AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Lesogaberan
Study Code	D9120C00019
Edition Number	1
Date	16 December 2010

A randomized, double-blind, placebo controlled, multi centre phase IIb dose finding study to assess the effect on GERD symptoms, safety and tolerability during four weeks treatment with lesogaberan (AZD3355) in doses 60 mg, 120 mg, 180 mg and 240 mg bid as add-on treatment to a PPI in patients with GERD that are partial responders to PPI treatment

Study dates:	First patient enrolled: 12 October 2009 Last patient last visit: 08 July 2010
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)

There were 109 study centres: 68 in the USA, 10 in Canada, 9 in France, 7 in Germany, 6 in Hungary, 6 in Romania and 3 in Latvia.

The first patient was enrolled on 12 October 2009.

The last patient completed the study on 08 July 2010.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Primary objectives

The primary objective was to evaluate the effect on gastroesophageal reflux disease (GERD) symptoms of 4 doses of lesogaberan (AZD3355) (60 mg, 120 mg, 180 mg and 240 mg bid) compared to placebo, as add-on treatment to a proton pump inhibitor (PPI) by using the responder definition; ie, at least 3 more days of not more than mild GERD symptoms on average per week during the whole treatment period compared to baseline, based on the Overall symptoms domain in the Reflux Symptom Questionnaire electronic Diary (RESQ-eD).

Secondary objectives

The secondary objectives of the study were:

- To evaluate the effect on GERD symptoms of 4 doses of lesogaberan (60 mg, 120 mg, 180 mg and 240 mg bid) compared to placebo, as add-on treatment to a PPI by using an alternative responder definition; ie, at least 5 days of not more than mild GERD symptoms on average per week during the whole treatment period based on the Overall symptoms domain in the RESQ-eD.

- To evaluate the effect on GERD symptoms of 4 doses of lesogaberan (60 mg, 120 mg, 180 mg and 240 mg bid) compared to placebo, as add-on treatment to a PPI

  - By analysing the change in the proportion of days of not more than mild GERD symptoms compared to baseline, based on the Overall symptoms domain and for each separate domain (Heartburn; Regurgitation; Hoarseness, cough and difficulty swallowing; Burping) in the RESQ-eD.

  - By analysing the proportion of symptom-free days, based on the heartburn item, on each separate domain (Heartburn, Regurgitation, Hoarseness, cough and difficulty swallowing and Burping) and on the Overall symptoms domain in the RESQ-eD.

- To evaluate the dose-response curve with respect to:
  - The responder definition.
  - The change in the proportion of days of not more than mild GERD symptoms compared to baseline, based on the Overall symptoms domain in the RESQ-eD.
- To assess basic measurement properties of the RESQ-eD.
- To assess the pharmacokinetics (PK) of lesogaberan by population PK analyses with special regard to variability in the patient population.
- To study the relationship between systemic exposure and response with special regard to the responder definition.
- To study the prevalence of mucosal breaks in the target population through endoscopy at baseline during the study or historical reports.
- To describe the endoscopic findings after the study treatment period, in patients with baseline endoscopy showing mucosal breaks.

Safety objective

To assess the safety and tolerability during 4 weeks treatment with 4 doses of lesogaberan as add-on treatment to a PPI, by evaluation of adverse events (AEs), laboratory variables, electrocardiogram (ECG), blood pressure, pulse, orthostatic tests and physical examination.

Exploratory objectives

To collect and store deoxyribonucleic acid (DNA) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to lesogaberan and/or susceptibility to or prognosis of GERD and associated disease under study.

Table 1 Primary and secondary objectives and outcome variables

Objective			Variable	
Priority	**Type**	**Description**	**Title and description**	**Method of assessment and derivation**
Primary	Efficacy	To evaluate the effect on GERD symptoms of 4 doses of lesogaberan (60 mg, 120 mg, 180 mg and 240 mg bid) compared to placebo, as add-on treatment to a PPI.	Responder (yes/no) The responder definition; ie, at least 3 more days of not more than mild GERD symptoms on average per week during the whole treatment period compared to baseline, based on the Overall symptoms domain in the RESQ-eD.	See CSP Section 6.5.1, 6.5.4 and 11.3.1
Secondary	Efficacy	To evaluate the effect on GERD symptoms of 4 doses of lesogaberan (60 mg, 120 mg, 180 mg and 240 mg bid) compared to placebo, as add-on treatment to a PPI.	Responder (yes/no) The alternative responder definition; ie, at least 5 days of not more than mild GERD symptoms on average per week during the whole treatment period based on the Overall symptoms domain in the RESQ-eD.	See CSP Section 6.5.1, 6.5.4 and 11.3.1
Secondary	Efficacy	To evaluate the effect on GERD symptoms of 4 doses of lesogaberan (60 mg, 120 mg, 180 mg and 240 mg bid) compared to placebo, as add-on treatment to a PPI.	Change in the proportion of days of not more than mild GERD symptoms compared to baseline, based on the Overall symptoms domain and each separate domain (Heartburn; Regurgitation; Hoarseness, cough and difficulty swallowing; Burping) in the RESQ-eD.	See CSP Section 6.5.1, 6.5.4 and 11.3.1

