic drug (example of Trade name)	Usual dose range*, mg	Daily frequency
Dihydropyridine CCBs	Felodipine (Plendil)	5 - 20	1
	Amlodipine (Norvasc)	5 - 10	1
	Nifedipine long-acting (Adalat CC, Procardia XL)	30–60	1
Fixed combinations	Felodipine/enalapril (Lexxel)	5/5	1
	Felodipine/metoprolol (Logimax)	5/50, 10/100	1

Table 1

Drug class	Generic drug (example of Trade name)	Usual dose range*, mg	Daily frequency
	Amlodipine/benazepril (Lotrel)	5/10, 5/20, 10/20	1
	Amlodipine/valsartan (Exforge)	5/80	1
ACEIs	Lisinopril (Prinivil, Zestril)	10 - 40	1
	Ramipril (Altace)	2.5 - 20	1
	Enalapril (Vasotec)	5 - 40	1-2
	Perindopril (Aceon)	4 - 8	1
	Trandolapril (Mavik)	1 - 4	1
	Benazepril (Lotensin)	10 - 40	1
	Quinapril (Accupril)	10 - 40	1
Fixed combinations	Lisinopril/hydrochlorothiazide (Prinzide)	10/12.5, 20/12.5, 20/25	1
	Enalapril/ hydrochlorothiazide (Vaseretic)	5/12.5, 10/25	1
	Benazepril/ hydrochlorothiazide (Lotensin HCT)	10/12.5, 20/12.5, 20/25	1
	Quinapril/ hydrochlorothiazide (Accuretic)	10/12.5, 20/12.5, 20/25	1
ARBs	Candesartan (Atacand)	8 - 32	1
	Losartan (Cozaar)	25 - 100	1-2
	Valsartan (Diovan)	80 - 320	1-2
	Irbesartan (Avapro)	150-300	1
Fixed combinations	Candesartan/ hydrochlorothiazide (Atacand Plus)	16/12.5, 32/12.5	1
	Losaqrtan/ hydrochlorothiazide (Hyzaar)	50/12.5, 100/25	1
	Valsartan/ hydrochlorothiazide (Diovan HCT)	80/12.5, 160 /12.5	1
	Irbesartan/ hydrochlorothiazide (Avalide)	150/12.5, 300/12.5	1
BBs	Metoprolol extended release (Toprol XL, Seloken ZOK)	50 - 100	1
	Atenolol (Tenormin)	25 - 100	1
	Nadolol (Corgard)	40 - 120	1

Table 1

Drug class	Generic drug (example of Trade name)	Usual dose range*, mg	Daily frequency
Fixed combinations	Atenolol/ chlorthalidone (Tenoretic)	50/25, 100/25	1
	Nadolol/ bendroflumethiazide (Corzide)	40/5, 80/5	1
Thiazide diuretics	Hydrochlorothiazide	12.5 - 25	1
	Chlorthalidone	12.5 - 25	1
	Indapamide (Lozol)	1.25 – 2.5	1
Fixed combinations	Triamterene/ hydrochlorothiazide (Dyazide)	37.5/25, 50/25	1
Aldosterone antagonists	Spironolactone (Aldactone)	25 - 50	1-2
Fixed combinations	Spironolactone /hydrochlorothiazide (Aldactone)	25/25	1

* - Dosages and brand names may vary from those listed in prescriber's information in your country.

For each agent, the product labeling should be consulted. For example, co-administration of NSAIDs may offset some of the antihypertensive effect of ARBs or ACEI s and also may increase the risk for renal adverse effects.

1.5 The management algorithm of elevated blood pressure

This may be summarized in the following 3 major steps:

Step 1:

If BP is ≥140 mmHg systolic and/or ≥90 mmHg diastolic at any visit after randomization,

- **Continue** with same dose of blinded study medication
- **Start or add** antihypertensive drug. Dihydropyridine CCB is recommended as first-line treatment
- Monitor BP and adjust anti-hypertensive therapy at least bi-weekly until controlled
- If BP is in the range 160-179 mmHg systolic and/or 100-109 mmHg diastolic promptly escalate anti-hypertensive therapy and re-assess within one week; consider going to Step 2
- Proceed to Step 2 if BP remains persistently elevated (≥140 mmHg systolic and/or ≥90 mmHg diastolic longer than 8 weeks) or to Step 3 if BP remains 160-179

mmHg systolic and/or 100-109 mmHg diastolic on two occasions within one week, or BP ≥180/110 mmHg at any time

Step 2:

- **Reduce** the dose of blinded study medication down to 100 mg once daily
- Monitor BP and adjust anti-hypertensive therapy at least bi-weekly until controlled
- Proceed to Step 3 if BP ≥180/110 mmHg at any time, or ≥ 160/100 mmHg on two occasions within one week, or is still ≥140 mmHg systolic and/or ≥90 mmHg diastolic longer than 4 weeks after blinded study medication dose reduction

Step 3:

- **Stop** blinded study medication
- If patient is symptomatic, treat as hypertensive emergency including possible hospitalization and iv anti-hypertensive treatment
- Follow up patient until hypertension is resolved
- Usually, the blood pressure can be managed without unblinding study treatment. If, however, knowledge of the study treatment is critical to the management of an important medical problem, the procedures for unblinding treatments are addressed in the Protocol (Section 5.4.2)

The frequency of the protocol-scheduled study visit should be sufficient to detect significant blood pressure changes since the anti-hypertensive effect of most drugs takes 2 to 4 weeks to fully develop. When the interval between study visits is 4 weeks, additional visits to assess BP and possibly adjust the medication may be needed at the discretion of the investigator. In rare cases, even de-escalation and down-titration of anti-hypertensive therapy may be required if relatively low BP is poorly tolerated (dizziness, fatigue, orthostatic symptoms).

