AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Lesogaberan
Study Code	D9120C00032
Edition Number	Final
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A double-blind, placebo controlled, randomised, phase IIA pharmacodynamic 4-way cross-over study to estimate the dose response relationship of lesogaberan (AZD3355) on the number of reflux episodes assessed by impedance/pH in patients with GERD and a partial response to PPI treatment

Study dates: First patient enrolled: 17 December 2009
Last patient last visit: 7 May 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

This study was performed at one centre in the United States of America.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables
Primary	**Primary**
To estimate the dose-response relationship of lesogaberan (AZD3355) on the total number of reflux episodes during 24 hours.	Total number of reflux episodes
Secondary	**Secondary**
To estimate the effect over 24 hours as total values, and in upright and supine position of 4 different doses of lesogaberan (AZD3355) compared to placebo measured as reduction in: • total number of reflux episodes • the number of acid-, weakly acidic- and weakly alkaline reflux episodes • the height (mean proximal extent), content (liquid, gas or a mixture) of the refluxate and esophageal pH in the pH interval 4-6.5 • the time with esophageal pH<4 • the time with intragastric pH<4	Total number of reflux episodes; number and percentage of acid (pH<4), weakly acidic (4≤pH<6.5) and weakly alkaline (pH≥6.5) reflux episodes in upright and supine position. Height and content of the refluxate and pH. Time with esophageal and intragastric pH<4
To study the relationship between total number of reflux episodes, acid-, weakly acidic- and weakly alkaline reflux and GERD symptoms during 24 hours.	Diary card/data logger for GERD symptoms
To study the pharmacokinetics of lesogaberan (AZD3355) after 30, 90, 120 and 240 mg MR 1h capsules.	AUC0-12 h, AUC12-24h, AUC 0-24, C_{max}, t_{max}
To study the relationship between exposure (area under curve, AUC0-12h, AUC12-24h, AUC0-24h) and reflux episodes after the first and second doses of lesogaberan (AZD3355)	AUC0-12 h, AUC12-24h, AUC 0-24, total number of reflux episodes and percentage of registration time of acid (pH<4)

Objectives	Outcome variables
To assess the safety and tolerability of 4 different doses of lesogaberan (AZD3355) as add-on treatment to a PPI, by evaluation of adverse events (AEs), laboratory variables, digital ECG (dECG) and physical examination.	AEs, laboratory variables, dECG, physical examination
To assess the effect of lesogaberan (AZD3355) on orthostatic blood pressure and pulse, as well as sitting blood pressure and pulse over 24 hours.	Orthostatic testing, vital signs, sitting blood pressure and pulse over 24 hours
To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, PK profile, safety, tolerability and efficacy) to lesogaberan (AZD3355) and/or susceptibility to GERD.	Genes/genetic variation that may influence response (ie PK profile, safety, tolerability and efficacy) to lesogaberan and/or susceptibility to GERD

Study design

This was a randomised, double-blind, placebo controlled, 4-way crossover study to estimate the dose response relationship of lesogaberan on the number of reflux episodes assessed by esophageal impedance/pH monitoring in patients with GERD with a partial response to PPI treatment, as characterized by persistent GERD symptoms. Each treatment period consisted of one treatment day with 2 doses given, i.e. 30 mg, 90 mg, 120 mg or 240 mg lesogaberan or matching placebo in the morning and in the evening (12 hours later). Each patient who completed the study received placebo and 3 of the 4 doses of lesogaberan in a randomised order.

Target subject population and sample size

Male or female patients with at least a 6 months history of GERD symptoms, with a partial response to PPI treatment, as characterized by persistent GERD symptoms were to be included.

In order to achieve the needed numbers of evaluable patients on each of the doses the study had to include 27 randomised patients, with at least 20 randomised patients who completed the study. All patients were to be assigned to placebo, at least 14 were to be assigned to lesogaberan 30 mg, 16 were to be assigned to lesogaberan 90 mg, 16 were to be assigned to lesogaberan 120 mg and 14 were to be assigned to lesogaberan 240 mg.

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

Lesogaberan (AZD3355) capsules or placebo capsules to match was given orally twice daily for 1 day to match the treatment arms of 30 mg, 90 mg, 120 mg, 240 mg or placebo.

Investigational products where manufactured by AstraZeneca AB. Four batches of lesogaberan were used in this study. Individual batch numbers and further information are included in the CSR.

Duration of treatment

This was a 4-way crossover study of 30 mg lesogaberan, 90 mg lesogaberan, 120 mg lesogaberan, 240 mg lesogaberan or placebo. Patients were randomised at Visit 2 to one of five treatment groups, and each patient received placebo and 3 of the 4 doses of lesogaberan in a randomised order. A washout period of 7-28 days was allowed between treatments.

Statistical methods

Primary analysis

The estimation of the dose-response curve were primarily made by two types of E_{max} models; a fixed effect model and a mixed effect model. The mixed effects model was considered as the primary model and the fixed effects model as supportive.

This study was similar to study D9120C00020 in terms of design features and patient population and therefore an additional analysis was made with data from D9120C00020 included.

The response variables were log-transformed prior to estimation of the dose-response curves. If zero values were obtained they were replaced by 0.5. After log-transformation and analysis, the estimated mean curves and the 95% confidence limits were transformed back to the original scale to give geometric mean curves and corresponding confidence intervals.

