AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Esomeprazole sodium
Study Code	D9614C00004
Date	25 September 2009

A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of esomeprazole once daily for the treatment of gastroesophageal reflux disease (GERD) in neonatal patients, including premature and up to 1 month corrected age

Study dates: First patient enrolled: 30 November 2006
Last patient completed: 14 April 2009

Phase of development: III

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Drug Product	NEXIUM®	**SYNOPSIS**	
Drug Substance	Esomeprazole magnesium		
Study Code	D9614C00004		
Date	25 September 2009		

A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of esomeprazole once daily for the treatment of gastroesophageal reflux disease (GERD) in neonatal patients, including premature and up to 1 month corrected age

Study center(s)

The study was conducted at 3 centers (1 each in Australia, Germany, and the United Kingdom).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	30 November 2006	III
Last patient completed	14 April 2009	

Objectives

Primary:

The primary objective of this study was to assess the difference between esomeprazole and placebo in the treatment of signs and symptoms of gastroesophageal reflux disease (GERD) as observed by 8-hour video and cardiorespiratory monitoring in neonatal patients.

Secondary:

The secondary objectives of this study were:

- to assess the difference between esomeprazole and placebo in the treatment of symptomatic reflux episodes of GERD
- to assess the difference between esomeprazole and placebo in the treatment of other GERD-related signs and symptoms via video, pH/impedance, and cardiorespiratory monitoring

- to assess the efficacy of esomeprazole, compared to placebo, in reducing the number of (a) all types of reflux episodes (acid or non-acid) and (b) acidic reflux episodes, defined as pH <4.0, via pH/impedance monitoring

- to assess the safety and tolerability of esomeprazole compared to placebo.

Study design

This was a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 0.5 mg/kg esomeprazole administered once daily for the treatment of symptomatic GERD in neonatal patients, including premature and up to 1 month corrected age. The patients' size and medical condition allowed for performance of all study related procedures and administration of investigational product as judged by the investigator.

Target healthy volunteer population and sample size

The patient population for this study was infants, either full term or those with a gestational age or post-conceptual age ≥28 to 44 weeks, and who were inpatients in the Neonatal Intensive Care Unit (NICU), special care nursery, or equivalent hospital ward at the point of study entry. Patients were suspected of having the following clinical findings: any 2 (either individually or in any combination) of (1) apnea +/- bradycardia +/- oxygen desaturations, (2) vomiting/gagging, (3) irritability/pain at least every second feed or at least twice every 8 hours so as to be reproducible on video.

The study planned to include a minimum of 90 randomized patients (to achieve 76 evaluable patients; 38 per treatment group). Because of challenges in recruitment, enrollment was stopped after 52 patients were randomized (26 per treatment group).

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

Esomeprazole was supplied as a concentrate for oral solution (2.5 mg/mL; Formulation #: H 1713-01-02) and was to be administered at 0.5 mg/kg/day. Placebo solution (Formulation #: H 1723-01-01) and sodium bicarbonate solution (Formulation #: H 1714 01-02) were also supplied. The esomeprazole concentrate and placebo solutions were prepared by dilution of the concentrate with sodium bicarbonate solution prior to use.

Esomeprazole or placebo was given once daily 30 minutes prior to a morning feeding during the treatment period. Study personnel performed drug administration by oral gavage (using a nasogastric or orogastric tube) or by nippling.

Duration of treatment

Final study day was planned to be Day 14; however, patients who completed a minimum of 10 days of treatment had all final study day procedures performed. A treatment period of less than 10 days (minimum 7 days) could be allowed on a case-by-case basis, with prior approval from the sponsor, provided the patient was considered to be medically stable and considered

for discharge from the hospital. Patients who discontinued early, prior to Day 10, had to complete all final study procedures except video/pH/impedance monitoring.

Criteria for evaluation - efficacy (main variables)

- **Primary:**
  Change from baseline in the number of occurrences of symptoms of GERD, as observed from video recording, and GERD-related signs detected from cardiorespiratory monitoring

- **Secondary:**
  Change from baseline in the number of occurrences of symptoms of GERD (impedance-detected events with pH <4.0), including only signs and symptoms of GERD temporally associated with reflux episodes (+/- 2 min, + 2 minutes, or + 5 minutes after reflux start)

- **Secondary:**
  Change from baseline in the:

  - number of GERD-related events observed during the video monitoring period by event type and the number of events that coincided with an acid reflux·
  - durations of sleep, waking hours, peaceful quietness, and crying observed during the video monitoring period
  - number of GERD-related signs as recorded in the clinical assessment charts·
  - Physician Global Assessment (PGA) score of GERD-related symptoms.

