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| Drug product:<br>Drug substance(s):<br>Document No.:<br>Edition No.:<br>Study code:<br>Date: | <br>AZD3355<br><br>1<br>D9120C00011<br>24 October 2007 | **SYNOPSIS** | |

# A randomized, double-blind, placebo controlled, multi-centre, phase IIA study to assess the effect on GERD symptoms, pharmacokinetics, safety and tolerability of four weeks treatment with AZD3355 65 mg bid as add-on treatment to a PPI in patients with an incomplete response to PPI treatment

**Publications**

Not applicable.

**Study dates**

**First patient enrolled** 15 Nov 2006

**Last patient completed** 1 Jun 2007

**Phase of development**

Therapeutic exploratory (IIA)

## Objectives

This was the first study in patients to explore the effect on Gastroesophageal Reflux Disease (GERD) symptoms of a new drug specifically developed to reduce the number of transient lower esophageal sphincter relaxations (TLESRs), ie, a new mechanism of action. The objective of this study was to collect data for the development of AZD3355, and also for the future development of other Reflux Inhibitors.

Primary objective:

- To estimate the effect of AZD3355 65 mg twice daily (bid) as add-on treatment to a PPI on GERD symptoms in patients with an incomplete response to PPI treatment with respect to improvement of each of the patient reported symptoms:
  - A burning feeling behind the breastbone (heartburn)
  - Unpleasant movement of material upwards from the stomach (regurgitation)

Secondary objectives:

- To explore the effect of AZD3355 65 mg bid as add-on treatment to a PPI in patients with GERD symptoms and an incomplete response to PPI treatment with respect to additional patient reported symptoms, ie, other gastrointestinal symptoms, cough and sleep disturbance
- To estimate the effect of AZD3355 65 mg bid as add-on treatment to a PPI in patients with GERD symptoms and an incomplete response to PPI treatment with respect to consumption of antacids
- To assess the pharmacokinetics of AZD3355 65 mg bid as add-on treatment to a PPI in patients with GERD symptoms and an incomplete response to PPI treatment
- To assess the safety and tolerability during 4 weeks treatment with AZD3355 65 mg bid as add-on treatment to a PPI in patients with GERD symptoms and an incomplete response to PPI treatment by evaluation of adverse events, laboratory variables, blood pressure (BP), pulse, electrocardiogram (ECG) and physical examination
- To explore the incidence of and the patients' perception of paraesthesiae and conditions with impaired wakefulness/alertness during 4 weeks treatment with AZD3355 65 mg bid as add-on treatment to a PPI
- To explore the relationship between patient reported symptoms and perceived overall treatment effect, symptom control and treatment satisfaction, respectively

## Study design

This was a double-blind, placebo controlled, randomised, multi-centre phase IIA study designed to explore the efficacy and safety of 4 weeks of treatment with oral doses of AZD3355 65 mg bid as an add-on treatment to a proton pump inhibitor (PPI) in patients who experience GERD symptoms despite PPI treatment.

## Target patient population and sample size

This study targeted male and female patients (not of child-bearing potential) aged 18-70 years who had long-term GERD symptoms (≥6 months) and an incomplete (partial or no) response to PPI treatment. The patients needed to have been on continuous PPI treatment with approved doses during the last 6 weeks prior to the enrolment visit. In the screening Reflux Disease Questionnaire (RDQ) patients needed to have reported a burning feeling behind the breastbone with a frequency of ≤3 days over the past 7 days and with at least mild intensity and/or unpleasant movement of material upwards from the stomach with a frequency of ≤3 days over the past 7 days and with at least mild intensity.

The assumed proportion of responders (primary variable) was 20% and 35% for placebo and AZD3355 respectively. With a sample size of 115 randomised patients per treatment group, a one-sided Chi-square test has 90% statistical power to detect a difference in proportions between the treatment groups at 10% significance level.

