AstraZeneca

Abbreviated Clinical Study Report Synopsis

Drug Substance	AZD4017
Study Code	D4250C00001
Edition Number	1
Date	
EudraCT Number	2010-020932-20

A Double-Masked, Placebo-Controlled, Randomized, Parallel Group Phase IIa Study to Assess the Tolerability, Safety, and Efficacy of AZD4017 for Raised Intra-Ocular Pressure

Study dates: First patient enrolled: 13 December 2010
Last patient last visit: 06 November 2012

Phase of development: Therapeutic exploratory (IIa)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre(s)

This study was conducted at 19 centers in the United States (US), United Kingdom (UK) and Sweden

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the efficacy of systemically administered AZD4017, compared with placebo, over a 28-day period in patients with raised intra-ocular pressure (IOP) not on anti-glaucoma medication or patients with raised IOP or primary open angle glaucoma (POAG) on anti-glaucoma monotherapy that has been stable in dose for at least 30 days prior to screening.	Percentage change in IOP compared with baseline after 28 days of treatment.	Efficacy
Key Secondary	**Key Secondary**	
To evaluate the efficacy of systemically administered AZD4017, compared with placebo, over a 28-day period in patients with raised IOP not on anti-glaucoma medication or patients with raised IOP or POAG on anti-glaucoma monotherapy that has been stable in dose for at least 30 days prior to screening.	The main secondary variable in this study is the proportion of patients experiencing a clinically relevant change in IOP at Visit 7.	Efficacy
Safety	**Safety**	
To compare the safety and tolerability of systemically administered AZD4017 with placebo	Eye exams IOP measurements Adverse events (AEs) Discontinuations due to AEs (DAEs) Serious AEs (SAEs) Clinical laboratory test results (ie, haematology and clinical chemistry including hepatic function tests) Vital signs Eye exams	Safety

Objectives	Outcome variables	Type
To assess the effect of AZD4017 on the hypothalamic-pituitary-adrenal (HPA) axis	Adreno-corticotropic hormone (ACTH) Dehydroepiandrosterone-S (DHEA-S) Testosterone Cortisol	Safety
Exploratory	**Exploratory**	
To investigate the pharmacokinetics (PK) of AZD4017 in this patient population.	AZD4017 plasma concentration levels	PK[a]
To collect and store serum/plasma samples for future exploratory research aimed at exploring biomarkers/profiles which could be used to predict response to treatment with AZD4017 or provide new insights into raised IOP and medical conditions for which this mechanism of action is relevant.	N/A	Bio-markers[a]

[a] Reported separately from this abbreviated clinical study report (aCSR).

Study design

This was a double-masked, placebo-controlled, randomized, parallel group multi-center study to assess the efficacy, safety, and tolerability of AZD4017 administered for 28 days in patients with raised IOP not on anti-glaucoma medication or patients with raised IOP or POAG on anti-glaucoma monotherapy that had been stable in dose for at least 30 days prior to screening.

Patients were randomized (1:1) to receive either AZD4017 200 mg once daily (OD) or placebo OD (United Kingdom [UK] and Sweden) or AZD4017 400 mg twice daily (BID) or placebo BID (United States [US]). Upon completion of AstraZeneca's review of the final datasets, due to the study not meeting its primary endpoint, a decision was made to present the results in an aCSR.

Target subject population and sample size

Per the most recent version of the protocol (UK and Sweden: Revision 5, 30 May 2012; US: Revision 2, 30 May 2012), approximately 60 patients were planned to be randomized to obtain at least 40 evaluable patients (ie, 10 per treatment group). A total of 117 patients were screened in the study and of these, 50 were randomized into the double-blind treatment period.

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

Oral doses of AZD4017 200 mg OD, AZD4017 400 mg BID, or matching placebo. Individual batch numbers and further information are available upon request.

Duration of treatment

The study duration was up to 11 weeks, consisting of an initial screening period lasting up to 4 weeks, a 4-week treatment period, and a follow-up visit up to 3 weeks after the last dose of study drug.

Statistical methods

Summary statistics for parametric data included the mean, standard deviation, median, and range. Summary statistics for log transformed data included the geometric mean, standard deviation, and the coefficient of variation. The geometric mean was calculated as the exponential of the arithmetic mean calculated from data on a log scale. Coefficient of variance (CV) was calculated as 100 x sqrt [exp (s^2)-1], where *s* is the standard deviation of the data on a log scale. Summary statistics for categorical data included the frequency and proportion.

Measures of location (mean, median, minimum and maximum) were reported up to the same degree of precision as the raw data. Measures of spread (standard deviation, standard error) were reported to one further degree of precision.

Listing output was sorted by strata, patient number (Ecode), and treatment.

Treatment comparisons were made between each active treatment group vs corresponding placebo group for all data analyzed.

The primary variable for the determination of efficacy was the percentage change in IOP compared with baseline after 4 weeks treatment. The percentage change assessed pre-dose at Visits 4, 5, and 7 was analyzed with a mixed-effect model of repeated measures (MMRM) with fixed effect terms for treatment, visit, treatment by visit interaction, strata and baseline IOP, and a random effect term of patient within treatment.

The analysis of the secondary efficacy variable of the number of patients experiencing a clinically relevant change in IOP at Visit 7 was performed using Fisher's Exact test. The effect of treatment was estimated by the calculated odds ratio together with its 95% confidence interval.

Subject population

A total of 117 patients were screened in the study and of these, 50 were randomized into the double-blind treatment period.

Of the 50 randomized patients, 50 (100%) received treatment, and 44 (88.0%) completed both treatment and the study. For patients who were not randomized, the most common reason for non-randomization was eligibility criteria not fulfilled in 66 (56.4%) of all screened patients.

Of the 50 randomized patients, 6 (12.0%) withdrew from the study. There were no notable differences in study completion rates and reasons for withdrawal from the study across

treatment groups. The most common reasons for study withdrawal were eligibility criteria not fulfilled and condition under investigation worsened, 2 patients (4.0%) each.

Summary of efficacy results

The results of this study did not indicate that AZD4017 200 mg OD or AZD4017 400 mg BID were superior to placebo in reducing IOP after 4 weeks of treatment.

The differences presented in the MMRM analysis (Table 6) were AZD4017 200 mg OD – placebo OD: -1.3 (95% CI -15.2, 12.6), and AZD4017 400 mg BID – placebo BID: -2.9 (95% CI -10.1, 4.3), neither of which was statistically significant (p=0.822 and p=0.413, respectively).

Summary of pharmacokinetic results

Full details of the bioanalytical part of the study, including the analytical methods used, will be provided in separate bioanalytical reports.

Summary of safety results

AZD4017 at dose levels of 200 mg OD and 400 mg BID was well tolerated over 4 weeks of treatment for raised IOP:

- The number of patients experiencing AEs was lower in the AZD4017 200 mg OD group (3 patients, 42.9%) than in the placebo OD group (5 patients, 83.3%). The number of patients experiencing AEs was higher in the AZD4017 400 mg BID group (7 patients, 36.8%) than in the placebo BID group (5 patients, 27.8%). The total number of AEs experienced during the study was 8 in the AZD4017 200 mg OD group, 11 in the AZD4017 400 mg BID group, 6 in the placebo OD group, and 9 in the placebo BID group. There is no evidence of a dose dependent relationship in the frequency of AEs.
- No deaths occurred and no SAEs were reported during this study.
- Two patients discontinued due to AEs, both of whom were receiving placebo.
- There were no clinically meaningful differences between AZD4017 and placebo at any dose with respect to clinical laboratory assessments, urinalysis, vital signs, ECGs, or physical examinations.