AstraZeneca

Clinical Study Report

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A Phase III, Multicenter, Open-Label Study To Evaluate the Control of Gastric Acid Secretion with Esomeprazole In Patients With Gastric Acid Hypersecretory States Including Idiopathic Hypersecretion and Zollinger-Ellison Syndrome For 12 Months

Study dates:	First patient enrolled: 04 December 2003 Last patient enrolled: 02 July 2004
Phase of development:	III

This study was performed in compliance with Good Clinical Practice.

Drug product:	NEXIUM®	**SYNOPSIS**	
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A Phase III, Multicenter, Open-Label Study To Evaluate the Control of Gastric Acid Secretion with Esomeprazole In Patients With Gastric Acid Hypersecretory States Including Idiopathic Hypersecretion and Zollinger-Ellison Syndrome For 12 Months

International co-ordinating investigator

Not applicable.

Study centers

This study was conducted in 5 centers located in the United States (3 centers) and France (2 centers).

Publications

Pisegna JR, Sostek MB, Ruszniewski P, Forsmark CE, Monyak J, Metz DC: Effects of esomeprazole on acid output in patients with Zollinger-Ellison syndrome (ZES) and idiopathic gastric acid hypersecretion (IGH): 6-month results. Am J Gastroenterol. 2005:100(suppl 9):S57 (abstr no. 104)

Study dates		**Phase of development**
First patient enrolled	04 December 2003	Therapeutic confirmatory (III)
Last patient completed	12 July 2005	

Objectives

Primary:

The primary objective of the study was to determine if esomeprazole in appropriately titrated doses controlled gastric acid hypersecretion in patients with acid hypersecretory states including idiopathic gastric hypersecretion (IH) and Zollinger-Ellison Syndrome (ZES) at Month 12 (through 12 months of treatment).

Secondary:

The secondary objectives of the study were:

1. To determine if esomeprazole in appropriately titrated doses controlled gastric acid hypersecretion in patients with acid hypersecretory states including IH and ZES at Month 6.

2. To evaluate the safety and tolerability of esomeprazole in patients with acid hypersecretory states including IH and ZES at Month 6 and Month 12.

Study design

This study was conducted as a multicenter, open-label study, which consisted of an acid control phase followed by a maintenance phase.

Target patient population and sample size

The target population for this study was patients 18 years of age and older diagnosed with IH or ZES. Prior to starting this study, a sample size of approximately 16 patients was chosen as the target based on clinical and regulatory judgment and not on the basis of a statistical power calculation. Twenty-one patients enrolled into the study.

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

Esomeprazole magnesium 40-mg capsules were administered orally: 40 mg, 80 mg, or 120 mg bid, or, if necessary, additional dosing regimens were allowed after consultation with AstraZeneca (formulation H1222-04-01; batch number H1222-04-01-11). There was no comparator.

Aluminum hydroxide 200 mg, magnesium hydroxide 200 mg, simethicone 25 mg (GELUSIL® tablets, Parke Davis, Morris Plains, NJ USA) up to 12 tablets daily as rescue medication as needed (batch numbers 09452B and 03674B) (the formulation in France was 260 mg alumin hydrate and 430 mg magnesium trisilicate; up to 10 tablets daily were allowed as rescue medication in France [(batch numbers 0539013 and 0336123]).

Duration of treatment

The entire treatment duration was approximately 12 months.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: The status (controlled or not controlled) of gastric acid secretory rate at the Month 12 visit.

- Secondary variable: The status (controlled or not controlled) of gastric acid secretory rate at the Month 6 visit.

Gastric acid secretory control was defined as gastric acid secretory rate (ie, basal acid output [BAO]) below 10 mmol/h (10 mEq/h) or, for patients with prior gastric acid reducing surgery, below 5 mmol/h (5 mEq/h).

Safety

Adverse events were recorded throughout the study, clinical laboratory results (chemistry, hematology, urinalysis) were assessed at screening and Months 1, 3, 6, 9, and 12; physical examinations and vital signs measurements at screening and Months 3, 6, and 12; and EGDs at screening and Months 6 and 12.