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

AZD3355 65 mg (drug in capsule) orally bid or placebo. Batch numbers were H1838-01-01-01, H1838-01-01-03, H1838-01-01-04, H1838-01-01-05 and H1838-01-01-06 for AZD3355 and H1839-01-01-01 for placebo.

## Duration of treatment

4 weeks.

## Criteria for evaluation (main variables)

### Efficacy

- Primary variable: seven consecutive days with at most one day with not more than mild intensity of the two Reflux Disease Questionnaire (RDQ) items: a burning feeling behind the breastbone and unpleasant movement of material upwards from the stomach (primary RDQ items)

- Secondary variables measured by the RDQ, the Gastrointestinal Symptom Rating Scale (GSRS) and Cough and sleep questions.

- Antacid use.

### Additional Patient Reported Outcomes

- Overall Treatment Evaluation (OTE), symptom control and treatment satisfaction questions.

### Pharmacokinetic

- Population pharmacokinetic (PK) model parameter estimates derived from plasma concentrations of AZD3355 (to be presented in a separate report).

### Safety

- AE recording, laboratory values, vital signs (BP and pulse), ECG and physical examination.

### Statistical methods

A one-sided Chi-square test was used to compare the proportion of responders with respect to the primary variable during the last week of treatment (last 7 consecutive days on investigational product) between AZD3355 and placebo. The difference between treatment groups was calculated with a two-sided 95 % confidence interval (based on standard normal approximation). Survival curves with Kaplan-Meier estimates and a log-rank test were used to study the time to response and time to sustained freedom of symptoms.

### Patient population

The patient population and disposition is summarised in Table S1. A total of 306 patients from 8 countries were enrolled in the study and 244 were randomised to treatment and received at least 1 dose of study drug. All randomised patients were analysed for safety and 232 patients were analysed for efficacy. The overall number of discontinuations was similar between the treatment groups. All patients were Caucasian and there were no differences between the treatment groups in weight, height and BMI. A greater proportion of females were randomised to the AZD3355 group (42%) than the placebo group (25%). The number of years with reflux disease was similarly distributed between the treatment groups and 58% of patients had a 5 year or longer history of reflux disease. Approximately 28% of patients were infected with *Helicobacter pylori* and approximately 51% had a history of hiatal hernia. These frequencies was as expected for this patient population and similar for the different treatment groups. In the AZD3355 treatment group, 52% of the patients had a history of erosive esophagitis compared to 61% in the placebo group. The patient population had a heavy symptom burden at baseline, despite PPI treatment. More than 75% of the patients had at least one of the symptoms measured by the primary RDQ items on each of the 7 days prior to randomisation, as recorded in the e-diary. Symptom frequency was similar between the groups, but fewer patients reported moderate to severe symptoms in the AZD3355 treatment group (81%) compared to placebo (92%). Gastrointestinal and nervous system disorders were more common in patients randomised to the AZD3355 group compared to those randomised to placebo. Vascular disorders were also common, most often related to hypertension, and did not differ between the treatment groups. More than 80% of patients in both treatment groups

had a compliance of greater than 90% (measured as pill count). The patients were on a wide variety of medication including antacids, PPIs and a variety of anti-hypertensive drugs.