Estimating the effect of lesogaberan compared to placebo on impedance/pH variables

The effect over 24 hours total values, in upright and in supine position of 4 different doses of lesogaberan were compared to placebo measured as reduction in:

- Total number of reflux episodes
- The number of acid-, weakly acidic- and weakly alkaline reflux episodes
- The height (mean proximal extent) and content (liquid, gas or a mixture) of the refluxate
- The time with esophageal pH<4, 4 ≤pH<6.5 and pH≥6.5
- The time with intragastric pH<4
- Acid clearance time (sec)
- Median bolus clearance time (sec)

These variables were assessed by estimating the inhibition (%) in the primary variables after treatment with lesogaberan 30 mg, 90 mg, 120 mg and 240 mg compared to placebo. Inhibition was defined as 100*(1-R) where R is the ratio (lesogaberan/placebo) of estimated geometric means. The estimated geometric or arithmetic means for each treatment (lesogaberan 30 mg, 90 mg, 120 mg and 240 mg and placebo) were also presented as well as 2-sided p-values. The analysis was based on a mixed effect model with treatment, period and

sequence as fixed effects and patient as a random effect. Confidence intervals for the true mean were calculated based on the percentiles from Student's t-distribution. The content of the refluxate, proximal extent and median bolus clearance time was presented in upright and supine position only by descriptive statistics.

Pharmacokinetic and pharmacokinetic-pharmacodynamic relationships

In the calculation of summary statistics for plasma concentrations, values below the assays lower limit of quantification (LLOQ) were handled with predefined rules.

The relationship was studied between exposure ($C_{ss,average,0-12h}$, $C_{ss,\ average,12-24h}$, $C_{ss,\ average,0-24h}$) and the two variables, total number of reflux episodes during 24 hours, and total duration of acid reflux episodes (pH<4) during 24 hours in relation to total registration time (%). $C_{ss,\ average,0-12h,}$ $C_{ss,\ average,12-24h}$, $C_{ss,\ average,0-24h}$ was related to the two variables 0-12, 12-24 and 0-24 hours post first dose, respectively. The primary analysis for dose-response was repeated as exposure-response with $C_{ss,\ average,}$ as exposure ($C_{ss,\ average,t}$=AUC/t).

Subject population

A total of 27 patients with GERD, 14 males and 13 females, between the ages of 18 to 68 years were randomised to the study and contributed to the analysis.

The safety analysis set included all 27 randomised patients.

One patient discontinued prematurely from the study; due to a positive drug of abuse screen at visit 4 and was excluded from the Efficacy Analysis Set and PK Analysis Set.

One patient was excluded from the Efficacy Analysis Set for the impedance/pH analysis due to poor quality of the tracings during all four study periods. In addition, 3 patients were partly excluded from the Efficacy Analysis Set for the impedance/pH analysis due to poor quality of the impedance/pH tracings during one of the study periods.

Summary of efficacy results

All four doses of lesogaberan significantly reduced the mean number of reflux episodes in a dose dependant manner in upright position and for the whole period whereas the reduction in supine position was significant for the highest dose only.

The reduction in the mean total number of reflux episodes, measured 0-24 h post first dose, was 52.8% (95% CI: -60.0; -44.3) after administration of lesogaberan 240mg (bid), was 45.0% (95% CI: -53.1; -35.5) after administration of lesogaberan 120 mg (bid), 37% (95% CI: -47.1; -25.0) after administration of lesogaberan 90 mg (bid) and 26.2% (95% CI: -37.6; -12.7) after administration of lesogaberan 30 mg (bid) as compared to placebo.

Summary of pharmacokinetic results

Lesogaberan (30 mg, 90 mg, 120 mg and 240 mg bid) was rapidly absorbed after both morning and evening dose, with median t_{max} values in the range of 1.5-2.0 h. As expected

plasma concentrations of lesogaberan were generally higher after the second (evening) dose due to accumulation. Exposure seemed to increase proportionally to the dose.

Summary of pharmacokinetic/pharmacodynamic relationships

The pharmacokinetic/pharmacodynamic relationship was explored by using an estimation of exposure-response by mixed effect E_{max} model, exploring mean values of number of reflux episodes measured for 0-24 h against mean values of average plasma concentrations ($C_{average}$). A relationships were observed between exposure/dose and the number of reflux episodes, as well as between dose and number of reflux episodes.

Summary of pharmacogenetic results

No results from pharmacogenetic analysis are available at the time of this report.

Summary of safety results

During active treatment with lesogaberan, 1 patient reported nausea and headache. On treatment with placebo 1 patient reported viral gastroenteritis. After treatment with lesogaberan, during the washout/follow-up periods, 1 patient reported sinusitis, and in 1 patient elevated ALT, AST and CK was reported followed by nausea and vomiting. The elevated ALT, AST and CK were assessed as serious and not related to study drug. After treatment with placebo, during the washout/follow-up periods, 1 patient reported viral gastroenteritis, and 1 patient reported contusion of chest wall. None of the patients discontinued from the study due to AEs.

There were no clinically relevant changes in the clinical laboratory safety parameters.

A slight increase in pulse rate and a slight decrease in blood pressure compared to placebo was seen. An orthostatic reaction was measured in three patients, but none of the patients showed any clinical signs and no cardiovascular AEs were reported. There were no clinically relevant ECG findings in this study.