Statistical methods

The number and percent of patients whose gastric acid secretory rate was controlled were calculated at the Month 6 visit (secondary variable) and the Month 12 visit (primary variable).

Basal acid output rates were summarized using counts, means, standard deviations, medians, minima, and maxima. In addition, the line plot of BAO by dose versus time for each patient was generated. The number and percentage of patients whose BAO was under control was summarized by last dose. The time to sustained control was summarized by number and percentage of patients who were under sustained control by visit. Time to sustained control of BAO was defined as the earliest time point from which the BAO was under control through the end of the study.

Patient population

Demographic and baseline data for all patients (21) who enrolled and completed this study are summarized in Table S1.

Table S1 Demographic and baseline characteristics (All patients)

Characteristic		Population			
		Intention-to-treat (N=21)		Per-protocol (N=19)	
Demographic characteristics					
Sex (n [%])	Male	15	(71)	14	(74)
	Female	6	(29)	5	(26)
Age (years)	Mean (SD)	55.5	(8.0)	55.5	(7.9)
	Median	55.0		55.0	
	Range	42 to 72		42 to 72	
Race (n [%])	Caucasian	18	(86)	16	(84)
	Black	3	(14)	3	(16)
Height (cm)	Mean (SD)	175.1	(8.6)	175.7	(8.9)
	Median	172.7		172.7	
	Range	165.1 to 190.5		165.1 to 190.5	
Baseline characteristics					
Weight (kg)	Mean (SD)	90.5	(23.5)	90.5	(24.4)
	Median	85.7		85.7	
	Range	52.6 to 144.2		52.6 to 144.2	

Table S1 Demographic and baseline characteristics (All patients)

Characteristic		Population			
		Intention-to-treat (N=21)		Per-protocol (N=19)	
BMI	Mean (SD)	29.3	(6.6)	29.1	(6.8)
	Median	27.4		27.4	
	Range	19.3 to 44.6		19.3 to 44.6	
Disease and surgical history					
Years with ZES/IH	Mean	8.7		8.1	
Underlying condition					
ZES (n [%])		19	(90)	17	(89)
IH (n [%])		2	(10)	2	(11)
ZES with MEN-1 (n [%])	Yes	3	(14)	2	(11)
	No	13	(62)	12	(63)
	Unknown	3	(14)	3	(16)
Metastatic ZES disease (n [%])		8	(38)	8	(42)
Complication with ZES/IH (n [%])		15	(71)	14	(74)
Surgery related to ZES/IH (n [%])		15	(71)	14	(74)
Previous gastric acid reducing surgery (n [%])		12	(57)	11	(58)

IH Idiopathic hypersecretion; MEN-1 Multiple endocrine neoplasia type 1; SD Standard deviation; ZES Zollinger-Ellison syndrome.

Efficacy and pharmacokinetic results

Gastric acid secretory rates were controlled with high-dose (from 80 mg [40 mg bid] up to 240 mg per day) esomeprazole in 19 (90%) patients at the Month 12 visit and in 20 (95%) patients at the Month 6 visit (Table S2). Median BAO values for all patients were 0.19 mmol/h and 0.18 mmol/h at Months 12 and 6, respectively. At the Month 12 visit, 14 (67%) of all 21 patients achieved gastric acid secretory control on 40 mg bid of esomeprazole, 4 (19%) on 80 mg bid, and 1 (5%) on 80 mg tid. Gastric acid secretory rates were controlled with pre-study PPI therapy in 19 (90%) patients in the ITT population at the baseline visit. At the Day 10 visit, gastric acid secretory rates were controlled with high-dose esomeprazole in 20 (95%) patients in the ITT population; 18 of these patients sustained control for the remainder of the study. An additional patient achieved sustained control at the second month.

