AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD3355
Study Code	D9120C00027
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Validation of patient-reported outcome measures for the assessment of GERD symptoms and their subsequent impact on patients with a partial response to PPI treatment in a two part multi-center phase IIA study including a four week randomised, double-blind, placebo-controlled parallel-group treatment period

Study dates: First patient enrolled: 27 May 2008
Last patient completed: 23 December 2008

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

The study was conducted at 77 sites in the USA.

Publications

None at the time of writing this report.

Objectives

Table S1 Objectives

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Validation of the Reflux Symptom Questionnaire e-diary
Validation of the modified QOLRAD
Evaluation of alternative impact diary
Assess the safety and tolerability during 4 weeks treatment with AZD3355 65 mg bid as add-on treatment to a PPI in partial responders to PPI treatment who still experience GERD symptoms

Study design

This was a double-blind, placebo-controlled, randomised, parallel group design study, conducted at multiple centres in the USA. The study validated electronic patient reported outcome instruments and their subsequent impact on patients with GERD, who have a partial response to proton pump inhibitor (PPI) therapy, as characterised by persistent GERD symptoms. In order to meet the objectives related to validation, the study had two parts.

Target patient population and sample size

The study population consisted of patients with Gastroesophageal reflux disease (GERD), who have a partial response to PPI therapy, as characterised by persistent GERD symptoms. The study was conducted in male and female patients aged 19-70 years. Patients were required to have long term GERD symptoms (≥6 months) and to have been on continuous optimized PPI treatment with approved doses for at least 4 weeks prior to enrolment. Non-responders to PPI treatment were excluded.

In the screening Reflux Symptom Questionnaire 7 days recall prior to enrolment into Part 1 patients needed to have reported either one or both of the following: a burning feeling behind the breastbone or unpleasant movement of materials upwards from the stomach with a frequency of ≥3 days over the past 7 days with a symptom intensity of at least mild.

The eligibility for randomisation into Part 2 was based on twice-daily symptom recording in the Reflux Symptom Questionnaire e-diary during the last 7 days in Part 1. Patients needed to

have recorded either one or a combination of the two following: a burning feeling behind the breastbone on ≥3 days or unpleasant movement of material upwards from the stomach on ≥3 days, with a symptom intensity of at least mild.

To meet the objectives of the study, 450 randomised patients were considered sufficient. The actual number of patients randomised and included in full analysis set was 478.

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

AZD3355 65 mg (immediate release capsule) orally bid or placebo bid. Batch number was H 1838-02-01-01 for AZD3355 and H 1990-01-01-01 for placebo.

Duration of treatment

4 weeks.

Subject population

A total of 875 patients were enrolled in the study. Of these were 580 patients eligible for Part 1, and 478 patients in Part 1 were further randomised to treatment in Part 2: 235 to the AZD3355 group and 243 to the placebo group. All randomised patients were analysed for safety. Fifty-five patients discontinued prematurely from the study: 30 from the AZD3355 group and 25 from the placebo group.

In general, patients were adequately representative of the intended patient population. They had a history of reflux disease for a mean of approximately 9 years. They were taking PPIs and a variety of medications for eg diseases in the cardiovascular and nervous system. At baseline, approximately 75% of the patients reported daily symptoms in the e-diary, and the average mean intensity was between mild and moderate, while taking PPI treatment for GERD. There were no important baseline differences observed between the treatment groups.

Summary of results

Results indicate that the Reflux Symptom Questionnaire e-diary is fit for purpose in patients who have a partial response to PPI treatment, characterised by persistent GERD symptoms.

The original five-factor structure of the QOLRAD could not be confirmed in the modified version. However, after item-reduction of the modified QOLRAD there was support for a three-factor solution.

Summary of safety results

Overall, AZD3355 65 mg bid did not reveal any new safety findings and patients tolerated the treatment well. There were no deaths. Three patients reported Serious Adverse Event (SAE): 1 in the AZD3355 group (operative haemorrhage following elective surgery) and 2 in the placebo group (suicide attempt and myocardial infarction, pulmonary oedema, respiratory failure). Seventeen patients discontinued from study drug due to adverse event (AE): 13 in the

AZD3355 group and 4 in the placebo group. In total, 128 AEs were reported by 84 (36%) patients on AZD3355 and 109 AEs were reported by 63 (26%) patients on placebo. The number of patients reporting AEs during follow up was similar in both treatment groups. The AE profile in this study was similar to previous studies in patients with AZD3355. There were no indications of any clinically relevant effect on haematology, clinical chemistry or urinalysis of AZD3355 or changes in vital signs. The outcome of orthostatic testing was similar for AZD3355 and placebo, with no reported AEs related to the test.