**Table S1 Patient population and disposition**

| | | AZD3355 (n=122) | | Placebo (n=122) | | Total (n=244) | |
|---|---|---|---|---|---|---|---|
| **Population** | | | | | | | |
| N randomised (N planned) | | 122 | (115) | 122 | (115) | 244 | (230) |
| **Demographic characteristics** | | | | | | | |
| Sex | Male (n (%)) | 71 | (58.2) | 91 | (74.6) | 162 | (66.4) |
| | Female (n (%)) | 51 | (41.8) | 31 | (25.4) | 82 | (33.6) |
| Age (years) | Mean (SD) | 51.1 | (11.9) | 48.7 | (12.6) | 49.9 | (12.3) |
| | Range | 23 to 70 | | 19 to 70 | | 19 to 70 | |
| BMI ($kg/m^2$) | Mean (SD) | 27.1 | (3.7) | 27.0 | (3.0) | 27.1 | (3.3) |
| **Baseline characteristics** | | **n and (% of patients)** | | | | | |
| History of reflux disease (years) | 0.5 - <1 | 7 | (6) | 6 | (5) | 13 | (5) |
| | 1 - <5 | 46 | (38) | 44 | (36) | 90 | (37) |
| | 5 - <10 | 31 | (25) | 34 | (28) | 65 | (27) |
| | ≥10 | 38 | (31) | 38 | (31) | 76 | (31) |
| History of erosive esophagitis | Yes | 64 | (52) | 74 | (61) | 138 | (57) |
| | No | 58 | (48) | 48 | (39) | 106 | (43) |
| History of hiatal hernia | Yes | 60 | (49) | 64 | (52) | 124 | (51) |
| | No | 52 | (43) | 52 | (43) | 104 | (43) |
| | Unknown | 10 | (8) | 6 | (5) | 16 | (7) |
| *Helicobacter pylori* | Positive | 32 | (28) | 30 | (27) | 62 | (28) |
| Primary RDQ items at baseline[a] | | | | | | | |
| Days with symptoms/week) | Daily | 91 | (75) | 90 | (77) | 181 | (76) |
| | 5-6 days | 23 | (19) | 14 | (12) | 37 | (16) |
| | 3-4 days | 5 | (4) | 8 | (7) | 13 | (5) |
| Max symptom intensity | Moderate-Severe | 98 | (81) | 108 | (92) | 206 | (87) |
| **Disposition** | | **N and (% of patients)** | | | | | |
| Patients who | Completed | 113 | (93) | 111 | (91) | 224 | (92) |

**Table S1 Patient population and disposition**

| | AZD3355 (n=122) | | Placebo (n=122) | | Total (n=244) | |
|---|---|---|---|---|---|---|
| **Population** | | | | | | |
| N randomised (N planned) | 122 | (115) | 122 | (115) | 244 | (230) |
| **Demographic characteristics** | | | | | | |
| Discontinued | 9 | (7) | 11 | (9) | 20 | (8) |
| Analysed for safety[b] | 122 | (100) | 122 | (100) | 244 | (100) |
| Analysed for efficacy (PP) | 114 | (93) | 118 | (97) | 232 | (95) |

[a] Measured with the e diary for each of the 7 days prior to randomisation
[b] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
N=Number
n=Number

### Summary of pharmacokinetic results

The mean AZD3355 plasma concentration for samples taken in the intervals 1-2 and 2-3 h after the first dose were similar (approximately 1 µmol/L) and lower than the mean concentration in the corresponding intervals after repeated dosing (approximately 1.8 µmol/L).

### Summary of efficacy results

The proportion of patients who had at most 1 day of mild symptom intensity during the last treatment week for either of the primary RDQ items was significantly greater for AZD3355 (16%) than for placebo (8%; primary variable p=0.026, one-sided chi square test). A two-sided 95% CI of the 9% difference in the proportion of responders between the groups ranged from 0 to 17.

There was a statistically significant difference between the cumulative distribution functions for placebo and AZD3355 for patients who had 7 consecutive days with at most 1 day with not more than mild intensity of the primary RDQ items during the 4-week treatment period. When the primary RDQ items were analysed separately, a difference between the groups was observed after the first treatment day and was maintained throughout the 4 week treatment period. Results from the analysis of all variables related to the primary objective are summarised in Table S2. Results from the analysis of variables related to the secondary objectives are summarised in Table S3.