If an Investigator needs to discuss BP management and possibly seek advice, please contact AstraZeneca Study Physician.

1.6 Reference

Maitland ML et al 2010
Maitland ML et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010:102(9);596-604.

Appendix J
Summary of Safety Review Committee (SRC) Charter for Fostamatinib Clinical Programme in Rheumatoid Arthritis

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1. INTRODUCTION

A Safety Review Committee is being set up to assure the safety of RA patients receiving fostamatinib. The SRC will provide a periodic review of the accumulating safety data across the fostamatinib RA programme. This document summarises the responsibilities of the SRC, the Investigator and AstraZeneca in respect of the ongoing review of accumulating safety data.

A full SRC Charter will provide further details relating to process and operational aspects of the SRC.

2. OVERVIEW OF OPERATION

The SRC will consist of at least 5 members, all external to AstraZeneca, including at least four medically qualified members and a statistician. Members of the SRC will be appointed by AstraZeneca and will be restricted to individuals free from financial or other conflict of interest.

A schedule of meetings will be established at the first SRC meeting, prior to randomisation of patients in the Phase III programme. SRC meetings will be held at minimum on a quarterly basis. The frequency of SRC meetings may be modified or additional safety reviews added as considered necessary by the SRC or the MSD as may be required in respect of recruitment rates and/or identification of potential safety issues.

SRC meetings will be conducted in open and closed sessions and separate minutes will be produced for each session. The MSD (or delegate) and other AstraZeneca staff as considered appropriate by the SRC may attend open SRC sessions to discuss any relevant issues such as further analyses, data or scientific advice that may be desirable to formulate recommendations, the provision of additional reports required by the SRC, discussion of blinded safety data, relevant information from other ongoing clinical studies with fostamatinib, administrative/operational issues or the communication of SRC recommendations. The treatment allocation of any blinded patients will not be discussed within the open sessions. Attendance at closed SRC sessions will be restricted to SRC members and external experts as may be considered relevant by the SRC. The SRC will be supported by one or more independent programmers with access to the safety data and randomisation schemes. As the SRC may review unblinded data during the study, this periodic review will facilitate the early identification and exploration of trends in the safety data without compromising the integrity of the blind for the study team.

Following each review of safety data the SRC will make recommendations to AstraZeneca regarding the actions considered appropriate in respect of the ongoing studies in light of the accumulating safety data for fostamatinib. Should a safety issue of concern be identified the SRC will consider if the ongoing studies should a) continue as planned, b) continue with amended design or conduct or c) be terminated.

The SRC will not review efficacy data from these studies.

AstraZeneca retains final accountability for patient safety. It is the responsibility of AstraZeneca to act as appropriate upon SRC recommendations.

3. REVIEW OF DATA

The following information will be provided prior to each SRC meeting:

- Reports containing information on general study progress (eg. recruitment updates, any study conduct issues)
- A listing of all SAEs on the AstraZeneca Global Patient Safety database
- Output reports from the Cardiovascular Adjudication Committee

The independent programmer(s) will provide safety listings and reports from the relevant clinical databases. These reports may include: numbers of patients experiencing adverse events (categories to include SAEs, ADRs, deaths, withdrawals, dose reductions etc) as agreed with the SRC. Additional reports will be provided at the request of the SRC.

Where requested, a narrative report from the AstraZeneca Physician (or delegate) describing the background, further investigations and outcome of significant events will be provided to the SRC.

For long term extension to the Phase II programme, the SRC will continue to be provided with the safety data/reports it currently receives.

4. OTHER PARTIES WITH SAFETY RESPONSIBILITIES

- The Investigator is responsible for the safety of patients under their care and must assess all safety data including laboratory results on a regular basis through to the end of the study. The Investigator will not have access to unblinded data prior to database lock.
- The AstraZeneca Physician (or delegate) is responsible for conducting ongoing reviews of the accumulating blinded safety data in each of the randomised pivotal fostamatinib studies and the long term extension to Phase II programme. The Study Team Physician will not have access to unblinded data prior to database lock for any study.
- The GSP ensures the ongoing safety evaluation of fostamatinib by providing Patient Safety medical expertise and judgment to safety surveillance and clinical development activities, including ongoing patient risk management. AstraZeneca's

Patient Safety department is responsible for the expedited reporting of relevant SAEs to regulatory authorities in line with AstraZeneca's Standard Operating Procedures (SOPs) and in line to the Safety Agreement with the Licensor for fostamatinib (Rigel).

- The independent programmer is responsible for the preparation of safety reports for the SRC but will not be involved in the SRC meetings or interact with the study teams.

