AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD5672
Study Code	D1710C00009
Edition Number	1
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A Randomised, Double-Blind, Placebo-Controlled, Phase IIb Dose-Ranging Study (with Open-label Etanercept Treatment Group) to Investigate Efficacy, Safety and Pharmacokinetics of AZD5672 Administered for 12 Weeks to Rheumatoid Arthritis Patients Receiving Methotrexate

Study dates:	First patient enrolled: 01 July 2008 Last patient completed: 08 April 2009
Phase of development:	Therapeutic exploratory, Phase IIb

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centres

A total of 61 centres recruited patients during the study. The number of centres that recruited patients per country was: Bulgaria (4), Colombia (4), Czech Republic (8), Hungary (6), Italy (1), Latvia (2), Malta (1), Poland (11), Serbia (3), Slovakia (4), South Africa (5), Romania (4), Russia (2), Ukraine (6).

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to evaluate the effect of AZD5672 (20, 50, 100 and 150 mg once daily) on the signs and symptoms of rheumatoid arthritis (RA) in patients on background methotrexate (MTX) therapy, as measured by the American College of Rheumatology 20% response criteria (ACR20) at 12 weeks. Both the treatment effect compared with placebo and the dose-response relationship were evaluated.

The secondary objectives of the study were:

- To further evaluate the effect of AZD5672 on the signs and symptoms of RA in patients on background MTX therapy as measured by:
  - ACR20 response at 4 and 8 weeks
  - ACR50, ACR70 response and hybrid ACR response (4, 8, and 12 weeks)
  - Individual components of the ACR response criteria (4, 8, and 12 weeks)
  - Erythrocyte sedimentation rate ([ESR] 4, 8, and 12 weeks)
  - Disease Activity Score (based on 28 joint count [DAS28]) scores, European League Against Rheumatism (EULAR), and response rates (4, 8, and 12 weeks)
- To evaluate the safety and tolerability of AZD5672 in patients on background MTX therapy
- To evaluate the effects of AZD5672 on physical function and quality of life (QoL) as measured by the Health Assessment Questionnaire – Disability Index (HAQ-DI) (one of the ACR response criteria above), individual dimensions of the HAQ-DI, the 36-item Short Form Health Survey (SF-36) Questionnaire and the Rheumatoid Arthritis QoL Questionnaire (RAQoL)
- To investigate the plasma pharmacokinetics (PK) of AZD5672 in the study population (the results of these analyses will be reported separately)

- To investigate possible relationships between systemic AZD5672 concentrations/exposures and adverse events (AEs), safety parameters and efficacy measurements (the results of these analyses will be reported separately).

The exploratory objectives of the study were:

- To investigate additional patient reported outcomes (PROs) using the Patient Insight Questionnaire (PIQ)
- To compare the effect of AZD5672 treatment with etanercept when given open-label in a parallel treatment group within the same study
- To investigate the effect of chemokine (C-C motif) receptor 5 (*CCR5)* genotype on AZD5672 treatment effect
- To provide DNA samples to allow investigation of genetic factors that may influence the absorption, distribution, metabolism and excretion (ADME), efficacy, safety and tolerability of AZD5672, MTX and etanercept and progression and prognosis of RA in the study population (the results of these analyses will be reported separately).

Study design

This was a randomised, double-blind (with an open-label etanercept treatment group), placebo-controlled, parallel group multi-centre study to evaluate the efficacy, safety, tolerability, and PK of 4 doses of AZD5672 administered once daily for 12 weeks in patients with RA. Patients were randomly assigned to receive AZD5672, at doses of 20, 50, 100 or 150 mg once daily, matching placebo (oral tablet form, once daily in the morning) or subcutaneous open-label etanercept (50 mg once per week). Allocation of study medication was achieved via a 2-stage randomisation process to ensure that only patients who had tested negative for latent tuberculosis infection were randomised to treatment with etanercept.

Target patient population and sample size

Male or female patients (over 18 years of age) with active RA and on background treatment with MTX were included in the study.

