AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3355
Study Code	D9120C00031
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A double blind, randomized, cross-over-design, phase 1 pharmacodynamic study to investigate the effect of different formulations of AZD3355 for the development of paraesthesiae after dosing in healthy subjects

Study dates: First healthy volunteer enrolled: 07 April 2008
Last healthy volunteer completed: 25 June 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

The primary objective of the study was to compare the development of paraesthesiae after administration of different formulations of AZD3355 with different release rates.

The secondary objectives of the study were:

1. To assess the pharmacokinetic (PK) parameters of AZD3355 after administration as immediate release (IR) formulation and as two different (modified release) MR formulations
2. To assess the safety and tolerability of AZD3355

Study design

This was a double blind, randomized, cross-over study to evaluate the effect of different formulations of AZD3355 for the development of paraesthesiae. AZD3355 is a novel reflux inhibitor specifically being developed as add-on treatment to a proton pump inhibitor for patients with gastroesophageal reflux disease. Each healthy volunteer (hereafter referred to as subjects) received single doses of 4 of the 5 possible treatments in a four-way cross-over design with wash-out periods of at least 5 days between dose administrations. The subjects were divided into 2 groups, where Group A (24 randomized subjects) had PK samples drawn for 36h post-dose and Group B (24 randomized subjects) had PK samples drawn for 4h post-dose.

Target healthy volunteer population and sample size

Healthy male or female subjects aged 18-45 years.

The study was planned to randomise 48 subjects in order to have at least 40 evaluable subjects.

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

Investigational product	Dosage form and strength	Mode of administration	Batch number
AZD3355, IR 65 mg	Capsule, 65 mg	Oral administration	H 1838-03-01-01
AZD3355, IR 150 mg	Capsule, 150 mg	Oral administration	H 2020-01-01-01
AZD3355, MR 1h 65 mg	Capsule, 65 mg	Oral administration	H 2021-01-01-01
AZD3355, MR 1h 150 mg	Capsule, 150 mg	Oral administration	H 2015-02-01-01
AZD3355, MR 2h 150 mg	Capsule, 150 mg	Oral administration	H 2015-03-01-04

Duration of treatment

A 4-way cross-over design was used. Each subject received 4 single doses with a wash-out period of at least 5 days between each dose. The subjects stayed at the investigational site for approximately 26h (Group A) and 6h (Group B) post-dose at each study session.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary: Occurrence of paraesthesiae, as response to active specific questioning, classified with regard to time of onset, duration, character, location, intensity and level of discomfort 0-4h post-dose.

Secondary: AUC, AUC_t, C_{max}, t_{max}, $t_{1/2}$, t_{lag}, and CL/F for Group A and C_{max}, t_{max} and t_{lag} for Group B

Criteria for evaluation - safety (main variables)

Adverse events (AEs), blood pressure (BP), orthostatic test, pulse, electrocardiography, physical examination and laboratory safety variables

Statistical methods

At the 150 mg dose level, all three different formulations were compared. The effect of dose adjustment was studied for the IR and MR 1h formulations. In addition, IR and MR 1h was compared at the 65 mg dose level. Pair wise comparisons between different formulations and dose levels were made by nonparametric analysis using the Prescott hypothesis test of treatment effects for binary (paraesthesia/no paraesthesia) crossover data using a 5% significance level.

Estimated ratios between the different formulations (MR 1h 65 mg/IR 65 mg, MR 1h 150 mg/IR 150 mg, MR 2h 150 mg/IR 150 mg, MR 1h 150 mg/MR 2h 150 mg) for AUC, AUC_t and C_{max} with 90% confidence interval (CI) were calculated.

The ratios were estimated in the following way. The variables AUC, AUC_t and C_{max} of AZD3355 for different formulations and dose levels were analysed in an analysis-of-variance (ANOVA), in a mixed linear model with factors for period, sequence and treatment as fixed

effects and subject-within sequence as a random effect. Estimates including two-sided 95% CIs of treatment means and two-sided 90% CIs of mean treatment differences, respectively, were first constructed in the logarithmic scale using the residual standard deviation from ANOVA and percentiles from Student's t-distribution. The results were anti-logarithmized and presented as estimated geometric means for each formulation and treatment and estimated ratios of true geometric means.

Due to the explorative nature of this study, no correction for multiplicity was used.

Subject population

A total of 48 healthy subjects, 30 male and 18 females were randomized, received IP and 47 subjects completed the study according to protocol. One subject was excluded from the study due to severe non-compliance to the protocol (use of drugs of abuse discovered at the random drug test). All 48 randomized subjects were included in the safety analysis set, 47 subjects were included in the PD analysis set and 47 subjects in the PK analysis set.

The treatment groups were balanced in terms of demography and baseline characteristics.