- The MSD has ultimate responsibility for the safety of subjects receiving fostamatinib and for considering the implications of any safety concerns emerging in individual fostamatinib studies for other ongoing clinical studies with fostamatinib. The MSD (or delegate(s)) is responsible for interacting with the SRC and for attending open SRC meeting sessions but will not have access to unblinded data prior to database lock.

Appendix K
ACR Patient and Clinician Reported Outcome Components (HAQ Disability Index; Patient's Assessment of Pain VAS; Patient's Assessment of Global Disease Activity VAS; Physician's Assessment of Global Disease Activity VAS)

Please note:

The questionnaires in this appendix will be completed by the patient using an electronic device (SitePad). Included in the appendix is the paper version, for ease of reference. The wording will be identical when viewed on the electronic device.

The paper version of the HAQ-DI includes the ability to collect an "other" category of aids and equipment. However, in this study, as the data is collected by an electronic device, which cannot score free text, this category will not be included in the electronic version of the HAQ-DI. This is as per the developers 2005 HAQ Instructions and Scoring document.

HAQ Disability Index:

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

Please tick the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing up buttons?	_____	_____	_____	_____
- Wash your hair?	_____	_____	_____	_____
RISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
- Cut up your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

Please tick any of the following AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:

_____ Walking stick
_____ Walking frame
_____ Crutches
_____ Wheelchair
_____ Aids used for dressing (button hook, zip-puller, long-handled shoe horn, etc.)
_____ Specially adapted utensils (such as for eating and cooking)
_____ Specially adapted chair
_____ Other (Please specify:_____)

Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming
_____ Rising
_____ Eating
_____ Walking

Please tick the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
HYGIENE				
Are you able to:				
- Wash and dry your body?	_____	_____	_____	_____
- Have a bath?	_____	_____	_____	_____
- Get on and off the toilet?	_____	_____	_____	_____
REACH				
Are you able to:				
- Reach up for and take down a 5 lb object (e.g. a bag of potatoes) from just above your head?	_____	_____	_____	_____
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____
GRIP				
Are you able to:				
- Open car doors?	_____	_____	_____	_____
- Open jars which have been previously opened?	_____	_____	_____	_____
- Turn taps on and off?	_____	_____	_____	_____
ACTIVITIES				
Are you able to:				
- Go shopping?	_____	_____	_____	_____
- Get in and out of a car?	_____	_____	_____	_____
- Do housework such as vacuuming or gardening?	_____	_____	_____	_____

Please tick any of the following AIDS OR EQUIPMENT that you usually use for any of the activities mentioned above:

____Raised toilet seat
____Bath seat
____Jar opener (for jars previously opened)
____Bath rail
____Long-handled appliances for reaching things
____Long-handled appliances in bathroom (e.g.: a long handled brush)
____Other (Please specify: _____)

Please tick any of the following categories for which you usually need HELP FROM ANOTHER PERSON:

____Hygiene
____Reaching
____Gripping and opening things
____Shopping and housework

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 ——— SEVERE PAIN 100

Considering all the ways that your arthritis affects you, rate how you are managing on the following scale by placing a vertical mark on the line.

VERY WELL 0 ——— VERY POORLY 100

Study code DnnnnXnnnnn Subj initials ..... E code E

Visit No. X

IA01:08

Investigator's Global Assessment of Rheumatoid Arthritis IARA

Assessment date year mm dd

Global assessment of Rheumatoid arthritis activity today

No Rheumatoid arthritis activity ⟷ *Extremely active Rheumatoid arthritis*

Appendix L
SF-36

Please note: The questionnaires in this appendix will be completed by the patient using an electronic device (SitePad). Included in the appendix is the paper version, for ease of reference. The wording will be identical when viewed on the electronic device.

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking more than a mile	☐ 1	☐ 2	☐ 3
h	Walking several hundred yards	☐ 1	☐ 2	☐ 3
i	Walking one hundred yards	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

		All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
C	Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Had difficulty performing the the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Page 2

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time <u>during the past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a	Did you feel full of life? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	Have you been very nervous? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	Have you felt so down in the dumps that nothing could cheer you up? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	Have you felt calm and peaceful? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e	Did you have a lot of energy? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f	Have you felt downhearted and low? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g	Did you feel worn out? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h	Have you been happy? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i	Did you feel tired? ☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

		Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix M
The Stages of Heart Failure – New York Heart Association Classification

THE STAGES OF HEART FAILURE – NEW YORK HEART ASSOCIATION CLASSIFICATION

Class I (Mild)

No Limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).

Class II (Mild)

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class III (Moderate)

Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, or dyspnoea.

Class IV (Severe)

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, physical discomfort is increased.

Reference

The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston (MA): Little, Brown & Co; 1994:253-256.

Appendix N

Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

1. ACTIONS REQUIRED IN CASES OF AST OR ALT ≥ 3X ULN OR TBL ≥ 2X ULN

The Investigator is responsible for, without delay, determining whether the subject meets potential Hy's law (PHL) criteria; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) **and** total bilirubin (TBL) ≥ 2xULN at any point during the study, irrespective of alkaline phosphatase (ALP). The AST or ALT and TBL values do not have to be elevated at the same visit or within any specified timeframe.

1.1 Identification

In cases of AST or ALT ≥ 3x ULN **or** TBL ≥ 2x ULN, please follow the instructions below.