- **Secondary:**
  Change from baseline in the pharmacodynamic endpoints evaluated over a 24-hour monitoring period

Criteria for evaluation - safety (main variables)

The safety variables included adverse events (AEs), clinical laboratory evaluations, physical examinations, and vital signs.

Statistical methods

All efficacy analyses were conducted in the intent-to-treat (ITT) population, and included all patients with evaluable data for a particular endpoint, at both baseline and the final visit. Per-protocol analyses were not conducted. All analyses were conducted at the nominal 2-sided 5% significance level.

The primary endpoint, change from baseline in signs and symptoms of GERD observed from video and cardiorespiratory monitoring, was analyzed by ANCOVA. Prior to the analysis, the number of events at baseline and final visit were normalized (to correspond to 8 hours

observation time) then log-transformed via a log(1+x) transformation. The ANCOVA of change from baseline on the log-scale was adjusted for treatment and baseline. The least square means (lsmeans) for each treatment group were transformed and expressed as estimated percentage changes from baseline, and the lsmean for the esomeprazole treatment effect was transformed similarly, and expressed as a percentage difference from placebo, which was presented with the associated 2-sided 95% CI and p-value.

The analysis of signs and symptoms of GERD temporally associated with acidic reflux events (referred to in the protocol as symptomatic reflux episodes of GERD) was performed in the same manner as the primary endpoint, as were similar analyses by individual symptom type, and by symptom class.

Signs and symptoms temporally associated with weakly acidic reflux episodes, non-acidic reflux episodes, and with reflux episodes of any type were also summarized, but not subjected to formal statistical analysis.

Change from baseline in duration of sleep, waking hours, peaceful quietness, and crying, as well as change from baseline in each of the pharmacodynamic variables were also analyzed by ANCOVA in a similar manner as outlined above, but these variables did not undergo a log-transformation prior to analysis.

The incidence rate of signs and symptoms of GERD observable on the video at the final visit were compared between treatment groups via Fisher's exact test. Analysis of the PGA at the end of the study, comparing esomeprazole with placebo, was via the Cochran Mantel-Haenszel test, stratifying by PGA score at baseline.

Data from the clinical assessment charts were summarized descriptively and were not subject to formal analysis.

All patients who received at least 1 dose of study medication were included in the safety analysis population. Safety analyses consisted of descriptive statistics only. No formal statistical analyses were planned or performed.

Subject population

The disposition of patients during the study is shown in Table S1.

Table S1 Patient disposition

	N (%) patients in each category	
Disposition	**Esomeprazole**	**Placebo**
Patients randomized	26 (100.0)	26 (100.0)
Patients evaluable for safety	26 (100.0)	26 (100.0)
Patients evaluable for ITT	25 (96.2)	26 (100.0)
Patients non-evaluable for ITT	1 (3.8)	0

	N (%) patients in each category	
Disposition	**Esomeprazole**	**Placebo**
Patient did not have valid efficacy measurements	1 (3.8)	0
Patients completed protocol	25 (96.2)	25 (96.2)
Patients discontinued treatment	1 (3.8)	1 (3.8)
Voluntary discontinuation by parent/guardian	1 (3.8)	0
Patient lost to follow-up[a]	0	1 (3.8)

a Patient E1002003 received all 14 doses of study medication and was discharged from the study. The patient was lost to follow-up between the study completion visit and the safety follow-up visit.
ITT Intent-to-treat

The demographic and key baseline characteristics of study patients in the ITT population are summarized in Table S2 and the standardized growth parameter of weight for length at baseline for the patients in the ITT population is presented in Table S3.

The mean dose for all patients was 0.5 mg/kg.

Table S2 Demographics and baseline characteristics (ITT population)

		ITT population		
Demographic characteristic		**Esomeprazole (n=25)**	**Placebo (n=26)**	**Total (n=51)**
Age (days)	Mean (SD)	48.1 (29.8)	46.5 (31.2)	47.3 (30.2)
	Median	43.0	38.0	42.0
	Range	7 to 104	9 to 111	7 to 111
Sex, n (%)	Male	10 (40.0)	11 (42.3)	21 (41.2)
	Female	15 (60.0)	15 (57.7)	31 (58.8)
Race, n (%)	Caucasian	20 (80.0)	21 (80.8)	41 (80.4)
	Black	2 (8.0)	0	2 (3.9)
	Oriental	0	2 (7.7)	2 (3.9)
	Other	3 (12.0)	3 (11.5)	6 (11.8)
Height (cm)	Mean (SD)	46.6 (4.4)	47.3 (5.3)	47.0 (4.8)
	Median	46.0	45.5	45.9
	Range	40.0 to 56.0	40.0 to 57.5	40.0 to 57.5
Weight (kg)	Mean (SD)	2.7 (0.8)	2.9 (1.2)	2.8 (1.0)
	Median	2.5	2.5	2.5
	Range	1.6 to 4.7	1.7 to 6.2	1.6 to 6.2
BMI (kg/m^2)	Mean (SD)	12.2 (1.5)	12.6 (2.6)	12.4 (2.1)
	Median	12.0	12.2	12.2
	Range	9.8 to 15.4	8.8 to 18.7	8.8 to 18.7
Head circumference (cm)	Mean (SD)	33.7 (2.1)	33.6 (2.6)	33.6 (2.4)
	Median	32.7	33.4	32.7
	Range	31.5 to 39.0	29.3 to 37.0	29.3 to 39.0

