AstraZeneca

Clinical Study Report	
Drug Substance	Esomeprazole sodium
Study Code	D9612L00107
Edition Number	
Date	09 January 2008

An Open-Label, Exploratory Trial to Assess Gastric Acid Control in Critically Ill Subjects Receiving Nexium® I.V. (esomeprazole sodium) 40 mg BID for up to 72 hours

Study dates: First patient enrolled: 08 November 2006
Last patient completed: 09 July 2007

Phase of development: Phase IV

Therapeutic use (IV)

This study was performed in compliance with Good Clinical Practice.

Drug Product	NEXIUM®	**SYNOPSIS**	
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An Open-Label, Exploratory Trial to Assess Gastric Acid Control in Critically Ill Subjects Receiving Nexium® I.V. (esomeprazole sodium) 40 mg BID for up to 72 hours

International co-ordinating investigator (Not applicable)

Study center(s)

This study was conducted at 5 centers in the United States (a total of 7 sites were initiated; 7 sites received study drug and 5 sites admitted patients).

Publications

None

Study dates		**Phase of development**
First patient enrolled	08 November 2006	Therapeutic use (Phase IV)
Last patient completed	09 July 2007	

Objectives

Primary: To assess gastric acid suppression by esomeprazole iv in critically ill patients.

Secondary: To assess time to stable pH ≥4 from start of drug, where stable pH ≥4 was defined as the time of the first of 2 or more consecutive gastric aspirates spanning at least 2 hours with pH ≥4.

Study design

This was an open-label, exploratory trial. After screening assessments, patients received esomeprazole iv 40 mg twice daily (bid), administered intravenously by 3-minute injection, over 48 hours with a 24-hour study extension for patients able to continue an additional 24 hours without pre-pyloric enteral feedings. After the first dose of study medication, gastric aspirates were collected and tested for pH at 30 minutes, 60 minutes, 90 minutes, and 120 minutes with a ±10-minute window for each time point. Thereafter, gastric aspirates were

collected and tested every 2 hours with a ±30-minute window until study completion (at Hour 48 or 72 or at termination).

Target patient population and sample size

The study population was to include critically ill male and female patients aged ≥18 years who had a baseline gastric aspirate pH ≤4. Patients were to be mechanically ventilated and were to have at least 1 additional stress ulcer risk factor. Approximately 57 patients were to be admitted to obtain approximately 30 evaluable patients.

Investigational product: dosage, mode of administration and batch numbers

40 mg esomeprazole sodium administered intravenously bid as a 3-minute injection (NDC # 0186-6040-01, lot # LL2172)

Duration of treatment

A total of 48 hours, with a 24-hour study extension for patients who were able to continue an additional 24 hours without pre-pyloric enteral feeds.

Criteria for evaluation (main variables)

Pharmacodynamic efficacy

- ***Primary***: Interpolated percent of time with pH ≥4 over the period of 24-48 hours after the first dose
- ***Secondary***: Interpolated percent of time with pH ≥4 over the first 24 hours
- ***Secondary***: Interpolated percent of time with pH ≥4 over the first 48 hours
- ***Secondary***: Interpolated percent of time with pH ≥4 over the period of 48-72 hours for patients participating in the 24-hour study extension
- ***Secondary***: Gastric pH over the entire study period
- ***Secondary***: Time to stable pH ≥4 (stable pH ≥4 was defined as the time of the first of 2 or more consecutive gastric aspirates spanning at least 2 hours with pH ≥4) .

Safety

Reported AEs were collected from the time of first dose of study drug medication until study completion (at Hour 48 or 72 or at termination). SAEs were collected from the time the patient signed the informed consent through 72 hours after the last dose of study medication was administered.

Statistical methods

The primary analysis used the modified intent-to-treat (MITT) analysis set for all efficacy analyses. Secondary analyses were performed on the corresponding intent-to-treat (ITT) and

per-protocol (PP) analysis sets. The primary analysis was the calculation of the mean and 95% confidence interval (CI) for the primary endpoint, interpolated percent of time pH ≥4 over the period of 24-48 hours after the first dose. Means and 95% CIs were calculated for the interpolated percent of time pH ≥4 over the first 24 hours, over the first 48 hours, and over the period of 48-72 hours after the first dose for patients participating in the study extension.