Objective			Variable	
Priority	**Type**	**Description**	**Title and description**	**Method of assessment and derivation**
Secondary	Efficacy	To evaluate the effect on GERD symptoms of 4 doses of lesogaberan (60 mg, 120 mg, 180 mg and 240 mg bid) compared to placebo, as add-on treatment to a PPI.	Proportion of symptom-free days based on heartburn item and the Heartburn, Regurgitation, Hoarseness, cough and difficulty swallowing, Burping and Overall symptoms domains in the RESQ-eD.	See CSP Section 6.5.1, 6.5.4 and 11.3.1
Secondary	Efficacy	To evaluate the dose-response curve for lesogaberan.	Evaluated with respect to change in proportion of days and based on the responder definition ie, the change in the proportion of days of not more than mild GERD symptoms compared to baseline, based on the Overall symptoms domain in the RESQ-eD.	See CSP Section 6.5.1, 6.5.4 and 11.3.1.
Secondary	PRO Validation	To assess basic measurement properties of the RESQ-eD.	Item intensity over baseline, domain intensity over baseline, domain intensity over the seven days prior to visit 4, domain intensity over the treatment period. Categories of magnitude and importance of change reported in the OTE questionnaire.	See CSP Section 6.5.1, 6.5.2, 6.5.4, 11.3.1 and 11.3.2.
Secondary	Pharmacokinetic	To assess the PK of lesogaberan by population PK analyses with special regard to variability in the patient population.	Total drug exposure, average concentration at steady state ($C_{average}$) and other PK parameters as applicable.	See CSP Section 6.6.1 and 12.2.3.9
Secondary	Pharmacokinetic	To study the relationship between systemic exposure and response with special regard to the responder definition.	Systemic exposure (estimated $C_{average}$) and response (yes/no).	See CSP Section 6.5.1, 6.5.4, 6.6.1 and 11.3.1.

Objective			Variable	
Priority	**Type**	**Description**	**Title and description**	**Method of assessment and derivation**
Secondary	Other	To study the prevalence of mucosal breaks in the target population through endoscopy at baseline during the study or historical reports.	Mucosal break status according to historical report or upper GI endoscopy at baseline.	See CSP Section 6.2.1
Secondary	Other	To describe the endoscopic findings after the study treatment period, in patients with baseline endoscopy showing mucosal breaks.	Endoscopic findings of mucosal breaks at baseline and after end of treatment.	See CSP Section 6.2.1
Safety	Safety	To assess the safety and tolerability during 4 weeks treatment with 4 doses of lesogaberan as add-on treatment to a PPI.	AEs, laboratory values, ECG, blood pressure, pulse, orthostatic tests and physical examination.	See CSP Section 6.4
Exploratory	Pharmacogenetic	To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to lesogaberan and/or susceptibility to or prognosis of GERD and associated disease as under study.	Voluntary sample donation: no results presented in this report.	See CSP Appendix D

AE Adverse event; CSP Clinical study protocol; PRO Patient reported outcomes; ECG Electrocardiogram; GERD Gastroesophageal reflux disease; DNA Deoxyribonucleic acid; PK pharmacokinetic; PPI proton pump inhibitor; bid twice daily; RESQ-eD Reflux Symptom Questionnaire electronic diary.

Study design

This was a randomized, double blind, placebo-controlled, parallel group designed, multi centre phase IIb dose finding study to assess the effect on GERD symptoms, safety and tolerability during 4 weeks of treatment with 4 doses of lesogaberan as add-on treatment to a PPI. The study consisted of a screening phase, a treatment phase and a follow-up phase. The patients were randomized to one of 4 doses of lesogaberan (60 mg, 120 mg, 180 mg or 240 mg bid) or matching placebo as add-on treatment to their optimized PPI treatment during the treatment phase.

Target subject population and sample size

The target patient population in this study was partial responders to PPI treatment, defined as those who experienced at least moderate intensity of GERD symptoms on at least 3 of the past 7 days despite optimised PPI treatment and also had a history of GERD symptoms for at least 6 months. Sample size calculations demonstrated that 130 randomized patients per treatment group would be sufficient to address the primary objective.