ITT Intent-to-treat; SD standard deviation; BMI body mass index
Note: For all patients: mean (SD) dose of study medication=0.5 (0) mg/kg; median dose=0.5 mg/kg; range=0.5 to 0.6 mg/kg.

Table S3 Standardized growth parameter[a] at baseline (ITT population)

Demographic characteristic		**Esomeprazole (n=25)**	**Placebo (n=26)**
Percentile weight for length	n	16	14
	Mean (SD)	43.73 (29.15)	54.49 (37.51)
	Median	45.04	52.91
	Range	0.52 to 91.32	0 to 99.39

[a] Standardized percentiles derived from the US CDC growth charts (2000). Growth charts not corrected for prematurity.
ITT Intent-to-treat

The study population was predominantly Caucasian and slightly more than half of the patients were female. The mean age of the patients was approximately 47 days, the mean weight was 2.8 kg, and the gestational age range at birth was 24 to 40 weeks. The weight for length of the babies in both treatment groups was similar to that of the general population in the US, although it is noted that the CDC growth charts are not based upon premature infants. The randomized treatment groups were balanced with respect to other baseline demographic factors. The study population was adequately representative of the target patient population.

Both procedural and study drug compliance were adequate for an assessment of efficacy and safety. Concomitant medication use in this study raised no concerns about the interpretation of the study results.

Summary of efficacy results

All efficacy analyses were performed on the ITT population. No statistically significant differences were detected between esomeprazole and placebo for the primary variable (change from baseline in the number of occurrences of symptoms of GERD as observed from video recording, and GERD-related signs detected from cardiorespiratory monitoring). The normalized number of GERD events observed from video and cardiorespiratory monitoring are summarized in Table S4. The analysis of the change from baseline in the total number of observed GERD events is shown in Table S5.

Statistically significant decreases from baseline were observed in the total number of GERD events associated with acid reflux in the esomeprazole treatment group compared with placebo (Table S6). These differences were not observed between treatment groups in signs and symptoms associated with any type of reflux episode (ie, refluxes of any acidity). These results were consistent for all 3 temporal associations (ie, +/- 2 minutes, + 2 minutes, + 5 minutes) analyzed.

Table S4 Summary of the normalized number of GERD events observed from video and cardiorespiratory monitoring (ITT Population)[a,b]

		Number of events			Change from baseline		
Treatment	**Visit**	**Mean (SD)**	**Median**	**Range**	**Mean (SD)**	**Median**	**Range**
Esomeprazole (n=25)	Baseline	184.66 (78.53)	159.88	101.84 to 412.90			
	Final	156.65 (75.11)	137.01	95.21 to 465.74	-28.01 (77.70)	-21.48	-209.32 to 240.02
Placebo (n=26)	Baseline	183.10 (77.46)	155.15	84.33 to 395.37			
	Final	158.31 (75.89)	139.41	79.43 to 425.90	-24.79 (44.25)	-16.24	-105 85 to 53.07

[a] Only patients with data at both baseline and final assessment are included in this summary table.
[b] Events are normalized prior to summary to correspond to a complete 8-hour monitoring period.
GERD gastroesophageal reflux disease; ITT intent–to-treat; SD standard deviation

Table S5 Analysis of the change from baseline in the total number of GERD events observed from video and cardiorespiratory monitoring (ITT Population)[a,b]

	Esomeprazole		Placebo		Estimated % difference from placebo			
						95% CI		
Endpoint	**n**	**% Change from baseline**	**n**	**% Change from baseline**	**Estimate**	**Lower**	**Upper**	**p-value[c]**
All Events	25	-14.74	26	-14.12	-0.71	-14.18	14.87	0.9217