**Table S2 Summary of efficacy results for the primary objective**

| Analysis | RDQ item(s) | AZD3355 | placebo | AZD3355-placebo [b] | |
|---|---|---|---|---|---|
| **Proportion of responders [a] during the last treatment week (primary variable)**<br>One-sided chi-square<br>Two-sided CI of the difference between the groups | A burning feeling behind the breastbone or unpleasant movement of material upwards from the stomach | 16% | 8% | 9% | p=0.026<br><br>95% CI (0,17) |
| **Estimated cumulative proportion of responders [a] over time**<br>Kaplan Meier curves. Log rank test | A burning feeling behind the breastbone or unpleasant movement of material upwards from the stomach | N/A | N/A | N/A | p=0.0195 |
| | A burning feeling behind the breastbone | N/A | N/A | N/A | p=0.0011 |
| | Unpleasant movement of material upwards from the stomach | N/A | N/A | N/A | p=0.0077 |
| **Estimated cumulative proportion of patients with 7 consecutive symptom free days over time**<br>Kaplan Meier curves. Log rank test. | A burning feeling behind the breastbone or unpleasant movement of material upwards from the stomach | N/A | N/A | N/A | p=0.0408 |
| **Proportion of symptom-free days**<br>Two-sided CI based on a t-distribution | A burning feeling behind the breastbone or unpleasant movement of material upwards from the stomach | 19% | 10% | 10% | 95% CI (4,15) |
| | A burning feeling behind the breastbone | 36% | 21% | 15% | 95% CI (7,23) |
| | Unpleasant movement of material upwards from the stomach | 37% | 23% | 14% | 95% CI (6,23) |

**Table S2 Summary of efficacy results for the primary objective**

| Analysis | RDQ item(s) | AZD3355 | placebo | AZD3355-placebo [b] | |
|---|---|---|---|---|---|
| **Mean maximum symptom intensity during the last treatment week**<br>(on a scale of 0-5)<br>Wilcoxon rank sum test for the difference between treatments | A burning feeling behind the breastbone or unpleasant movement of material upwards from the stomach | 2.4 | 2.9 | N/A | p=0.0032 |
| | A burning feeling behind the breastbone | 1.8 | 2.3 | N/A | p=0.0197 |
| | Unpleasant movement of material upwards from the stomach | 1.7 | 2.4 | N/A | p=0.0007 |

[a] Patients that had 7 consecutive days with not more than 1 day with not more than mild symptom intensity
[b] Rounded to the nearest whole number

**Table S3 Summary of results for secondary objectives**

| Analysis | Summary of result |
|---|---|
| **Secondary RDQ items:** | |
| Proportion of symptom-free days (%)<br>Two-sided CI based on a t-distribution | The lower limit of the two-sided 95% CI for the difference in mean proportion of symptom free days (AZD3355-placebo) was greater than zero for pain behind the breastbone, a burning feeling in the centre of the upper stomach and an acid taste in the mouth, as well as heartburn, regurgitation and GERD dimension items. |
| Mean maximum symptom intensity during the last treatment week<br>No hypothesis test | The mean maximum symptom intensity of secondary RDQ items was less for AZD3355 than for placebo during all treatment weeks and at baseline (no statistics). |
| **The GSRS:** | |
| Change from baseline (visit 2) at visits 3, 4 and 6 and the last treatment week | No relevant differences between AZD3355 and placebo were noted in variables measured by the GSRS. |
| **Cough and sleep questions:** | |
| Number of days and nights with cough for 7 consecutive days prior to each visit: change from baseline (visit 2) during the last treatment week | More patients on AZD3355 reported improvements in the frequency of day-time cough during the last treatment week compared to placebo. The number of patients that reported improvements in the frequency of night-time cough or sleep disturbance during the last treatment week did not differ between the groups. |
| **Antacid consumption:** | |