Summary of pharmacokinetic results

The bioavailabilities of MR 1h 150 mg and IR 150 mg were nearly identical based on AZD3355 AUC values. Estimated geometric mean AUCs for MR 1h 150 mg and IR 150 mg were 32.59 µmol*h/L and 32.04 µmol*h/L with ratio 1.017 and 90% CI (0.950-1.089). The estimated geometric mean C_{max} value for MR 1h 150 mg was 3.22 µmol/L, which was lower than 3.73 µmol/L for the IR 150 mg form. The MR 1h 150 mg vs. IR 150 mg ratio was 0.865 with the 90% CI (0.813-0.920) for the ratio separated from 1.

The estimated geometric mean AUC for the MR 2h 150mg formulation was 29.28 µmol*h/L. Comparison with the IR 150 mg formulation revealed an AUC ratio of 0.914 with the 90% CI (0.855-0.977) for the ratio separated from 1. Estimated geometric mean C_{max} was 2.60 µmol/L for the MR 2h 150 mg form, with a MR 2h 150 mg vs. IR 150 mg formulation ratio of 0.697 and with the 90% CI (0.655-0.741) for the ratio separated from 1.

In accordance with the lower C_{max} for the MR 1h 150 mg and 65 mg formulations and the MR 2h 150 mg formulation, the t_{max} values were prolonged for these formulations compared to the IR formulations.

Median t_{max} was 1.53h (range 1.00-3.00h) for the IR 150 mg formulation and 1.50h (range 1.00-2.50h) for the IR 65 mg formulation. For both MR 1h formulations the median t_{max} was 2.00h (range 1.50-3.00h). Median t_{max} for the MR 2h 150 mg formulation was 2.50h (2.00-4.02h) which was 0.5h later than the MR 1h formulations and 1h later than the IR formulations.

The median lag-time for the IR and MR 1h formulations was 0.25h with slightly different ranges: (0.00-0.75 h) for IR 65 mg; (0.00-0.52h) for IR 150 mg; (0.25-0.75h) for MR 1h 65 mg and (0.00-0.75h) for MR 1h 150 mg. The median lag-time for the MR 2h 150 mg

formulation was 0.5h (0.25-0.75h), which was 0.25h later than the IR and MR 1h formulations.

Geometric mean apparent terminal half-life was between 8.97h (6.73-11.05h) for MR 1h 65 mg and 9.44h (7.53-11.43h) for IR 65 mg. There was no systematic dependency of the half-lives on the release type.

Geometric mean total clearance (CL/F) was 32.35-33.13 L/h for the IR and MR 1h formulations and 36.18 L/h for the MR 2h 150 mg formulation.

Summary of pharmacodynamic results

In total 142 episodes of paraesthesiae were reported by 37 subjects 0-4h post-dose after active questioning. Five (5) episodes of paraesthesiae were reported (as AEs) by 3 subjects more than 4h post-dose (7.5->24 h post-dose).

The maximum reported intensity was none, minimal, mild or moderate (with a scale of none, minimal, mild, moderate, rather severe, severe and very severe) for all but two episodes of paraesthesiae. Two subjects reported rather severe paraesthesiae after administration of MR 1h 150 mg. The most frequently reported intensity was minimal or mild for all formulations, except for the IR 150 mg formulation were moderate intensity was most frequently reported.

The maximum level of discomfort was none, minimal, mild or moderate for all but one episode of paraesthesiae. One (1) subject reported the level of discomfort as rather severe after administration of MR 1h 65 mg. The most frequently reported level of discomfort was minimal for all formulations, except for the IR 65 mg formulation were mild level of discomfort was most frequently reported.

The mean minimum time to onset was approximately 30 min (range 0-88 min) for the IR 65 mg, IR 150 mg, MR 1h 65 mg, and MR 1h 150 mg formulations. The MR 2h 150 mg formulation had 69 min mean minimum time to onset (range 11-230 min). The mean maximum duration of the paraesthesiae was approximately 50-100 min (range 3-360 min) for all formulations. For paraesthesiae starting within 4h post-dose, the total time (including also after 4h) was included in the calculation of the duration.

There was no statistically significant difference in occurrence of paraesthesiae during 0-4 h post-dose between the different formulations and doses of AZD3355.

Summary of pharmacokinetic/pharmacodynamic relationships

The plasma concentration and paraesthesiae data in this study were used in further development of a previously developed PK/PD model for the relationship between plasma concentration and paraesthesiae. These data are not included in this CSR.

Summary of safety results

There were no SAEs and no discontinuations due to AEs in the study. All AEs but 2 were mild or moderate in intensity. The most common AEs were headache, dizziness and pollakiuria. Paraesthesiae with onset within 4h post-dose were not recorded as AEs.

There were no clinically relevant effects observed on laboratory safety variables and no clinically relevant effects observed on vital signs or ECG.