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

The details of the investigational products and any other study treatment are given in Table 2.

Table 2 Details of investigational product and any other study treatments

Investigational product	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number	Batch number
Lesogaberan, MR 1h	Capsules 30 mg	AstraZeneca AB	09-003817AZ	H 2095-01-02-01
	Capsules 60 mg	AstraZeneca AB	09-001900AZ	H 2099-01-01-01
	Capsules 120 mg	AstraZeneca AB	09-001901AZ	H 2096-01-02-01
Placebo for lesogaberan	Capsules	AstraZeneca AB	09-001902AZ	H 2102-01-01-01

The capsules contained no lactose or gelatine.

Doses and treatment regimens

At visit 2 the patients were randomized to receive one of 5 treatments, as add-on to their optimised PPI treatment, for 4 weeks:

- Lesogaberan 60 mg twice daily (bid).
- Lesogaberan 120 mg bid.
- Lesogaberan 180 mg bid.
- Lesogaberan 240 mg bid.

- Placebo bid.

Duration of treatment

The study consisted of a screening phase (8 to 26 days), a treatment phase (26 to 30 days) and a follow-up phase (12 to 16 days).

Statistical methods

The statistical analysis was performed by Statistics and Informatics, AstraZeneca R&D Mölndal, using SAS® version 8.2.

The primary analysis consisted of pairwise comparisons between doses of lesogaberan and placebo using the responder definition, ie, at least 3 more days of not more than mild GERD symptoms on average per week during the whole treatment period compared to baseline, based on the Overall symptoms domain in the RESQ-eD. Active dose levels were compared to placebo using a logistic regression model with the primary outcome variable as response variable and dose as a factor variable. The proportion of days of not more than mild symptoms during baseline was included as a covariate. The tests were one-sided with a significance level of 10%. Multiplicity was handled by using a step down procedure where lesogaberan was tested sequentially starting with the highest dose 240 mg and continuing with the 180 mg and 120 mg dose as long as all preceding null-hypotheses could be rejected. The estimate and two-sided 95% likelihood ratio confidence interval of the odds ratio are presented for all active dose levels. For the dose levels that were compared to placebo in the test procedure, the p-value is also presented.

The pairwise comparisons to placebo were also evaluated using the alternative responder definition, ie, at least 5 days of not more than mild GERD symptoms on average per week during the whole treatment period based on the Overall symptoms domain in the RESQ-eD. Estimates and two-sided 95% likelihood ratio confidence intervals of the odds ratios of each dose level compared to placebo are presented.

The change in proportion of days of not more than mild symptoms compared to baseline, both on the Overall symptoms domain in the RESQ-eD as well as for each domain separately, was analysed. The proportion (%) of symptom-free days was analysed for the heartburn item, for each of the RESQ-eD domains (Heartburn; Regurgitation; Burping; Hoarseness, cough and difficulty swallowing) and for the Overall symptoms domain. For these variables the active treatment groups were compared pairwise with placebo using the Wilcoxon rank-sum test. Odds ratios based on pairwise comparisons with logistic regression using cumulative logits and a proportional odds model were computed for the active treatment groups versus placebo along with 95% confidence intervals.

The internal consistency of RESQ-eD domains was evaluated by using Cronbach's alpha. Test-retest reliability of the RESQ-eD was investigated using intraclass correlation coefficients (ICCs). The ability to detect change (responsiveness) was analysed by calculating the effect size (ES), defined as the mean change over time divided by the SD at baseline.

The frequency of mucosal breaks based on historical reports was calculated by dividing the number of patients with mucosal breaks present in the most recent historical report with the total number of patients with an available historical report where the status of mucosal breaks was reported. The frequency was also calculated by Los Angeles classification grade.

The frequency of mucosal breaks obtained through upper endoscopy in the study was calculated by dividing the number of patients with mucosal breaks present with the total number of patients subjected to endoscopy. The frequency was also calculated by Los Angeles classification grade.

Endoscopic findings of mucosal breaks after the study treatment period in patients with baseline endoscopy showing mucosal breaks were presented in a frequency table showing the shift from the endoscopy during the enrolment period (mucosal breaks present and by Los Angeles classification grade) to the endoscopy after end of treatment (mucosal breaks absent or present and by Los Angeles classification grade if present).

Safety data were evaluated by descriptive tables and graphs. In addition, the relationship between dose and pre-specified types of AEs was evaluated by logistic regression with the binary variable indicating if a patient had the type of AE during treatment as response variable and dose as a continuous explanatory variable.

Exploratory analyses using multivariate regression were performed to assess the impact of multiple covariates, including age, sex, presence of esophagitis and history of depression/anxiety on the relationship between treatment group and response.