When a subject has an AST or ALT ≥ 3xULN **or** TBL ≥ 2xULN at any visit, the central laboratory will immediately send an alert to the Investigator (also sent to the AstraZeneca representative).

If a subject is found to meet PHL criteria from a local laboratory sample:

- Repeat test with the central laboratory
- Complete the appropriate laboratory case report form (CRF) modules with the original local laboratory test result.

1.2 Determination and Follow-up

1.2.1 Potential Hy's Law Criteria not met

If the subject **has not** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP

- Inform the AZ representative that the subject has not met PHL criteria
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

1.2.2 Potential Hy's Law Criteria met

If the subject **has** had AST or ALT ≥ 3xULN **and TBL** ≥ 2xULN at any point in the study even if on different visits, irrespective of ALP:

- Notify the AZ representative who will then inform the central study team

The Study Physician (SP) contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data.

The Investigator:

- Follows the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigates the etiology of the event and perform diagnostic investigations as discussed with the SP
- Completes the Liver CRF Modules.
- If at any time (in consultation with the SP) the PHL case meets serious criteria, it should be reported as an SAE using standard reporting procedures.

1.3 Review and Assessment

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP,

For the purpose of this process a Hy's Law case is defined as:

Any subject with an increase in both AST or ALT ≥ 3x ULN and TBL ≥ 2xULN, where no other reason can be found to explain the combination of increases, eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug

If there **is** an agreed alternative explanation for the AST or ALT **and TBL** elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE.

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** other explanation that would explain the AST or ALT and TBL elevations:

- Report an SAE (report term Hy's Law') according to AZ standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

– As there is no alternative explanation for the HL case, a causality assessment of related should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for a HL case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

2. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064993.htm

Clinical Study Protocol Appendix O

Drug Substance	Fostamatinib
Study Code	D4300C00004
Edition Number	1
Date	

Appendix O
Management of Diarrhoea - Guidance for Investigators

Management of Diarrhoea - Guidance for Investigators

This is intended as guidance only for investigators when managing patients who experience diarrhoea during the study.

DIARRHOEA (defined by WHO as ≥ 3 loose or liquid stools per day)

- Based on Phase 2 data, fostamatinib may be associated with diarrhoea. Therefore action should be taken to minimize its effects **as soon as symptoms develop**.
- Treatment induced diarrhoea should be carefully monitored **and treated aggressively** to ensure that severe complications are avoided.

Initial management of diarrhoea:

- Patients should be made aware that they may experience diarrhoea from study drug.
- If diarrhoea occurs patients should be encouraged to drink plenty of fluids to prevent dehydration, ie, soft drinks containing sugar, sports drinks such as Gatorade, water.

Management of persistent (>48h) diarrhoea:

- Patients should contact the site if diarrhoea persists for >48h.
- If the PI assesses the diarrhoea not to be due to an infectious cause (no fever or bloody stool), it is reasonable to have the patient begin an anti-motility medication such as loperamide, administered per label instructions.
- Care should be taken to prevent dehydration.

Management of persistent diarrhoea despite taking loperamide for 24 hours:

- The patient should be evaluated by the PI and a stool culture obtained to rule out infectious causes.
- Care should be taken to prevent dehydration.
- Patients should be advised to **temporarily withhold** study drug (per CSP section 5.8) and the PI should contact *the Medical Monitor* to discuss patient.
  - If diarrhoea resolves with dose interruption, discuss with your *Medical Monitor* if study drug should be reintroduced at prior dose or at a reduced dose. If a reduced dose is reintroduced, patient is to remain on the reduced dose for the remainder of the study.

Management of persistent diarrhoea despite dose reduction or dose interruption:

- The patient should be evaluated by the PI and assessed for dehydration. Hospitalisation and IV fluids may be needed. The PI should *contact the Medical Monitor* to discuss the patient.

- Dose interruption of study drug should continue until diarrhoea resolves.

Clinical Study Protocol Appendix P

Drug Substance	Fostamatinib
Study Code	D4300C00004
Edition Number	1
Date	

Appendix P
Fostamatinib Clinical Program in Rheumatoid Arthritis Cardiovascular Adjudication Committee Charter

AstraZeneca
Fostamatinib Clinical Program in
Rheumatoid Arthritis

Cardiovascular Adjudication Committee Charter

Final
Version Date:

CEVA – CV EVENTS ADJUDICATION COMMITTEE CHARTER

ASTRAZENECA FOSTAMATINIB CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER

CVAC CHARTER TABLE OF CONTENTS

Charter Version Date: Final (

CEVA – CV EVENTS ADJUDICATION COMMITTEE CHARTER

ASTRAZENECA FOSTAMATINIB CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER

CEVA – CV EVENTS ADJUDICATION COMMITTEE CHARTER

ASTRAZENECA FOSTAMATINIB CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER

CVAC ROSTER

Committee Members

CHAIRPERSON

MEMBERS

CEVA – CV EVENTS ADJUDICATION COMMITTEE CHARTER

ASTRAZENECA FOSTAMATINIB CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER

Contacts from Study Sponsor and Clinical Research Organization

SPONSOR PRIMARY CONTACT

m

CEVA COORDINATOR

PROGRAM DIRECTOR

ASTRAZENECA FOSTAMATINIB CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER

CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER SIGNATURE PAGE

Name	Title	Signature	Date
Committee Members			
	Chairperson **CVAC**		
	Member **CVAC**		
	Member **CVAC**		
Sponsor and Clinical Research Support Team			
	Senior Research Physician AstraZeneca		
	Medical Science Director AstraZeneca		
	CEVA Sr. Lead Lifecycle Safety Management Quintiles, Inc.		