The profile of gastric acid suppression over time was estimated with plots of mean pH vs time for the first 48 hours after the first dose and for the 72-hour study period for patients participating in the 24-hour study extension. Time to stable pH ≥4 was analyzed with Kaplan Meier estimates of the percentage of patients reaching stable pH ≥4 over time and estimates of the median time to stable pH ≥4.

Patient population

Disposition and demographic data of the study population are shown in Table S1.

Table S1 Patient disposition, demographics, and baseline characteristics

Disposition	**n (%)**
Admitted	45 (100.0)
Completed protocol	22 (48.9)
Withdrawals	23 (51.1)
Death[a]	1 (2.2)
Other	22 (48.9)
Included in ITT population	45 (100.0)
Included in primary MITT population[b]	26 (57.8)
Included in primary PP population[c]	22 (48.9)
Included in safety population[d]	45 (100.0)

Demographic or baseline characteristic		**Analysis population**			
		Safety[d] (n=45)	**ITT (n=45)**	**MITT[b] (n=26)**	**PP[c] (n=22)**
Demographic characteristics					
Gender, n (%)	Male	26 (57.8)	26 (57.8)	14 (53.8)	12 (54.5)
	Female	19 (42.2)	19 (42.2)	12 (46.2)	10 (45.5)
Age (years)	Mean (SD)	51.5 (19.8)	51.5 (19.8)	57.1 (16.1)	56.4 (16.2)
	Range	18.0 to 94.0	18.0 to 94.0	20.0 to 86.0	20.0 to 83.0
Race, n (%)	Caucasian	28 (62.2)	28 (62.2)	16 (61.5)	12 (54.4)
	Black	16 (35.6)	16 (35.6)	10 (38.5)	10 (45.5)
	Middle Eastern	1 (2.2)	1 (2.2)	0	0
Baseline characteristics					
Baseline pH	Mean (SD)	2.8 (0.9)	2.8 (0.9)	2.7 (0.9)	2.7 (0.9)
	Range	1.0 to 4.0	1.0 to 4.0	1.1 to 4.0	1.1 to 4.0
APACHE II Score	Mean (SD)	19.6 (6.1)	19.6 (6.1)	20.4 (7.0)	21.4 (6.8)
	Range	6.0 to 31.0	6.0 to 31.0	6.0 to 31.0	11.0 to 31.0

Table S1 Patient disposition, demographics, and baseline characteristics

		Analysis population			
		Safety[d] (n=45)	ITT (n=45)	MITT[b] (n=26)	PP[c] (n=22)
Baseline characteristics					
Additional stress ulcer risk factor	Acute renal failure	3 (6.7)	3 (6.7)	2 (7.7)	2 (9.1)
	Acute heart failure	2 (4.4)	2 (4.4)	2 (7.7)	2 (9.1)
	Acid base disorder	16 (35.6)	16 (35.6)	9 (34.6)	9 (40.9)
	Multiple trauma	19 (42.2)	19 (42.2)	8 (30.8)	8 (36.4)
	Post-neurosurgery	4 (8.9)	4 (8.9)	1 (3.8)	1 (4.5)
	Coma	11 (24.2)	11 (24.2)	9 (34.6)	9 (40.9)
	Closed head injury	15 (33.3)	15 (33.3)	8 (30.8)	8 (36.4)
	Post-major surgical procedure	19 (42.2)	19 (42.2)	15 (57.7)	11 (50.0)
	Hypotension	11 (24.4)	11 (24.4)	7 (26.9)	6 (27.3)
	Sepsis	6 (13.3)	6 (13.3)	3 (11.5)	2 (9.1)

[a] Three deaths occurred during this study; however, only 1 death was reported as a withdrawal.
[b] Patients with MITT evaluable data included in the analysis of the primary endpoint.
[c] Patients with PP evaluable data included in the analysis of the primary endpoint.
[d] Number of patients who received study drug.
ITT = intent-to-treat; MITT = modified intent-to-treat; PP = per-protocol; n = number of patients; SD = standard deviation; APACHE = Acute Physiologic and Chronic Health Evaluation

Pharmacodynamic results

The primary variable in this study was the interpolated percent of time pH ≥4 over the period of 24-48 hours after the first dose of esomeprazole iv 40 mg for patients in the MITT population. As shown in Table S2, esomeprazole iv 40 mg bid was associated with substantial post-baseline gastric acid suppression over the 24-48 hour post-dose time period, with the mean percent time with pH ≥4 equal to 88.8%.