Table S2 Number (%) of patients with controlled gastric acid secretory rates by visit by dosage (All patients)

Visit	Intention-to-treat population (N=21)			Per-protocol population (N=19)		
Dosage	**n**	**N**	**%**	**n**	**N**	**%**
Month 6						
40 mg bid	16	17	94	15	15	100
80 mg bid	3	3	100	3	3	100
80 mg tid	1	1	100	1	1	100
All	20	21	95	19	19	100
Month 12						
40 mg bid	14[a]	16	88	13	14	93
80 mg bid	4	4	100	4	4	100
80 mg tid	1	1	100	1	1	100
All	19	21	90	18	19	95

[a] Data from one patient was carried forward from the Month 6 visit.

Safety results

Nineteen (90%) patients received esomeprazole 40 mg bid, 4 of whom subsequently received dosage increases to 80 mg bid; 2 patients started on 80 mg bid, 1 of whom subsequently received 120 mg bid, then 80 mg tid. No patients died during the study. Four patients experienced serious adverse events (SAEs) (Table S3). Three SAEs were not attributed to study drug by the investigator, 1 SAE (hypomagnesemia) was considered by the investigator to be possibly related to study drug. The patient with hypomagnesemia remained on esomeprazole 240 mg per day for the remainder of the study without recurrence of hypomagnesemia; however, the dosing regimen was changed from 120 mg bid to 80 mg tid and the patient received magnesium supplements (1600 mg daily) for the remainder of the study. Eighteen (86%) patients reported a total of 98 adverse events during the study; no adverse event led to discontinuation from the study. All adverse events except 7 were of mild or moderate intensity. Two patients experienced adverse events that were possibly related to study drug by the investigator. The most common adverse events experienced by at least 4 (19%) patients were diarrhea (6 patients), nausea and cough (5 patients each), and headache (4 patients).

Table S3 Categories of adverse events (Safety population)

Category	Number (%) of patients[a]		Number of events
	n	(%)	
Patients in safety population	21	(100)	
Any adverse events	18	(86)	98
Led to discontinuation	0		
Treatment-related	2	(10)	2
Death	0		
Nonfatal serious adverse events	4	(19)	4
Life threatening	1	(5)	1
Hospitalization required	4	(19)	4
Important medical event	1	(5)	1

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

No patient had a clinically important abnormality in hematology. Three patients had laboratory results considered to be of potential clinical relevance by AstraZeneca: 1 patient experienced increasing levels of alkaline phosphatase (ALP) from Months 3 to 12 that exceeded the upper limit of the laboratory normal reference range (on 80 mg tid), another experienced levels of sodium that were below the lower limit of the laboratory normal reference range from Months 3 to 12 (on 40 mg bid), and the third, with non-insulin-dependent diabetes mellitus, had urine glucose levels of 3+ at all post-baseline assessments (on 40 mg bid). Corresponding baseline results were all within the laboratory normal reference range or normal. The investigator did not consider the steady increase in ALP clinically relevant, nor were any of these abnormal clinical laboratory values considered adverse events by the investigator.

The highest recorded baseline serum gastrin concentration was 15840 ng/L, which was 6.9-fold higher than the next highest baseline concentration. At Months 1 and 3, gastrin concentrations for this patient were 17310 ng/L and 11533 ng/L, respectively; gastrin levels were not assessed at other visits for this patient. Mild to moderate elevations of serum gastrin are expected with chronic use of proton pump inhibitors; however, extremely high concentrations (>1000 ng/L) are attributed to gastrinoma associated with ZES.

One patient had an elevated systolic and diastolic blood pressure of potential clinical relevance at the Month 12 visit (on 80 mg bid); his baseline blood pressure measurements were within the normal range. The investigator did not consider these measurements to be adverse or clinically relevant. There were no clinically relevant changes in physical examination or EGD findings, or pregnancy test results. At the Month 12 visit, no patient had endoscopic evidence of erosive esophagitis or gastric or duodenal ulcer.

Date of the report

03 November 2005