It was planned to randomise approximately 360 patients in total, 60 to the open-label etanercept arm and 300 in total to the AZD5672 or placebo treatment arms. The sample size calculation was based on detecting a difference of 30% in the proportion of patients achieving an ACR20 response at 12 weeks between each dose of AZD5672 and placebo.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Eight batches of AZD5672 and 4 batches of matching placebo, and 6 marketed product batches of etanercept (Enbrel®) were used in this study. Individual batch numbers and further information are included in the CSR.

Duration of treatment

The duration of treatment for all groups in the study was 12 weeks.

Criteria for evaluation

Efficacy

The outcome variables were ACR scores (ACR20, 50 and 70, hybrid ACR, ACRn and individual ACR components: C-reactive protein; swollen joint count, tender joint count, patient's assessment of pain, patient's global assessment of disease activity, physician's assessment of disease activity and patient's assessment of physical function, as measured by HAQ-DI), ESR, and DAS28 during 12 weeks' treatment.

Patient reported outcomes (PROs)

Patient reported outcomes were the patient's assessment of pain and global disease activity (measured using separate visual analogue scales), the patient's assessment of physical function as measured by the HAQ-DI, and functional health and well-being using the SF-36 and RAQoL questionnaires.

Pharmacokinetic

The total concentration of AZD5672 in plasma was determined. Pharmacokinetic analyses were only performed on the plasma samples collected from a subgroup of patients receiving AZD5672. Results will be reported separately.

Safety

Adverse events, safety laboratory analyses, (clinical chemistry, haematology and urinalysis), 12-lead electrocardiogram (ECG), vital signs (blood pressure and pulse), and physical examination.

Exploratory

Patient reported outcomes (PIQ assessing joint pain and stiffness, fatigue, depression, ability to work and sleep, pain on physical contact and analgesic use); efficacy (comparison of AZD5672 and open-label etanercept treatment); and pharmacogenetics (*CCR5Δ32* genotype). Other pharmacogenetic results do not form part of the main study database and are not included in this clinical study report (CSR).

Statistical methods

The primary efficacy variable of this trial was the proportion of treated patients who achieved ACR20 at Week 12, which was compared by the 2-sided chi-square test with α=0.05, as a confirmatory analysis. A hierarchical testing strategy was applied for the multiple testing of different doses versus placebo. Initially, the highest dose of AZD5672 (150 mg) was compared with placebo. If a statistical difference was obtained, then the next lower dose (100 mg) was to be compared with placebo. This process was to be repeated until a statistical difference was not obtained or all AZD5672 doses had been compared with placebo. The overall type I error for this hierarchical testing strategy maintained the nominal level of α=0.05.

ACR50 and ACR70 were analysed in complete analogy to the primary efficacy parameter, except for the hierarchical test procedure. The hybrid ACR score and ACRn were analysed using non-parametric methods. The ACR components were analysed using an analysis of covariance (ANCOVA) model on the absolute improvement from baseline including terms for baseline and treatment. CRP was log transformed prior to analysis.

The improvement from baseline in DAS28 score was similarly analysed using an ANCOVA model as described above. DAS28 was also analysed based on the EULAR response criteria. The number of patients reaching DAS28 remission (DAS28 score <2.6), a clinically important change (improvement from baseline of at least 1.2 in DAS28 score) and low disease activity (DAS28 score <3.2) were summarised.

Changes in other secondary endpoints were analysed using either ANCOVA models (dimensions of the HAQ-DI and SF-36) or non-parametric models (ESR and RAQoL).

Unless otherwise stated, missing efficacy data were imputed using a last observation carried forward (LOCF) approach at each visit, except for patients withdrawn due to an AE. Such patients were considered non-responders for subsequent visits.

Patient population

It was intended to recruit 360 patients in total, 60 to the open-label etanercept arm and 300 in total to the AZD5672 or placebo treatment arms. Figure S1 and Figure S2 display the patient disposition in the study across all treatment groups.