[a] Only patients with data at both baseline and final assessment are included in this table.
[b] Events are normalized prior to summary to correspond to a complete 8-hour monitoring period.
[c] via ANCOVA of change from baseline in log-transformed normalized events, adjusting for treatment and baseline.
GERD gastroesophageal reflux disease; ITT intent–to-treat; ANCOVA analysis of covariance

Table S6 Analysis of the change from baseline in the total number of GERD events observed from video and cardiorespiratory monitoring associated with acid reflux (ITT Population)[a,b]

	Esomeprazole		Placebo		Estimated % difference from placebo			
						95% CI		
Endpoint	n	% Change from baseline	n	% Change from baseline	Estimate	Lower	Upper	p-value[c]
Signs/symptoms associated with acid reflux (+/- 2 minutes)	25	-80.69	26	-36.82	-69.44	-81.84	-48.58	<0.0001
Signs/symptoms associated with acid reflux (+2 minutes)	25	-71.85	26	-39.42	-53.54	-71.49	-24.28	0.0028
Signs/symptoms associated with acid reflux (+5 minutes)	25	-79.80	26	-40.00	-66.33	-80.28	-42.50	0.0002

[a] Only patients with data at both baseline and final assessment are included in this table.

[b] Events are normalized prior to summary to correspond to a complete 8-hour monitoring period.

[c] via ANCOVA of change from baseline in log-transformed normalized events, adjusting for treatment and baseline.

GERD gastroesophageal reflux disease; ITT intent–to-treat; ANCOVA analysis of covariance; CI confidence interval

Following esomeprazole treatment, no statistically significant difference in change from baseline in the total number of gastrointestinal, neurobehavioral, or cardiorespiratory events was observed compared to placebo and the change from baseline in the numbers of gastrointestinal, neurobehavioral, or cardiorespiratory events associated with any type of reflux (ie, refluxes of any acidity) was similar between treatment groups.

A statistically significant decrease from baseline was observed for neurobehavioral signs and symptoms associated with acid reflux at all 3 time association windows compared to placebo. These included only back arching and irritability/crying/fussing, but not gagging. When interpreting these statistically significant differences, it is important to consider the mechanism of action of esomeprazole (reduced gastric acidity) and the resulting decrease in the number of acidic reflux events available for analysis.

Table S7 presents the analysis of change from baseline for the impedance variables. The change from baseline in all reflux episodes was similar between treatment groups. For the esomeprazole treatment group, compared to placebo the number of acidic reflux episodes was significantly reduced and the number of weakly acidic reflux episodes was significantly increased. Analysis of the pH variables (Table S8) showed results consistent with the results from the impedance monitoring. No statistically significant difference between treatment groups in the change from baseline of all reflux episodes was observed. For the esomeprazole treatment group, compared to placebo there was a statistically significant reduction in acidic reflux episodes greater than 5 minutes, a statistically significant reduction in % time pH< 4.0, and a statistically significant increase in % time with pH 4.0-6.9.

Table S7 Analysis of change from baseline for impedance variables (24-hour monitoring period); ITT population with evaluable pH/impedance data[a]

	Esomeprazole (n=20)	Placebo (n=22)	Treatment difference (esomeprazole-placebo)			
				95% CI		
Variable	LS Mean (SE)	LS Mean (SE)	LS mean (SE)	Lower	Upper	p-value
All reflux episodes	-7.43 (8.12)	-0.2 (7.72)	-7.23 (11.53)	-30.55	16.08	0.5338
Acidic reflux episodes	-30.40 (3.20)	-4.32 (3.04)	-26.07 (4.52)	-35.22	-16.93	<0.0001
Weakly-acidic reflux episodes	26.05 (7.55)	0.46 (7.18)	25.59 (10.61)	4.13	47.05	0.0207
Non-acidic reflux episodes	0.57 (0.24)	0.35 (0.23)	0.22 (0.33)	-0.45	0.89	0.5119
Liquid reflux episodes	-8.98 (7.59)	-6.07 (7.21)	-2.91 (10.78)	-24.72	18.90	0.7888
Mixed gas/liquid reflux episodes	5.02 (3.44)	2.75 (3.28)	2.27 (4.78)	-7.40	11.94	0.6374
Mean bolus clearance time (sec)	1.11 (4.82)	-5.32 (4.59)	6.43 (6.67)	-7.06	19.93	0.3409
Mean acid clearance time (sec)	13.46 (9.67)	-13.21 (9.21)	26.67 (13.49)	-0.61	53.96	0.0551

[a] Only patients with evaluable pH data at baseline and final visit were included in this analysis.
ITT intent-to-treat; acidic reflux pH <4.0; weakly acidic reflux pH 4.0 – 6.9; non-acidic reflux pH ≥7.0; sec seconds; LS least square; SE standard error; CI confidence interval