I. INTRODUCTION: FOSTAMATINIB IN RHEUMATOID ARTHRITIS PROGRAM

This Charter applies to the Cardiovascular Adjudication Committee (CVAC) activities for the protocols outlined in Attachment A.

Quintiles, Inc. is contracted by the Sponsor of this trial, AstraZeneca, to provide CVAC coordination services.

II. SCOPE OF THIS CVAC CHARTER

The Cardiovascular Adjudication Committee (CVAC) provides independent and objective review and adjudication across the Fostamatinib Clinical Program for the treatment of Rheumatoid Arthritis (RA), which includes (but is not limited to) the protocols in the OSKIRA program.

The charge of the Committee is to evaluate all deaths and any potential cardiovascular events including but not limited to: myocardial infarction, stroke, transient ischemic attack, hospitalization for unstable

CEVA – CV EVENTS ADJUDICATION COMMITTEE CHARTER

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angina, hospitalization for heart failure, cardiac arrhythmias, venous and peripheral arterial thromboembolic events andhypertensive events of a serious nature.

The objective of the Charter is to outline the specific purposes and functions of the CVAC. In addition, it describes the procedures for obtaining and delivering clinical data and source documentation to the CVAC members for review and adjudication purposes.

III. COMPOSITION OF THE CVAC

The CVAC is composed of a chair and 2 additional members. Physicians who have a specialty in cardiovascular medicine and stroke neurology comprise the CVAC. The members of the CVAC and their affiliations are detailed on page 3. The sponsor of the studies, AstraZeneca, approves all members of the CVAC.

In order to be members of the Committee, CVAC members may not be involved as investigators in any of the protocols adjudicated by the committee. In addition, CVAC members shall not have a serious conflict of interest that would bias their review of trial data (e.g. CVAC members do not have a financial interest that could be substantially affected by the outcome of the study, intellectual bias, or relationships with individuals in trial leadership positions that could be considered reasonably likely to affect their objectivity). The members of the Committee will remain blinded to patient treatment throughout the duration of the trials.

All CVAC members are expected to serve on the Committee until the final study is completed that requires evaluation of possible cardiovascular events. If a member resigns, the member must submit the effective date of resignation in writing to AstraZeneca and the CVAC Chairperson. In the event a CVAC member resigns, AstraZeneca, in consultation with the CVAC Chairperson, will initiate the process to identify a replacement member.

IV. CVAC ROLE & RESPONSIBILITIES

The CVAC is an independent expert advisory group responsible for reviewing data to confirm diagnoses of potential CV events described below in Section VIII for protocols outlined in Attachment A.

The CVAC conducts all of its operations in accordance with ICH Good Clinical Practices (GCP).

The CVAC members are authorized and charged to perform the following functions:

- Operate according to processes, procedures and guidelines outlined in the CVAC Charter.
- Based on CV event dossiers received for review, adjudicate specified events in a timely manner.
- Communicate with other CVAC members, Sponsor or any procedural concerns or if further information is needed from the site in order to provide an adjudication decision.

CEVA – CV EVENTS ADJUDICATION COMMITTEE CHARTER

ASTRAZENECA FOSTAMATINIB CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER

Throughout the adjudication phase of the trial, the CVAC Chairperson is authorized and charged with the following additional responsibilities:

- Review with the CVAC members details on the protocols, event definitions and the adjudication processes and ensure CVAC members are appropriately trained
- Ensure that allocation of events for adjudication to the designated CVAC members are appropriate
- Liaise with the CEVA group, who coordinates the provision of packages and receipt of event reports to the CVAC
- Oversee CVAC meetings
- Support CVAC members to assist with questions regarding the interpretations of definitions by the members and ensure adherence with agreed processes and timelines
- Review trial serious adverse event (SAE) listings to choose potential CV events for the Committee review blinded to study treatment allocation.
- Manage meetings and discussions where adjudicators are in disagreement to ensure a consensus report
- Provide a Final adjudication assessment form and brief narrative for each potential nonfatal CV event and death reviewed by the CVAC. Each CVAC member will complete an "electronic adjudication worksheet" to document their independent assessment of the event, including any relevant comments describing their adjudication decision. The Final adjudication assessment form will record the final adjudication decision following full committee review and discussion of each case.

The CVAC Chair will represent the Committee and present on their activities where required in internal and external forums.

All CVAC outcomes for cardiovascular and neurological CV events for each protocol will be finalized prior to the lock of each clinical database, and these data will be considered to be the final, official CV event outcomes to be utilized in statistical analyses.

V. ASTRAZENECA RESPONSIBILITIES

The Sponsor, AstraZeneca, will have the following responsibilities with respect to the CVAC:

- Provide an AstraZeneca representative to serve as primary Sponsor contact for the CVAC.
- Provide final approval of the CVAC membership.