Figure S1 Flowchart of patient disposition (part 1)

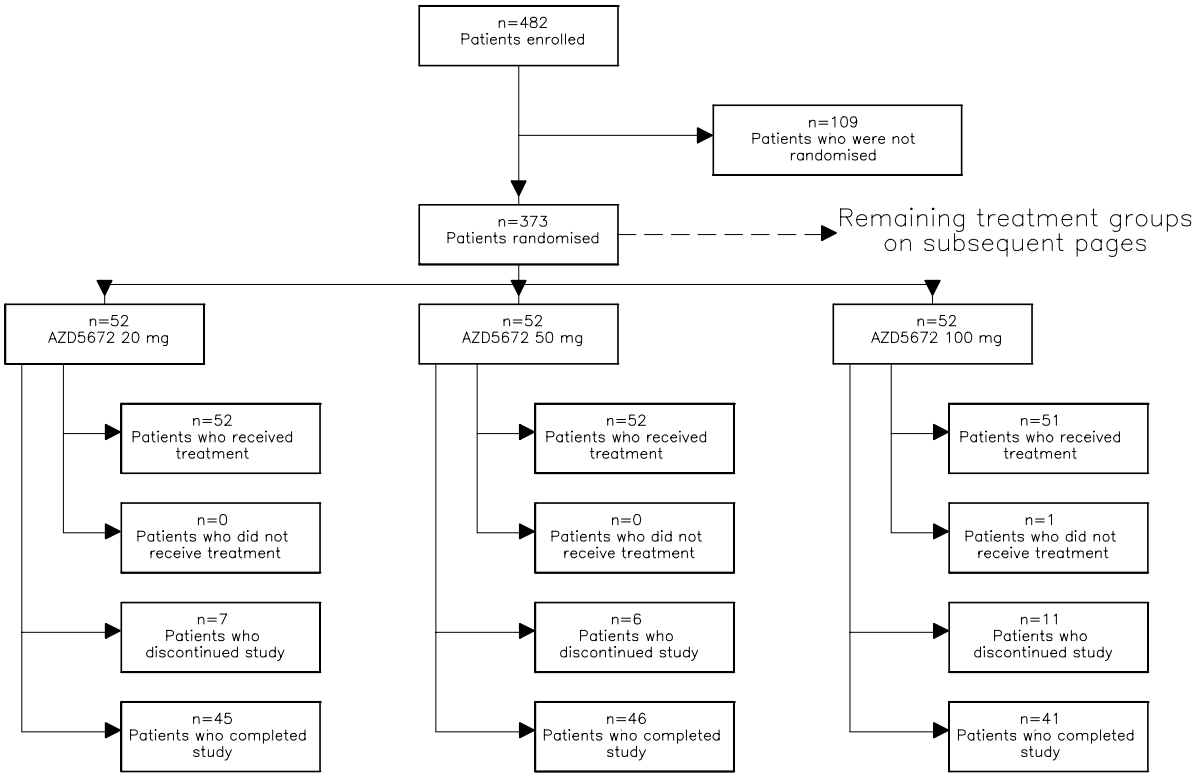
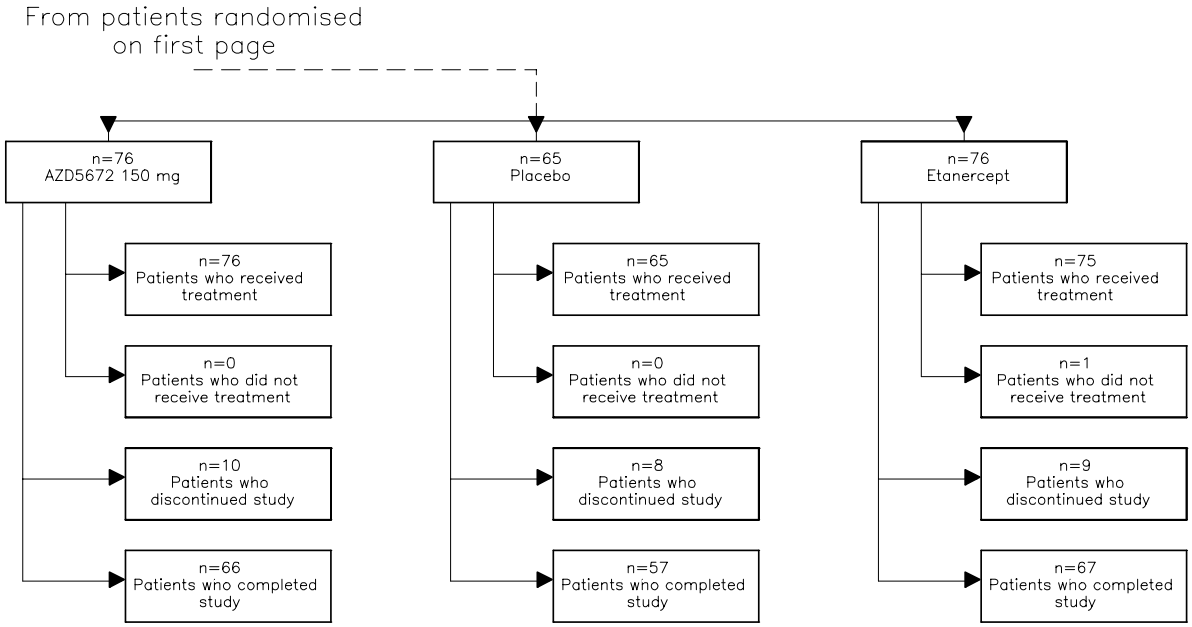