**Table S3 Summary of results for secondary objectives**

| Analysis | Summary of result |
| --- | --- |
| Number of antacids consumed during each day | No effect of AZD3355 on daily antacid consumption was observed when compared to placebo. |
| **OTE, symptom control and treatment satisfaction:** | |
| OTE scores were related to the patient's response to each of the primary RDQ items during the last treatment week.<br>The patients' perception of symptom control and level of treatment satisfaction were related to their response to the primary variable during the last treatment week. | Responders (individual primary RDQ items) more frequently reported large or moderate improvements in symptoms in the OTE compared to non-responders. Responders (primary variable) more frequently reported that the study medication provided sufficient symptom control and were more likely to be completely or quite satisfied with their treatment than non-responders. |
| **Pharmacokinetics:** | |
| Plasma concentration of AZD3355 | The mean AZD3355 plasma concentration for samples taken in the intervals 1-2 and 2-3 h after the first dose were similar (approximately 1 µmol/L) and lower than the mean concentration in the corresponding intervals after repeated dosing (approximately 1.8 µmolL). |

**Summary of safety results**

AZD3355 was generally safe and well-tolerated in this study. The number of patients who had at least 1 adverse event (AE) in any category during the active treatment period is shown in Table S4 and the most common AEs are shown in Table S5. There were 2 serious adverse events (SAEs) in the AZD3355 treatment group: 1 patient had hypertension during the treatment period that continued during follow up, and 1 patient had appendicitis during follow up. Neither event was thought to be related to the AZD3355 according the investigator. Seven patients on AZD3355 and 3 patients on placebo discontinued study treatment due to AEs. The most commonly reported AEs during the active treatment period were diarrhoea, nausea and paraesthesiae. No clinically significant differences in laboratory values, vital signs, ECG or physical examination were seen between the treatment groups.

## Table S4 Number (%) of patients who had at least one adverse event in any category during the active treatment periods (safety analysis set)

| Category of adverse events[a] | AZD3355 (n= 122) | Placebo (n= 122) |
|---|---|---|
| Any AE | 54 (44%) | 44 (36%) |
| AE with outcome death | 0 (0%) | 0 (0%) |
| Any SAE | 1 (1%) | 0 (0%) |
| AE that caused discontinuation of study | 7 (6%) | 3 (2%) |
| Causally related AE[b] | 30 (25%) | 24 (20%) |
| Severe AE | 12 (10%) | 4 (3%) |

[a] Patients with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

[b] Causality AEs are those for which there was a relationship to study treatment as judged by the investigator

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## Table S5 Number (%) of patients who had at least 1 AE by preferred term, including only PTs with frequency>2% in AZD3355 group (safety analysis set)

| Preferred term | Number (%) of patients[a] | |
|---|---|---|
| | AZD3355 n= 122 | Placebo n= 122 |
| **Patients with any AE** | 55 (45.1%) | 45 (36.9%) |
| Diarrhoea | 13 (10.7%) | 4 (3.3%) |
| Paraesthesia | 10 (8.2%) | 6 (4.9%) |
| Nausea | 9 (7.4%) | 4 (3.3%) |
| Fatigue | 7 (5.7%) | 7 (5.7%) |
| Abdominal pain upper | 6 (4.9%) | 4 (3.3%) |
| Dyspepsia | 6 (4.9%) | 2 (1.6%) |
| Headache | 6 (4.9%) | 5 (4.1%) |
| Vomiting | 5 (4.1%) | 2 (1.6%) |
| Nasopharyngitis | 4 (3.3%) | 2 (1.6%) |
| Pruritus | 4 (3.3%) | 0 (0%) |
| Abdominal distension | 3 (2.5%) | 0 (0%) |
| Constipation | 3 (2.5%) | 4 (3.3%) |
| Cough | 3 (2.5%) | 2 (1.6%) |
| Hypertension | 3 (2.5%) | 0 (0%) |
| Influenza | 3 (2.5%) | 0 (0%) |
| Myalgia | 3 (2.5%) | 1 (0.8%) |
| Somnolence | 3 (2.5%) | 1 (0.8%) |

[a]Number (%) of patients who reported at least 1 AE for a PT, sorted in decreasing order of frequency (sorted by total number on AZ IP)

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