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- Provide approval for and operate in accordance with the specifications outlined in this CVAC Charter.
- Ensure that clinical or other data or documents available to AstraZeneca which are relevant to the CVAC, including new and updated study protocols and Investigator Brochures, are provided to the CEVA Coordinator in a timely manner for communication to the CVAC.
- Provide monthly (blinded) trial serious adverse event (SAE) listings to
- Collaborate with to ensure that CVAC members are informed of study progress and any relevant issues on a regular basis.
- Provide Sponsor representation at the CVAC Kick-off meeting
- Provide review and approval, in conjunction with the CVAC Chairperson, of minutes of the CVAC Kick-off meeting
- Ensure fair and reasonable reimbursement to CVAC members (i.e., for adjudication services provided and any related travel costs, such as transportation, lodging, and meals). Payments and reimbursements are to be coordinated and executed by the CEVA Coordinator, on the behalf of AstraZeneca.
- Maintain ultimate responsibility for safe study conduct, according to ICH Good Clinical Practices (GCP) Guideline.

VI. CEVA COORDINATOR RESPONSIBILITIES

Clinical Event Validation & Adjudication (CEVA) Services is providing a CEVA Coordinator for the study. The CEVA Coordinator provides administrative, logistical and coordinating support to the CVAC members.

The CEVA Coordinator is charged with the following responsibilities:

- Serve as the primary point of contact for the CVAC members and CVAC-related issues.
- Oversee dossier compilation activities completed by the CEVA Data Coordinating Center.
- Submit all CV event data requiring CVAC review directly to CVAC members
- Receive CVAC requests for additional documentation, and follow-up to obtain all available documents in response to those requests from site investigators.
- Coordinate and make arrangements for all CVAC meetings.
- Attend CVAC Kick-off meeting to facilitate meeting discussion and agenda items
- Confirm that all expected adjudication forms/outcomes are completed and are captured in the appropriate database.

- Maintain a central file of all key CVAC-related correspondences.
- Process CVAC member invoices, expense reports, and check requests on behalf of AstraZeneca.

VII. CVAC MEMBER TRAINING

All CVAC members will receive protocol overview and CVAC process training. To this end, a CVAC Kickoff Meeting will be held. The objectives of the CVAC Kickoff meeting will be to orient the CVAC members to the relevant study protocols, familiarize members with the CVAC Charter, and review operations of the adjudication processes.

VIII. CARDIOVASCULAR EVENT DEFINITIONS

Members of the CVAC will adjudicate each potential blinded event, based on pre-specified definitions, and render an assessment as to whether the case represents a confirmed event (meeting an event definition with all necessary documentation), a non-event (does not meet the event definition and likely represents an alternative or nonevent diagnosis), or lacks sufficient documentation for confirmation of an event. If there are limited or missing data, the Committee will adjudicate events based on their clinical expertise and the totality of the evidence available. The potential CV events to be adjudicated are defined as outlined below, or per the FDA guidance paper titled "Standardized Definitions for End Point Events in Cardiovascular Trials" (Draft, , included as Appendix F to this Charter.

The specific events to be adjudicated are as follows:

Death

- Cardiovascular Death
- Non-Cardiovascular Death
- Undetermined Cause of Death

Cause of death will be adjudicated per the definitions provided in the paper titled "Standardized Definitions for End Point Events in Cardiovascular Trials" Death will be classified as due to Cardiac Arrhythmia if, for example, any of the following occurred: ventricular fibrillation, ventricular tachycardia, or asystole.

Myocardial Infarction

- **Type:** Spontaneous myocardial infarction related to ischemia due to a primary coronary event e.g., plaque erosion and/or rupture, fissuring, or dissection

- **Type:** Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or related to other hemodynamic changes (e.g. hypotension, vasospasm).
- **Type:** Myocardial infarction associated with PCI
- **Type:** Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
- **Type:** Myocardial infarction associated with CABG
- **Type**: Undetermined

Myocardial infarctions will be adjudicated per the definitions provided in the paper titled "Standardized Definitions for End Point Events in Cardiovascular Trials"

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Stroke

- Ischemic
- Hemorrhagic
- Unknown

Strokes will be adjudicated per the definitions provided in the paper titled "Standardized Definitions for End Point Events in Cardiovascular Trials").

Transient Ischemic Attack (TIA)

TIAs will be adjudicated per the definitions provided in the paper titled "Standardized Definitions for End Point Events in Cardiovascular Trials" (

Hospitalization for Unstable Angina
Hospitalizations for Unstable Angina will be adjudicated per the definitions provided in the paper titled "Standardized Definitions for End Point Events in Cardiovascular Trials" (

Hospitalization for Heart Failure

Hospitalizations for Heart Failure will be adjudicated per the definitions provided in the paper titled "Standardized Definitions for End Point Events in Cardiovascular Trials" (

Cardiac Arrhythmias

Any atrial or ventricular arrhythmia documented by electrocardiography not associated with an acute or ongoing cardiac ischemic event.

Venous and peripheral arterial thromboembolic events

- **Deep vein thrombosis and pulmonary embolism:** Any event of deep venous thrombosis and pulmonary embolism as defined by clinical history, signs and imaging findings
- **Peripheral arterial events:** This includes but is not limited to: arterial dissection, arterial thrombosis requiring percutaneous intervention or vascular bypass surgery: evidence of embolism or occlusion should be documented by clinical notes, physical examination and imaging studies..