Table S2 Summary of interpolated percent time pH ≥4, 24-48 hours post-dose esomeprazole iv 40 mg bid, (MITT population, n=26)

Mean interpolated percent time pH ≥4	95% CI	
	Lower	Upper
88.8	80.9	96.6

iv = intravenous; bid = twice daily; n = number of patients; MITT = modified intent-to-treat; CI = confidence interval
Data derived from Table 11.2.1.1, Section 11.1.

Secondary variables addressing the primary objective of this study were the interpolated percent of time pH ≥4 over the first 24 hours and over the first 48 hours after the first dose of esomeprazole iv 40 mg for patients in the MITT population, and over the period of 48-72 hours after the first dose for patients in the MITT population participating in the 24-hour study extension. Esomeprazole iv 40 mg bid was associated with substantial

post-baseline gastric acid suppression over the first 24 hours (mean percent time with pH ≥4 equal to 80.7%) and over the first 48 hours post-dose (mean percent time with pH ≥4 equal to 83.5%) in the MITT population. There was low participation in the 24-hour study extension (only 9 of the 22 patients who completed the 48-hour treatment period had MITT evaluable data for the study extension); however, the data from these patients suggest that esomeprazole iv 40 mg bid continued to maintain pH ≥4 for these patients during the study extension period (mean percent time with pH ≥4 equal to 97.8%). Similar results were observed for patients in the ITT and PP populations.

An additional secondary variable addressing the primary objective of the study was the percent of gastric aspirates collected with pH ≥4 over the first 24 hours after the first dose, after the first 48 hours after the first dose, and over the period of 24-48 hours after the first dose of study drug in the MITT population, and over the period of 48-72 hours after the first dose for patients in the MITT population participating in the 24-hour study extension. During the time periods studied, the mean percentage of gastric aspirates having pH values ≥4 was at least 78.2%. Similar results were observed for patients in the ITT and PP populations.

Another secondary variable supporting the primary objective was the gastric pH over the entire study period for the MITT population. Relative to baseline, the mean gastric pH increased to above 4.0 within 30 minutes to 1 hour, then reached a plateau at a pH of 5.5-6.0 at approximately 3 hours. Similar results were observed for patients in the ITT and PP populations.

The secondary variables that addressed the secondary objective of this study were the time to stable pH ≥4 in the MITT, ITT, and PP populations. For approximately half of the patients, stable pH ≥4 was reached within 1 hour.

Safety results

As shown in Table S3 and S4, esomeprazole iv 40 mg bid was well tolerated in this population of critically ill patients. Three patients died during the study; the deaths were not attributed to study treatment. There were no treatment-related serious adverse events (SAEs) or adverse events (AEs). Seven SAEs other than death were reported for 6 patients. The most frequently reported AEs were hypophosphatemia, hypokalemia, pyrexia, and thrombocytopenia. Any relevant change following first dose of study drug, as determined by the investigator based on standard of care laboratory values, was considered an AE and recorded in the appropriate CRF page. The adverse events reported in this small clinical study are consistent with what would be expected in a population of critically ill patients.

Table S3 Summary of AEs by category following esomeprazole 40 mg iv bid treatment, (Safety population, n=45)

Category of adverse event	n (%) of patients who had an AE in each category[a]	Total number of adverse events
Any adverse event	34 (75.6)	75
Discontinuations of study treatment due to adverse events	1 (2.2)	1
Serious adverse events leading to death	3 (6.7)	3
Serious adverse events not leading to death	6 (13.3)	7
Life-threatening	3 (6.7)	3
Hospitalization	3 (6.7)	3
Important medical event	4 (8.9)	5

[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.

iv = intravenous; bid = twice daily; AE = adverse event; n = number of patients.

Table S4 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarized over all treatment groups (Safety analysis set, n=45)

	Esomeprazole iv 40 mg bid
Preferred term	n (%)
Hypophosphatemia	6 (13.3)
Hypokalemia	4 (8.9)
Pyrexia	4 (8.9)
Thrombocytopenia	4 (8.9)
Agitation	3 (6.7)
Bradycardia	3 (6.7)
Fluid overload	3 (6.7)
Hypertension	2 (4.4)
Hypomagnesemia	2 (4.4)
Hypotension	2 (4.4)
Insomnia	2 (4.4)
Leukocytosis	2 (4.4)
Pneumonia	2 (4.4)

[a] This table includes only those events that occurred in at least 2 patients during the study.

iv = intravenous; bid = twice daily

Note: Patients with multiple episodes of an AE are counted only once for that AE.

Date of the report

09 January 2008