AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	AZD9056 hydrochloride
Study Code	D1520C00001
Edition Number	1
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A Randomised, Double-Blind (with Open Comparator Etanercept Limb), Placebo-Controlled, Phase IIb, Multicentre Study to Evaluate the Efficacy of 4 Doses of AZD9056 Administered for 6 Months on the Signs and Symptoms of Rheumatoid Arthritis in Patients with Active Disease Receiving Background Methotrexate or Sulphasalazine

Study dates:	First patient enrolled: 01 August 2007 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 59 centres recruited patients during the study. The number of centres that recruited patients per country was: Argentina (8), Australia (4), Belgium (1), Canada (2), Czech Republic (3), France (3), Mexico (7), Poland (11), Romania (8), Russia (1), Slovakia (3) and USA (8).

Publications

None at the time of writing this report.

Objectives

AZD9056 hydrochloride (AZD9056) was evaluated in this study and doses are expressed in mg AZD9056 free base.

The primary objective of the study was to evaluate the dose response relationship across 4 doses of AZD9056 (50, 100, 200 and 400 mg) on signs and symptoms of rheumatoid arthritis (RA), as measured by the proportion of patients meeting the American College of Rheumatology 20% improvement response criteria (ACR20) criteria at 6 months.

The secondary objectives of the study were:

- To evaluate the dose response relationship across 4 doses of AZD9056 on signs and symptoms and disease activity of RA, as measured by the proportion of patients meeting the ACR50 and ACR70 criteria, changes in the individual ACR components[1], the Disease Activity Score (based on the 28 joint count) (DAS28) remission[2] rate, and changes in diseases activity score based on the 28 joint count (DAS28) scores, erythrocyte sedimentation rate (ESR), individual dimensions of the Health Assessment Questionnaire - Disability Index (HAQ-DI) and the patient's assessment of fatigue (as measured on a visual analogue scale [VAS]) at 6 months
- To investigate AZD9056 population pharmacokinetics (PK) in plasma in patients with RA
- To evaluate the safety and tolerability of AZD9056 (body weight, vital signs, electrocardiogram [ECG], clinical chemistry, serum autoantibodies, haematology, urinalysis, physical examination [including fundoscopy] and adverse event [AE] reporting)

[1] The ACR components are C-reactive protein (CRP), 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 HAQ-DI.

[2] Referred to as DAS28 response rate in the CSP.

- To provide information on the effects of AZD9056 on the quality of life measured by 36-item Short Form- 36 (SF-36) and Rheumatoid Arthritis Quality of Life (RAQoL) Questionnaires

- To investigate radiological changes using standard X-ray (using the Sharp score as modified according to the method of van der Heijde).

The exploratory objectives of the study are separately explained/reported in the clinical study report.

Study design

This was a randomised, double-blind (with an open etanercept treatment group), placebo-controlled, parallel group multi-centre study to evaluate the efficacy of 4 doses of AZD9056 administered for 6 months. Male or female patients (≥18 years of age) with active RA who were to be receiving background treatment with either methotrexate or sulphasalazine (but not both together) were randomly assigned (without formal stratification) in equal numbers (approximately 60 patients per group) to receive 6 months treatment with 50, 100, 200 or 400 mg AZD9056 or matching placebo (oral tablet form, once daily in the morning) or subcutaneous etanercept (50 mg once a week).

Target population and sample size

Male or female patients with active RA and on background treatment with methotrexate or sulphasalazine were included in the study.

It was planned to randomise approximately 360 patients in total, 60 to the etanercept arm and 300 in total to the AZD9056 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 6 months between each dose of AZD9056 and placebo.

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

AZD9056 tablets: 50 and 200 mg size matched tablets for oral administration containing AZD9056 hydrochloride. Batches: 07-11314AZ, 07-010822AZ, 07-011955AZ, 07-011197AZ (50 mg tablets) and 07-011250AZ, 07-010821AZ, 07-011979AZ (200 mg tablets).

Placebo: identical size matched to AZD9056 tablets. Batch: 07-010603AZ.

Enbrel®: etanercept 50 mg pre-filled syringes (Wyeth Europa Ltd) and water for injections. Batches: 24884, 25767, 28209, 28228, 30831, 30832, 32260, 32984, G48523, P082150, P086297, P106817.

Duration of treatment

The duration of treatment for all groups in the study was 6 months.

Criteria for evaluation

Efficacy

The outcome variables were ACR scores (ACR20, 50 and 70, hybrid ACR and ACRn[3], 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 global assessment of disease activity and patient's assessment of physical function, as measured by HAQ-DI), ESR, DAS28, and X-ray (using the Sharp score as modified according to the method of van der Heijde) during 6 months of treatment. Subsequent to the protocol but prior to finalising the SAP, it was considered important to add the ACRn and ACR hybrid measures of RA response as supportive endpoints.

