AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3355
Study Code	D9120C00030
Edition Number	1
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A Phase I, Single Centre, Single-blind, Randomised, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of oral AZD3355 after Administration of Single Ascending Doses, and Multiple Repeated Doses in Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 4 September 2008
Last healthy volunteer completed: 22 December 2008

Phase of development: Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives

Primary objective

The primary objective of the study is to investigate the safety and tolerability following twice daily repeated oral doses of AZD3355 capsules in healthy male subjects by assessment of adverse events (AEs), electrocardiogram (ECG), blood pressure (BP), pulse rate, urine weight and osmolality, body temperature, blood and urine laboratory variables.

Secondary objectives

The secondary objectives of the study are:

1. to investigate the safety and tolerability following single ascending oral doses of AZD3355 capsules in healthy male subjects by assessment of adverse events (AEs), electrocardiogram (ECG), blood pressure (BP), pulse rate, urine weight and osmolality, body temperature, blood and urine laboratory variables, and to estimate the maximum tolerated dose (MTD)

2. to investigate the pharmacokinetics following twice daily repeated oral doses of AZD3355 capsules in healthy male subjects by assessment of plasma concentration of AZD3355 and AUC, AUC_t, AUC_{0-12h}, C_{max}, $C_{ss,max}$, C_{trough}, CL_{ss}/F, t_{max}, $t_{½}$ and R_{ac}.

3. to investigate the pharmacokinetics, including dose proportionality, following single ascending oral doses of AZD3355 capsules in healthy male subjects by assessment of plasma concentration of AZD3355 and AUC, AUC_t, AUC_{0-12h}, C_{max}, CL/F, t_{max} and $t_{½}$.

Study design

This randomised, single-blind, placebo-controlled, single centre phase I study evaluated the safety, tolerability and pharmacokinetics of AZD3355 after single ascending doses and multiple repeated doses. The study consisted of two separate parts, an initial single ascending dose part (SAD, Part A) and a subsequent multiple repeated dose part (MRD, Part B). The starting dose of Part A was 600 mg once daily. Before the start of repeated dosing, single dose pharmacokinetics were evaluated. The starting dose in Part B was 400 mg given bid (twice daily).

Target healthy volunteer population and sample size

The study was conducted in healthy male volunteers aged 18 to 45 years. The inclusion and exclusion criteria were defined such that healthy volunteers who were known to be free from any significant illness were to be selected. The planned number of healthy male volunteers randomised to the SAD part was approximately 36, and to the MRD part 18 to 27 depending on the number of dose levels tested in SAD. Nine (9) healthy volunteers were to be enrolled in each dose level, 6 on AZD3355 and 3 on placebo.

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

Oral doses of AZD3355 were given as modified release 200 mg capsules (MR 1h), batch number H 2060-01-01-01. Corresponding oral capsules of placebo were used in this study, batch number H 2061-01-01-01.

Duration of treatment

Part A (SAD)

Each subject received a single dose of AZD3355 or placebo.

Part B (MRD)

Each subject received a single morning dose of AZD3355 or placebo on Day 1. Day 2 was washout, and repeated twice daily dosing commenced on Day 3 with AZD3355 or placebo. On the last study day (Day 7) only the morning dose was administered.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

AUC, AUC_t, $AUC_{0\text{-}12h}$, C_{max}, CL/F, t_{max} and $t_{½}$.

Criteria for evaluation - safety (main variables)

AEs, ECG, BP, pulse rate and laboratory variables.

Statistical methods

The safety analysis set included all healthy volunteers who received study treatment and had data collected post-dose. The data were summarized using descriptive statistics within the dose of AZD3355 and study day. The geometric means of plasma concentration were plotted versus time profiles. In the SAD part, geometric means were calculated for AUC, AUC_t, $AUC_{0\text{-}12h}$, C_{max}, $t_{1/2}$ and CL/F. In the MRD part, geometric means were calculated for AUC, AUC_t, $AUC_{0\text{-}12h}$, C_{max}, $t_{1/2}$ and CL/F on day 1 and for AUC_t, $C_{ss,max}$, C_{trough}, Cl_{ss}/F and R_{ac}. Potential time dependency in pharmacokinetics was investigated by the geometric mean (95% CI) ratio of $AUC_{t\ day\ 7}/AUC_{\ day\ 1}$. $C_{ss,max}$ on day 7 was compared to C_{max} on day 1 in the same way. Dose proportionality was analysed by using a linear mixed effect model.

Dose proportionality was analysed using a linear mixed effect model with the logarithm of AUC (and C_{max}) as the dependent variable and the logarithm of the dose as independent factor

and subject as random factor. The intercept α and the slope β (in AUC (C_{max}) = α * dose$^{\beta}$) together with confidence intervals (two-sided 95%) were estimated for AUC and C_{max}. To illustrate the effect of a doubling of the dose a confidence interval for 2^{β} is presented.

The sample size was primarily based on experience from previous similar studies with other compounds, and it was determined without formal statistical considerations or formal power calculation.

Subject population

Part A (SAD)

Twenty-seven (27) healthy volunteers were randomised to treatment, whereof 18 were exposed to AZD3355 and 9 to placebo. All healthy volunteers randomised to treatment completed the study. No healthy volunteers discontinued from the SAD part due to any AEs.

Part B (MRD)

Eighteen (18) healthy volunteers were randomised to treatment, whereof 12 were exposed to AZD3355 and 6 to placebo. One healthy volunteer exposed to placebo treatment discontinued from the MRD part due to an AE.

Summary of pharmacokinetic results

The predefined maximum exposure limit for AUC was reached, whereas C_{max} values approached the predefined limit of exposure at a single dose of 1800 mg AZD3355, why further dose escalation was not performed. After 5-day repeated bid doses of 800 mg AZD3355, both $AUC_{0\text{-}12\,h}$ and C_{max} values were below the predefined limit of exposure. The results of this study did not indicate a clear deviation from dose proportionality of AUC or C_{max}. Steady state condition for plasma concentrations of AZD3355 was reached within 3 days bid dosing and there were no influence of time on the pharmacokinetics of AZD3355.

Summary of safety results

No new safety or tolerability concerns were identified in this study in healthy male volunteers after single (600 mg to 1800 mg) and repeated (400 mg and 800 mg) doses of AZD3355. The most commonly collected AE was paraesthesiae. Other commonly reported AEs were feeling hot and postural dizziness in conjunction with orthostatic tests. AEs were more frequently reported by AZD3355 treated than placebo treated healthy volunteers, especially for postural dizziness (orthostatic tests) that was more frequent in AZD3355 single dose groups 1200 mg and 1800 mg, than in placebo groups. Apart from an isolated, slight elevation of ASAT and ALAT in some healthy volunteers during repeated dosing of AZD3355, no clinically relevant treatment-related changes or trends were detected in laboratory variables. A slight orthostatic decrease in SBP was observed in all AZD3355 treated groups compared to placebo. Also, a supine increase in heart rate (decrease in RR interval) and a corresponding transient QTcF prolongation was observed. Overall, the changes in vital signs and ECG were considered not to raise any safety concerns.