Figure S2 Flowchart of patient disposition (part 2)



Male or female patients (over 18 years of age) with active RA and on background treatment with MTX were included in the study; and the baseline and demographic characteristics of the patient population were representative of these patients. The majority of patients were female (322 patients, 87%) and white (347 patients, 94%). The mean age of the patients was 53 years and most patients had Class II RA functional capacity (254 patients, 68%). Mean DAS28 scores at baseline ranged from 6.3 in the AZD5672 150 mg group to 6.7 in the etanercept group. The mean DAS score for all patients was 6.5.

Summary of efficacy results

A comparison of the proportion of patients achieving ACR20, ACR50 and ACR70 at Week 12 is presented in Table S1 below.

Table S1 Comparison of proportion of patients achieving ACR20/50/70 at Week 12 between AZD5672 and placebo (LOCF) (full analysis set)

			Comparison to placebo			
Treatment group	**n**	**Number (%) of patients**	**Difference in proportion**	**95% CI**	**Raw p-value**	**Adjusted p-value**
ACR20						
AZD5672 20 mg	52	20 (38)	0.00	-0.18, 0.18	1.0000	1.0000
AZD5672 50 mg	52	15 (29)	-0.10	-0.27, 0.07	0.2759	0.5684
AZD5672 100 mg	51	17 (33)	-0.05	-0.23, 0.12	0.5684	0.5684
AZD5672 150 mg	76	34 (45)	0.06	-0.10, 0.23	0.4515	0.4515
Placebo	65	25 (38)				
Etanercept	75	58 (77)				
ACR50						
AZD5672 20 mg	52	10 (19)	0.10	-0.03, 0.23	0.1177	
AZD5672 50 mg	52	5 (10)	0.00	-0.10, 0.11	0.9435	
AZD5672 100 mg	51	6 (12)	0.03	-0.09, 0.14	0.6565	
AZD5672 150 mg	76	11 (14)	0.05	-0.05, 0.16	0.3406	
Placebo	65	6 (9)				
Etanercept	75	35 (47)				
ACR70						
AZD5672 20 mg	52	3 (6)	0.01	-0.07, 0.09	1.000	
AZD5672 50 mg	52	2 (4)	-0.01	-0.08, 0.07	1.0000	
AZD5672 100 mg	51	3 (6)	0.01	-0.07, 0.09	1.0000	
AZD5672 150 mg	76	2 (3)	-0.02	-0.08, 0.04	0.6617	
Placebo	65	3 (5)				
Etanercept	75	12 (16)				

CI = confidence interval, LOCF = last observation carried forward.

There was no statistically significant difference between any AZD5672 dose and placebo for the proportion of patients reaching ACR20, ACR50 or ACR70 at Week 12.

For all AZD5672 treatment groups, open-label etanercept and placebo groups, a general increase over time in the proportion of patients achieving ACR20, ACR50 and ACR70 was seen up to Week 12. There was no observable difference in the proportion of patients achieving ACR20/50/70 over time between any of the AZD5672 groups and placebo, and no dose relationship within the different AZD5672 treatment groups was seen.

The individual components of ACR, HAQ-DI, hybrid ACR, ACRn, DAS28, ESR and the PROs (individual components of the HAQ-DI, SF-36, RAQoL and PIQ) confirmed a lack of clinically or statistically significant effect of AZD5672 and that there was no dose relationship seen between the AZD5672 treatment groups.