Hypertensive events of a serious nature

This includes malignant (accelerated) hypertension and hypertensive target organ disease requiring hospitalization such as cardiac, cerebrovascular, renal, and retinal but could be cross-coded with other types of events, e.g. heart failure. Also included are vascular emergencies such as aortic dissection and aortic aneurysm.

IX. CARDIOVASCULAR EVENT DOSSIER PREPARATION & SUBMISSION

Under the direction of the CVAC Coordinator, the CEVA Data Coordinating Center will collect, assemble and provide patient data to the CVAC members for review and adjudication.

Dossier Components

Dossiers for adjudication by the CVAC members will include select CRF data, CIOMS, as well as relevant source documentation from the patient's chart. Receipt of updated CIOMS forms may result in a CVAC re-review, if an updated CIOMS form is received that updates the diagnosis for a CV event or is received for a CV event that the CVAC felt had insufficient information during their initial adjudication.

CRF Data

The CRF data included in the dossiers for CVAC adjudication will be provided via a programmed CVAC CV Event Data Listing which will be generated from the clinical database with the CRF data available at the time of generation.

The data to be included within the CVAC CV Event Data Listing are specified in the CV Event-Lock Specifications document [Attachment B], and is expected to be background data, only. In other words, data does not require query-clean status in order to be provided to the CVAC, nor will post-adjudication CRF data changes result in the need for CVAC re-review.

Source Documentation

The following source documents will be provided to the CVAC as part of the standard endpoint dossier contents (as available):

CEVA – CV EVENTS ADJUDICATION COMMITTEE CHARTER

ASTRAZENECA FOSTAMATINIB CARDIOVASCULAR ADJUDICATION COMMITTEE CHARTER

Death

- Discharge/Death Summary (Hospital, ambulance/paramedic notes and any narratives provided if death occurred out-of-hospital)
- Autopsy Report (if done/available)
- Death Certificate (if available)

Myocardial Infarction

- Cardiologist consultation notes
- Cardiac Catheterization Procedure Report for any imaging cardiac procedures, echocardiogram, catheterization reports, or stress test reports
- PCI or CABG Procedure Report
- Biomarker Lab Reports (with reference ranges)
- Baseline ECG Tracing
- Event ECG Tracing (s)
- Post-event ECG Tracing
- Discharge Summary
- Total CK and CK-MB and local lab reference ranges
- Troponin I or T and local lab reference ranges

Stroke

- Neurology consultation notes
- CT or MRI Imaging Study Report
- Discharge Summary
- Documentation of neurological deficit, including clear documentation of duration
- History and Physical

Transient ischaemic attack

- Neurologist consultation notes
- CT or MRI Imaging Study Report
- Discharge Summary
- ER notes
- History and physical

Hospitalization for Unstable Angina

- Cardiologist Consultation notes
- Discharge Summary
- All cardiac marker reports (i.e. CKMB, CK, Troponin I, Troponin T) and reference ranges for the lab parameters

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- Pre-event ECG
- During-event ECG (s)

Hospitalization for Heart failure

- Discharge Summary
- Chest x-ray report (prior to event)
- Chest x-ray report (event)
- Critical Care Flow Sheet
- Medication Administration Record
- History and Physical

Cardiac Arrhythmias

- Cardiologist consultation notes
- Cardiac Catheterization Procedure Report for any imaging cardiac procedures, echocardiogram, catheterization reports, or stress test reports
- PCI or CABG Procedure Report
- Biomarker Lab Reports (with reference ranges)
- Baseline ECG Tracing
- Event ECG Tracing (s)
- Post-event ECG Tracing
- Discharge Summary
- Total CK and CK-MB and local lab reference ranges
- Troponin I or T and local lab reference ranges

Venous and Peripheral arterial thromboembolic events

- History and Physical
- Discharge Summary
- Laboratory reports
- Operative report/Procedure reports
- Imaging studies, including duplex US, venogram, MRI, and CT reports

Hypertensive events of a serious nature

- Admission History and Physical
- Discharge Summary
- Imaging studies including echocardiography and chest x-ray
- Laboratory data
- Any Emergency physician, cardiologist, critical care or neurologist consult

- Site should provide narrative if patient is not hospitalized if site considers hypertension to be an SAE.

Translations

The CEVA Coordinator will obtain English translations for non-English source documentation.

If it is not feasible to translate an entire document, mapped translations of relevant sections of the non-English source document will be obtained.

The CEVA Coordinator will include the original language documents, as well as the translated documents, in the dossiers submitted for CVAC adjudication.

Dossier Format

The following documents will constitute the standard contents of each dossier assembled:

- Adjudication Forms for Individual and Final (Chair only) assessments [Attachment C]
- CVAC CV Event Data Listing [Attachment D]
- Source Documentation

X. THE CVAC ADJUDICATION PROCESS

CVAC Data Review Venue & Format

CV event dossiers will be submitted to the CVAC on a monthly basis, although the submission frequency can be increased or decreased, depending upon the number of CV events reported and study timelines. CV events will be submitted to all 3 Committee members.