Patient reported outcomes (PROs)

Patient reported outcomes were the patient's assessment of pain and global disease activity as measured by the HAQ-DI, patient's assessment of fatigue, and health related quality of life using the SF-36 and RAQoL questionnaires.

Pharmacokinetic

The total concentration of AZD9056 in plasma was determined. Pharmacokinetics analyses were only performed on the plasma samples collected from a subgroup of patients receiving AZD9056. Plasma concentrations were provided but PK results will be reported separately.

Safety

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

Exploratory

The exploratory objectives of the study are separately explained/reported in the clinical study report.

Statistical methods

The primary efficacy variable of this trial was the proportion of treated patients who achieved ACR20 at Week 24, which was compared by the 2-sided chi-square test with $\alpha=0.05$, as a confirmatory analysis. A hierarchical testing strategy was applied for the multiple testing of different doses versus placebo. Initially, the highest dose was compared with placebo. If a statistical difference was obtained, then the next lower dose was to be compared with placebo. This process was to be repeated until a statistical difference was not obtained or all doses had been compared to placebo. The overall type I error for this hierarchical testing strategy maintained the nominal level of $\alpha=0.05$.

[3] Hybrid ACR and ACRn were added after the protocol was finalised but prior to unblinding as secondary efficacy variables.

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 (being the smallest percentage improvement in either tender joint count or swollen joint count or the median of the other ACR components) 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 analysed as percentage change from baseline.

The improvement from baseline in DAS28 score was similarly analysed using an ANCOVA model as described above. DAS28 was also analysed based on the European League Against Rheumatism (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 (including ESR, dimensions of the HAQ, SF-36 and RAQoL and modified Total Sharp Score) were analysed using ANCOVA models or non-parametric methods as appropriate.

Missing ACR and DAS components were imputed using a last observation carried forward (LOCF) approach at each visit, except for patients withdrawn due to AE. Such patients were considered non-responders for subsequent visits. For X-ray, missing change scores were imputed using linear extrapolation in the case of termination prior to week 24, otherwise the median percentage change from baseline in the placebo patients.

Patient population

Having signed the informed consent form, 658 patients were enrolled into the study; 385 of whom were subsequently randomised to study treatment (64 patients assigned to etanercept and each of the AZD9056 dose levels and 65 patients to placebo). One patient randomised to 50 mg AZD9056 and one patient randomised to 200 mg AZD9056 groups were not treated. Between 12 and 15 patients prematurely discontinued study participation in the in each of the AZD9056 treatment groups (compared to 12 patients on placebo and 2 patients on etanercept).

The demographic and baseline characteristics were consistent with the expected study population. In each treatment group, compliance with study medication was high. The concomitant medications reported were as expected for the study population.

Overall, there were no remarkable differences between the treatment groups and findings were not considered to have affected the interpretation of the results.

Summary of efficacy results

Each of the AZD9056 treatment groups was similar to the placebo group in terms of the ACR20 response rates at week 24. The observed effect in the open-label etanercept arm was clearly distinguishable from placebo and consistent with expectations. A similar pattern was seen for the ACR50 and ACR70.

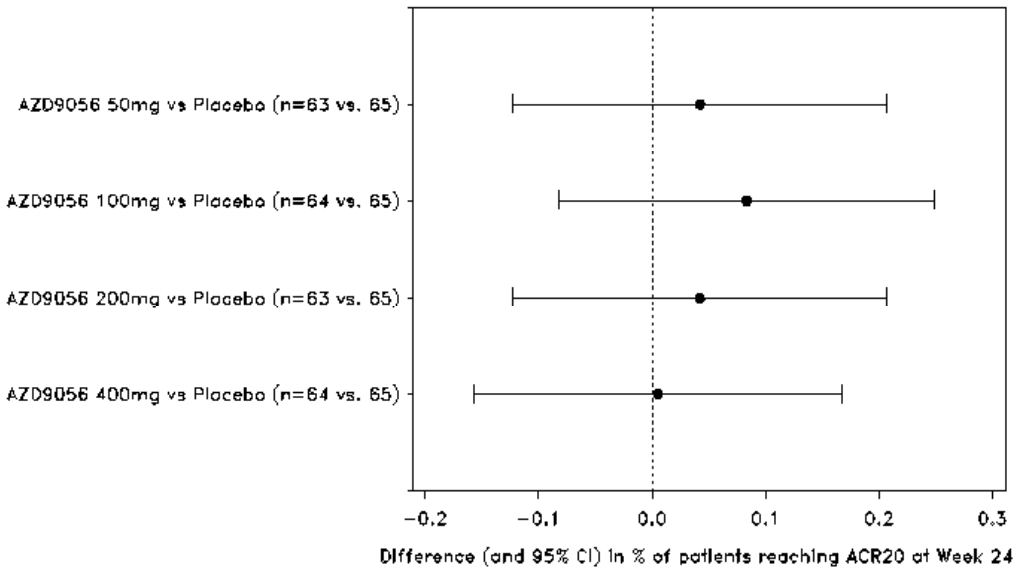
Table S1 **Comparison of proportion of patients achieving ACR20/50/70 at Week 24 between AZD9056 and placebo (LOCF) (full analysis set)**