Table S8 Analysis of the change from baseline in pH variables (24-hour monitoring period); ITT population with evaluable pH/impedance data[a]

	Esomeprazole (n=20)	Placebo (n=22)	Treatment difference (esomeprazole-placebo)			
				95% CI		
Variable	LS Mean (SE)	LS Mean (SE)	LS mean (SE)	Lower	Upper	p-value
Number of acidic reflux events	-19.10 (9.90)	6.05 (9.44)	-25.14 (13.68)	-52.82	2.53	0.0737

	Esomeprazole (n=20)	Placebo (n=22)	Treatment difference (esomeprazole-placebo)			
				95% CI		
Variable	LS Mean (SE)	LS Mean (SE)	LS mean (SE)	Lower	Upper	p-value
Number of acidic reflux events greater than 5 minutes	-4.96 (1.10)	0.51 (1.05)	-5.46 (1.53)	-8.55	-2.38	0.0009
% time pH <4.0	-8.68 (1.93)	0.37 (1.84)	-9.05 (2.69)	-14.49	-3.60	0.0017
% time pH 4.0 – 6.9	7.83 (1.88)	-0.77 (1.79)	8.59 (2.63)	3.28	13.91	0.0022

[a] Only patients with evaluable pH data at baseline and final visit were included in this analysis.
Acidic reflux events pH< 4.0; SE standard error; CI confidence interval

There was no statistically significant difference between treatment groups in the change from baseline in the duration variables (sleep, peaceful quietness, crying) and there was no statistically significant difference in the PGA at the end of the study.

Summary of safety results

Table S9 provides a summary of adverse events (AEs) in this study. There were no deaths or premature discontinuations of treatment with investigational product due to an adverse event (DAEs) during the study. A total of 6 (23.1%) esomeprazole treated patients experienced 10 AEs, while 9 (34.6%) placebo patients experienced 14 AEs. Three placebo patients experienced 4 serious adverse events (SAEs); no SAEs occurred in the esomeprazole treatment group. One (3.8%) placebo patient experienced an AE considered by the investigator to be treatment-related.

Table S9 Summary of AEs by category (Safety population)

Category of AE	Esomeprazole (n=26)	Placebo (n=26)
	n (%) of patients who had an AE in each category[a]	
Any AE	6 (23.1)	9 (34.6)
SAE leading to death	0	0
SAE not leading to death	0	3 (11.5)
DAE	0	0
Treatment-related AE	0	1 (3.8)
	Total number of AEs[b]	
Any AE	10	14
SAE leading to death	0	0
SAE not leading to death	0	4
DAE	0	0
Treatment-related AE	0	1

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

[b] Events counted by preferred term, ie for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

AE adverse event; SAE serious adverse event; DAE premature discontinuation of treatment with investigational product due to an adverse event

The most commonly reported AEs were in the gastrointestinal disorders (9.6%), infections/infestations (7.7%), and investigations (5.8%) SOCs. Adverse events are listed by preferred term in Table S10. The most commonly reported AE was oxygen saturation decreased (2 esomeprazole treated patients, 1 placebo patient).

Table S10 Number (%) of patients with adverse events, sorted by decreasing order of frequency[a] (Safety population)

MedDRA preferred term	Esomeprazole n (%)	Placebo n (%)
Any AE	6 (23.1)	9 (34.6)
Oxygen saturation decreased	2 (7.7)	1 (3.8)
Anemia neonatal	1 (3.8)	1 (3.8)
Constipation	0	2 (7.7)
Cyanosis	0	2 (7.7)
Flatulence	1 (3.8)	1 (3.8)
Bradycardia neonatal	0	1 (3.8)
Bronchiolitis	0	1 (3.8)
Conjunctivitis	1 (3.8)	0
Deafness neurosensory	1 (3.8)	0
Diarrhea	0	1 (3.8)
Edema peripheral	1 (3.8)	0
Gastroesophageal reflux disease	1 (3.8)	0
Inappropriate device signal detection	0	1 (3.8)
Infantile apneic attack	0	1 (3.8)
Nasopharyngitis	0	1 (3.8)
Neonatal infection	1 (3.8)	0
Retinopathy of prematurity	1 (3.8)	0
Urinary tract infection neonatal	0	1 (3.8)

[a] Number (%) of patients with AEs by preferred term in decreasing order of frequency, sorted by total number.

Overall, the most common and most severe AEs reported in the study were consistent with the natural history of health and disease-related events in this pediatric age group. No new safety signals were identified in this population of infants.

Date of the report

25 September 2009