Adjudication of cases in which there is not unanimous agreement will be performed rapidly after completion of the individual assessments through deliberations between the Chair and the members. This will be done through brief teleconferences of the entire CVAC. The Chair will draft the minutes of the final decisions that occur during these deliberations.

Operational Flow

Once a package is complete for a potential CV event, the CVAC Coordinator will forward it to all three committee members from different institutions. The CVAC members will independently review the package within 10 working days and complete their adjudication worksheet within the Electronic Adjudication System (EAS) to document their individual assessment. Once all three worksheets are completed, the EAS will automatically compare the results. Agreement cases will be automatically routed to the Chair and a system-generated Chair confirmation adjudication eCRF will be produced for completion by the CVAC Chair. Disagreement cases will automatically be routed to a full committee

workflow dashboard, and a system-generated adjudication eCRF will be produced for the CVAC Chair to complete following full-CVAC discussion.

The CVAC will meet as needed until the conclusion of the trials and all potential events have been adjudicated. A quorum (all three members including the chairman) is required for all meetings. The frequency of meetings will be determined by the Chair.

Events will be considered adjudicated when a majority of the participating CVAC members reach a consensus on the event classification. In case of split adjudication, the chairman will determine the event classification.

For all events that are adjudicated by the CVAC, the Chair will electronically complete and sign the Final Clinical Endpoint Adjudication Form indicating the committee's agreement and judgment for each individual clinical event.

If the CVAC is unable to adjudicate the event due to inadequate documentation, a specific query of required information will be sent to the sites via the Coordinator. The Coordinator will then contact the study site for this additional information and will provide it to the CVAC. If after considerable effort, it is apparent no additional information is likely to be available, and uncertainty exists, the committee will use its best judgment based on clinical expertise to adjudicate the event.

CVAC Adjudication Forms

Individual Adjudication Worksheets will be completed by each member within the EAS. In addition, the CVAC Chair will complete a final, adjudication eCRF to document the final adjudication decision for each event requiring CVAC review.

CVAC Adjudication Data Queries

If a completed adjudication CRF contains a data discrepancy, the Electronic Adjudication System (EAS) will generate a query for the CVAC member who entered the adjudication CRF data into the system. The CVAC member will address the query directly in the EAS.

CVAC Requests for Additional Documentation (RADs)

If any additional documents are determined by the CVAC to be necessary for adjudication purposes, the CVAC will notify the CEVA Coordinator by completing a query within the Electronic Adjudication System indicating the Request for Additional Documentation (RAD).

Upon notification of the RAD, the CEVA Coordinator will initiate follow-up to obtain any available documentation.

The CEVA Coordinator will submit all additional information collected for a given case to each CVAC member involved in the adjudication of that case.

The final adjudication form (completed by the chair) will have an option for "Insufficient information", which will be selected only after the CVAC has requested additional documentation, determined nothing else is available, and they cannot provide a decision with information available.

XI. FOSTAMATINIB CLINICAL PROGRAM IN RHEUMATOID ARTHRITIS:CVAC CONFIDENTIALITY AND RECORDS RETENTION

Confidentiality

The CVAC must maintain a strictly confidential relationship to all study data and study materials.

Data Handling & Records Retention

The CVAC Chairperson and members will maintain sufficient documentation to support the outcomes and recommendations produced as part of the adjudication process. The CVAC Chairperson will also maintain a correspondence file related to CVAC activities.

CVAC-related documentation should be retained for two years following the date a marketing application is approved for the study medication for the indication for which it is being studied, or until two years after investigation of the study medication is discontinued. After the two-year period, the CVAC Chairperson and members should contact the sponsor, to determine if further retention and/or archiving is necessary.

ATTACHMENTS:

Attachment A: List of trials requiring cardiovascular event adjudication by the CVAC

Attachment B: CV Event-Lock Specifications Document

Attachment C: Adjudication Forms for Individual and Final (Chair only) Assessments

Attachment D: CVAC CV Event Data Listing

Attachment E: Acronym Table

Attachment F: Paper entitled “Standardized Definitions for End Point Events in Cardiovascular Trials” ( )

Attachment A: Protocols

This Charter applies to the Cardiovascular Adjudication Committee (CVAC) activities for the following protocols:

- Protocol D4300C00001 titled: “OSKIRA 1”
- Protocol D4300C00002 titled: “OSKIRA 2”
- Protocol D4300C00003 titled: “OSKIRA 3”
- Protocol D4300C00004 titled: “OSKIRA 4”
- Protocol D4300C00005 titled: “OSKIRA-X”

Attachment B: CV Event-Lock Specifications Document

Attachment C: Adjudication Forms for Individual and Final (Chair only) Assessments

Attachment D: CVAC CV Event Data Listing

Attachment E: Acronym Table

Acronym	Name
CEVA	Clinical Event Validation and Adjudication
CRF	Case Report Form
CVAC	Cardiovascular Adjudication Committee
DSL	Documentation Submission List
GCP	Good Clinical Practices
ICH	International Conference on Harmonization
MI	Myocardial Infarction
RAD	Request for Additional Documentation
TIA	Transient Ischemic Attack

Attachment F: "Standardized Definitions for End Point Events in Cardiovascular Trials" (Draft,)