CLINICAL STUDY REPORT SYNOPSIS

Study Title

Randomised, double-blind, placebo-controlled multicenter study to assess management strategies in the treatment of Helicobacter pylori infected patients with gastro-oesophageal reflux disease (GERD)

Protocol No.: D9612L00201

Version: Final 1.0

Date: 15 May 2009

Sponsor

AstraZeneca AG
Switzerland

1. SYNOPSIS

Name of Sponsor/Company: AstraZeneca AG	**Individual study table referring to part of the dossier** **Volume:** **Page:**	(***For national authority use only)***
Name of finished product: Nexium®		
Name of active ingredient: Esomeprazole		

Title of study:

Randomised, double-blind, placebo-controlled multicenter study to assess management strategies in the treatment of Helicobacter pylori infected patients with gastro-oesophageal reflux disease (GERD)

Investigators:

the ERASTRAT group

Study centre(s):

Switzerland (7 centres), Germany (10 centres) and Austria (2 centres). It was planned to recruit between 10 and 20 patients per centre.

Publication(s):

Schwizer W et al. Randomized, double-blind, placebo-controlled multicenter study to assess the effect of Helicobacter pylori (HP) eradication in patients with gastro-esophageal reflux diease (GERD): the Erastrat Study. Gastroenterology 2008; 134 (4 Suppl 1): A-175. Abstract S1089 and poster presented at DDW 2008, San Diego.

Study period:	**Phase of development:**
First patient in: 20 November 2003 **Last patient out:** 25 July 2007	Phase IV

Objectives:

To investigate whether eradication treatment of Helicobacter pylori followed by therapy with esomeprazole for a total of 8 weeks extends the time to relapse in patients with gastroesophageal reflux disease (GERD).

Methodology:

This was a multicentre, randomised, double-blind, placebo-controlled, 3 parallel groups, phase IV study. Patients were treated in 3 Groups: Group A (H. pylori positive, eradication treatment group), Group B (H. pylori positive, placebo treatment group) and H. pylori negative; placebo treatment group. All patients received Esomeprazole (Nexium®). Amoxicillin and Clarithromycin were given to Group A only. In Group B and Group C, patients received antibiotics placebo.

Time to re-occurrence of GERD symptoms was measured with the Eraflux-score in the eradication treatment and the H. pylori positive placebo group based on an intent-to-treat analysis in the follow-up period. In addition, time to relapse and pattern of inflammation and atrophy in the two H. pylori positive study groups was compared to the H. pylori negative control group. Severity and frequency of adverse events was assessed also.

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Number of patients (planned and analysed):

This study was planned to be conducted in 318 patients recruited from study centres in Switzerland, Germany and Austria. Patients were planned to be recruited for 12 months. It was assumed that around 27 patients must be recruited per month.

A total of 589 patients were screened and 311 patients from 19 centres were enrolled into the study. The first patient entered into the study on 20 November 2003 and the last patient completed the study on 25 July 2007.

Diagnosis and main criteria for inclusion:

Male and female patients aged between 18 and 70 years with H. pylori positive and negative gastro-oesophageal reflux disease (GERD) in whom an endoscopy is indicated.

Test product, dose and mode of administration, batch number:

Group A (H. pylori positive, eradication treatment group) received Esomeprazole (Nexium®) 20 mg and 40 mg tablets (20 mg twice daily from Day 1–7 and 40 mg once daily from Day 8–56 via oral route), Amoxicillin 1000 mg tablets (twice daily via oral route) and Clarithromycin 500 mg tablets (twice daily via oral route).

Group B (H. pylori positive, placebo treatment group) received Esomeprazole (Nexium®) 20 mg and 40 mg tablets as described above, Amoxicillin placebo tablets and Clarithromycin placebo tablets (both twice daily from Day 1–7 via oral route).

Group C (H. pylori negative; placebo treatment group) was treated with Esomeprazole (Nexium®) 20 mg and 40 mg tablets as described above, Amoxicillin placebo tablets and Clarithromycin placebo tablets (both twice daily from Day 1–7 via oral route).

Batch nos.: multiple batches were used;

Duration of treatment:

The patients in each group were treated for 56 days. The total study duration was planned to be 40 weeks (280 days) or till relapse.

The start of the study period was on 20 November 2003 followed by a treatment period of 56 days and a follow-up period of 36 weeks. Study period was completed on 25 July 2007.

Reference therapy, dose and mode of administration, batch number:

Not applicable in this part of the study.

Criteria for evaluation:

The primary efficacy endpoint was the time to re-occurrence of GERD symptoms measured with the Eraflux-score in Group A and Group B. Secondary endpoints were the comparison of time to relapse and pattern of inflammation and atrophy in Group A and Group B with Group C. The above endpoints were analysed for the efficacy subset (per-protocol patients broke down by effective H. pylori eradication). Secondary endpoints were analysed by the following parameters and their interactions: Treatment, oesophagitis, gender, alcohol and NSAID/ASS intake. Safety endpoints were severity and frequency of adverse events.

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Statistical methods:

Descriptive statistical analysis, Intention-to-treat, LOCF method for missing values, Cox proportional-hazard regression, chi-square test for four-way tables, generalised linear model for inflammation and atrophy.

No interim analysis was done. Blinding was broken only after all patients completed the study, completed data entry and decision on LOCF values.

Summary - Conclusion:

Efficacy results:

A total of 169 females and 142 males participated in the study. Six (6) patients were older than 70 years. In deviation to the protocol, analysis by gender was not shown in the results section because there was no evidence for any gender-specific effects. No breakdown for alcohol consumption was done, because the number of patients consuming relevant amounts of alcohol was too low.

Concerning the primary efficacy endpoint no difference in time to relapse between the antibiotics and the placebo eradication groups could be found. Time to relapse was more rapid in Hp negative controls than Hp positive patients irrespective of eradication therapy. Time to relapse was more rapid in patients with oesophagitis BCD at baseline. Time to relapse from the As-Treated (AT) subset was not qualitatively different from that of the ITT subset. Unexpectedly, the differences between groups were less pronounced in the AT subset than in the ITT subset.

Of the 67 patients treated with antibiotics and with complete Hp status available, the eradication failed in 12 cases, giving an effective eradication rate of 82%. After treatment, 84 of the 197 patients in the As-treated (AT) subset were Hp-positive, 54 were Hp-negative and 59 were in the AT control group that is Hp-negative before and after treatment.

From the 311 patients in the ITT set, 35 had critical symptomatic reflux symptoms after 8 weeks of treatment with esomeprazole. This corresponds to a symptomatic treatment failure rate of 11%. There was no indication that the frequencies of treatment failures and early dropouts were systematically influenced by the degree of oesophagitis, by initial Hp status or by treatment.

The relapse rate of GERD symptoms after PPI treatment at 36 weeks follow-up was 61%.

Oesophagitis grade between Visit 1 and Visit 4 was unchanged for 33 patients; it deteriorated for 6 and improved for 24 patients. Non-relapsed patients had only a marginally significant (p=0.088) better improvement in oesophagitis compared to relapsed patients.

Safety results:

In 76 patients, adverse events were observed. For 13 patients, adverse events were related to the study drug, which includes the eradication antibiotics. The most frequent reported drug related symptoms were nausea (N=5) and diarrhoea (N=4). For 11 patients, serious adverse events were reported. None of the serious event was related to the study drug. For 20 patients, adverse advents were the reason for study discontinuation.