Treatment group	n	Number (%) of patients		
		ACR20	ACR50	ACR70
AZD9056 50 mg	63	23 (36.5)	13 (20.6)	6 (9.5)
AZD9056 100 mg	64	26 (40.6)	8 (12.5)	7 (10.9)
AZD9056 200 mg	63	23 (36.5)	9 (14.3)	5 (7.9)
AZD9056 400 mg	64	21 (32.8)	13 (20.3)	5 (7.8)
Placebo	65	21 (32.3)	11 (16.9)	3 (4.6)
Etanercept	64	42 (65.6)	30 (46.9)	15 (23.4)

ACR 20, 50, 70 American College of Rheumatology response criteria (20, 50, 70% improvement); LOCF last observation carried forward.

The estimated difference (and 95% confidence interval [CI]) in the proportion of patients reaching ACR20 at Week 24 between AZD9056 and placebo is shown in the figure below. The 95% CIs crossed the no effect line for all comparisons of AZD9056 doses versus placebo, hence no significant difference between the effect of AZD9056 and placebo on achieving ARC20 was seen.

Figure S1 **Estimated difference (and 95% CI) in the proportion of patients reaching ACR20 at Week 24 between AZD9056 and placebo (full analysis set)**



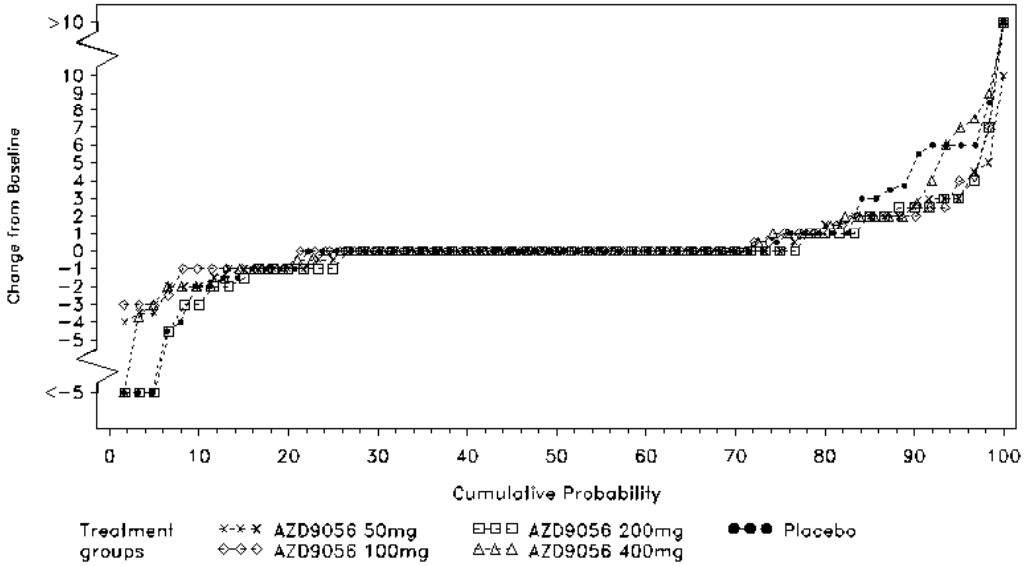
ACR American College of Rheumatology; CI confidence interval; LOCF last observation carried forward.

Findings for the various subgroup and sensitivity analyses performed supported the conclusions of the primary analysis.

The AZD9056 treatment groups were similar to the placebo group in terms of the secondary efficacy variables whereas the observed effect in the open-label etanercept arm was clearly distinguishable from placebo and consistent with expectations.

Some separation from placebo was observed for the AZD9056 treatment groups in the total Sharp score (see below), which was primarily evident in the erosion score.

Figure S2 Cumulative probability for the change in the modified total Sharp score (full analysis set)



Summary of safety results

The number of patients experiencing any AE was similar across all groups. No patients experienced an AE with the outcome of death during the study. Seven patients experienced SAEs during the study, with the number of patients experiencing SAEs being similar across groups. AEs leading to discontinuation of IP (DAEs) were reported at a similar frequency across the AZD9056 treatment groups (ranging from 9.4% [100 mg] to 14.1% patients [400 mg]) and the placebo group (9.2%), while DAEs were rather less frequent in the open-label etanercept group (3.1%). No patients experienced an event that was considered an "other significant AE".

Gastrointestinal AEs were the most commonly reported AEs, were dose-related, and mainly mild to moderate in nature. Although infections were commonly reported, the frequency was similar to placebo, and no serious infective events were observed. Hepatic AEs and liver abnormalities were reported infrequently and with a similar frequency to placebo.

There were no notable safety concerns arising from the clinical laboratory, ECG, physical examination or fundoscopy data.