Patient population

- A greater percentage of female patients were randomised in total than males, however there were more males than females in the placebo group, compared to the other treatment groups.

- Based on historical reports, the prevalence of mucosal breaks in the study population was estimated to be approximately 20%. Baseline endoscopy was performed in 72% of patients and the prevalence of mucosal breaks among these patients was 31%. Mucosal breaks were classified as LA grade A and B in >80% of historical reports and >90% in baseline endoscopy.

- The most frequently used PPI before randomisation was Omeprazole 20 mg. The most frequently taken disease-related concomitant medications during the study by first level ATC code (after alimentary tract and metabolism) were nervous system and cardiovascular system. There were no notable differences across treatment groups.

- The patient population had a heavy symptom burden at baseline. A total of 96% of patients reported at least 5 days of at least one of the RESQ-eD symptoms with at least moderate intensity.

- Overall, the patient population is considered to be representative of the intended target population for lesogaberan and the treatment groups were reasonably balanced, with the exception of gender.

Summary of efficacy results

- In the primary analysis, a greater response was indicated in the lesogaberan 240 mg treatment group compared to the placebo group and this comparison was statistically significant (p= 0.0506). However, the difference between the lesogaberan 240 mg treatment group and the placebo group in proportion of responders was small (26% versus 18%).

- In the explorative logistic regression and also the sensitivity analyses, similar results were observed to the primary analysis, indicating that the treatment comparison results were robust and also maintained when adjusting for covariates.

- In assessing treatment comparisons utilising the alternative responder definition, no relevant treatment effects were observed.

- The change in proportion of days of not more than mild symptoms increased compared to placebo for all lesogaberan doses above 60 mg for each domain, with the exception of hoarsenss, cough and difficulty swallowing domain.

- No relevant treatment-effect was observed for any treatment group in the proportion of heartburn-free days, based on the analysis of the heartburn item of the RESQ-eD, which was performed following the recommendation of the FDA.

- The dose-response estimate indicated a plateau in the dose range which corresponded to doses of 120 mg or higher. This was in accordance with results from pairwise comparisons with placebo.

- The RESQ-eD demonstrated good to excellent reliability and ability to detect change in this study.

- The evaluation of the responder definition in this study, using the OTE as an anchor, supports that the responder definition derived in the PRO validation study (D9120C00027) represents a change that is meaningful to patients.

Summary of pharmacokinetic results

The Population PK Analysis Report is provided separately.

Summary of pharmacodynamic results – Not applicable

Summary of pharmacokinetic/pharmacodynamic relationships

- The exposure-response estimate indicated a plateau in the exposure range which corresponded to doses of 120 mg or higher. This was in accordance with results from pair wise comparisons with placebo.

Summary of pharmacogenetic results – Not applicable

Summary of safety results

- Overall, lesogaberan treatment was well tolerated.
- The most frequently reported AEs by SOC in the study were gastrointestinal disorders, nervous system disorders and infections and infestations. Gastrointestinal disorders and nervous system disorders were reported by a marginally greater proportion of patients in the lesogaberan 180 mg and 240 mg treatment groups.
- The most frequently reported AEs in the study by preferred term were paraesthesia, diarrhoea and pruritus. AEs of diarrhoea and pruritus were more frequent in the lesogaberan treatment groups compared to placebo.
- The number of patients with paraesthesia symptoms was similar in all treatment groups.
- The number of patients reporting syncope, feeling faint, light-headedness or dizziness after active questioning during the study was similar across treatment groups.
- Two SAEs were reported after intiation of the IP. One patient during follow-up in the lesogaberan 240 mg treatment group and 1 patient in the placebo group. Neither of the SAEs were considered to be related to the study drug by the investigator.
- Paraesthesia and pruritus were the AEs with the highest frequencies leading to discontinuation.
- There was a minor haemodynamic effect observed with lesogaberan treatment but it was not of any clinical importance.
- There was no clinically relevant orthostatic mean change over time in pulse or BP. The frequency of patients with an orthostatic reaction at any time during treatment showed a slight increase with the increase in lesogaberan dose. No patients with an orthostatic reaction reported symptoms related to orthostatic test.
- Individual clinically important abnormalities in liver enzymes were observed and in 6 patients, all treated with lesogaberan, ALT values >5xULN were observed.

- Regarding ECG assessments, there was a transient, non-dose related mean change in HR (5 to 7 beats/min) from baseline to 2 hours post-first dose in the lesogaberan treatment groups but no notable change in other subsequent visits.

- No clinically relevant changes in mean values for QTcF (ms), or in individual patients were observed.