Summary of pharmacogenetic results

The observed genotype frequencies at the *CCR5Δ32* locus was 88% *Δ32* non-carriers (+/+) (252 patients), 13% heterozygote (Δ32/+) (36 patients), and 0% homozygotes (Δ32/Δ32). There was no clear link between patients achieving ACR20 and *CCR5Δ32* genotype.

Summary of safety results

The proportion of patients experiencing AEs and DAEs was slightly imbalanced, with more patients experiencing AEs and DAEs in the AZD5672 groups. The proportion of patients experiencing AEs and DAEs was slightly imbalanced, with more patients experiencing AEs and DAEs in the AZD5672 groups. A total of 48% of patients receiving AZD5672 experienced AEs, compared to 34% receiving placebo and 40% receiving open-label etanercept. A total of 9% of patients experienced DAEs in the AZD5672 groups compared to 5% and 7% in the placebo and open-label etanercept groups. Two percent of patients experienced SAEs in the AZD5672 and placebo groups, with no patients experiencing these events in the open-label etanercept group; however, the proportion of patients with SAEs was small so any possible imbalance should be interpreted with caution.

The majority of patients receiving AZD5672 experienced AEs that were mild in severity. Two percent of all patients receiving AZD5672 experienced severe AEs; 1% in the AZD5672 50 mg group and 2% of patients in the 150 mg group, and 6% of patients in the AZD5672 100 mg group. The majority of all AEs were considered unrelated to study medication by the investigator.

A total of 23% in the AZD5672 groups experienced infection AEs. The proportion of patients experiencing infection AEs was similar in the open-label etanercept group (20% of patients), with the smallest proportion of patients experiencing these AEs in the placebo group (12% of patients). There was a slight indication of dose relationship, with 27% and 25% of patients experiencing infection AEs in the AZD5672 100 and 150 mg groups, respectively, versus 15% and 21% of patients in the AZD5672 20 and 50 mg groups, respectively. There was an indication of dose relationship for the severity of the infection AEs.

Serious infective events were reported by 2% of patients taking AZD5672 during the study; 2% of patients in the AZD5672 50 mg group, and 4% of patients in the AZD5672 150 mg group. In total, 6 serious infective events were reported by these patients; 3 of which were SAEs (gastroenteritis, sepsis and community-acquired pneumonia). The pneumonia and sepsis were reported in patients in the AZD5672 150 mg dose group, and the gastroenteritis was reported in a patient in the AZD5672 50 mg group. The serious infective events that were not also classified as SAEs were gastroenteritis and pneumonia, which were experienced by the same patients as the sepsis SAE, and 1 separate case of acute pyelonephritis.

Skin disorder AEs (those AEs appearing in the skin and subcutaneous disorders system organ class [SOC]) were experienced by 3% of patients in the AZD5672 groups. Three percent of patients each in the placebo group and the open-label etanercept group experienced skin disorder AEs. One patient had a skin disorder SAE: angiodema, reported in a patient in the AZD5672 100 mg group. This event was not considered related to study medication by the investigator and led to the discontinuation of the patient from the study. According to the investigator, the patient had consumed hot pepperoni pizza the previous evening, followed by fish pâté in the morning of the next day. The investigator confirmed that the patient experienced an allergic reaction due to food allergens. In addition, 4 other skin disorders were DAEs; all were rashes (preferred terms: rash, papular rash, allergic dermatitis and urticaria), all of which were reported in patients in the AZD5672 groups.

Musculoskeletal AEs (those AEs appearing in the musculoskeletal disorders SOC) were experienced by 8% of patients in the AZD5672 groups. A mixture of AEs were reported in this SOC, with each event occurring in <1% of patients receiving AZD5672 with the exception of worsening of RA, which occurred in 3% of patients receiving AZD5672 and back pain, which occurred in 2% of patients receiving AZD5672. One musculoskeletal SAE occurred: polymyositis during the follow-up period in a patient in the AZD5672 100 mg group. Two AEs of elevated blood creatine phosphokinase were reported in patients taking AZD5672 in the 50 and 150 mg groups; both AEs were asymptomatic.

There were no notable safety concerns for laboratory safety parameters, vital signs, ECG or physical examination results.