AstraZeneca

Clinical Pharmacology Study Report	
Drug Substance	Esomeprazole magnesium
Study Code	D9614C00007
Date	19 September 2008

A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

Study dates:	First subject enrolled:	14 August 2006
	Last subject completed:	08 May 2008
Phase of development:	Clinical Pharmacology (I)	

This study was performed in compliance with Good Clinical Practice

Drug Substance(s)	Esomeprazole magnesium	**SYNOPSIS**	(For national authority use only)
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A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

Study centers

This study was conducted at 7 study centers in the United States (US); 1 was closed because of inactivity.

Study dates		**Phase of development**
First subject enrolled	14 August 2006	Clinical pharmacology (I)
Last subject completed	08 May 2008	

Objectives

The primary objective of the study was to determine the area under the plasma concentration-time curve (AUC) of esomeprazole after single oral doses of 5 mg, 10 mg, or 20 mg esomeprazole in pediatric patients 1 to 11 years old, inclusive, with endoscopically proven GERD.

The secondary objectives were as follows:

1. To determine the area under the plasma concentration-time curve from time zero to the last quantifiable concentration ($AUC_{(0-t)}$), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}), terminal half-life ($t_{1/2?z}$), apparent oral clearance (CL/F), and apparent volume of distribution during terminal phase ($V_{?z}/F$) of esomeprazole after single oral doses of 5 mg, 10 mg, and 20 mg esomeprazole in pediatric patients 1 to 11 years old, inclusive, with endoscopically-proven GERD.

2. To determine AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, and $t_{1/2?z}$ of the 5-hydroxy and sulphone metabolites of esomeprazole after a single oral dose of 5 mg, 10 mg, and 20 mg esomeprazole in pediatric patients 1 to 11 years old, inclusive, with endoscopically-proven GERD.

3. To assess the safety and tolerability of esomeprazole in pediatric patients 1 to 11 years old, inclusive, with endoscopically-proven GERD.

Study design

This was a randomized, open-label study designed to evaluate the pharmacokinetics, safety, and tolerability of esomeprazole 5 mg, 10 mg, and 20 mg when given as a single oral dose to pediatric patients 1 to 11 years old, inclusive, with endoscopically-proven GERD.

Patients were randomized into the study based on weight. Patients who weighed from 8 kg to <20 kg were randomized into 1 of 2 dosing groups (Group A or Group B). Patients randomized to Group A received a single, 5-mg oral dose of esomeprazole. Patients randomized to Group B received a single, 10-mg oral dose of esomeprazole.

Patients who weighed ≥20 kg were randomized into 1 of 2 dosing groups (Group C or Group D). Patients randomized to Group C received a single, 10-mg oral dose of esomeprazole. Patients randomized to Group D received a single, 20-mg oral dose of esomeprazole.

Target subject population and sample size

The target was to enroll approximately 40 male and female patients from 1 to 11 years of age, inclusive, with endoscopically-proven GERD in order to obtain at least 24 evaluable patients.

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

Esomeprazole magnesium blue, clinical-image capsules, formulated as 5 mg, 10 mg, and 20 mg, were used for oral administration as either intact with water or as an opened capsule mixed with up to 1 tablespoon of applesauce followed by water (batch numbers 2000095328 [5 mg], 2000095327 [10 mg], 2000095326 [20 mg]).

Duration of treatment

1 day

Variables

- **Pharmacokinetic**

  Blood samples were analyzed to determine the pharmacokinetics of esomeprazole (AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2?z,}$ CL/F, $V_{?z}$/F) and its 5-hydroxy and sulphone metabolites (AUC, $AUC_{(0-t)}$, C_{max}, t_{max}, $t_{1/2?z}$).

- **Safety**

  Safety and tolerability were evaluated from the incidence and severity of all adverse events and the assessment of laboratory parameters, vital signs measurements, and physical examination findings.

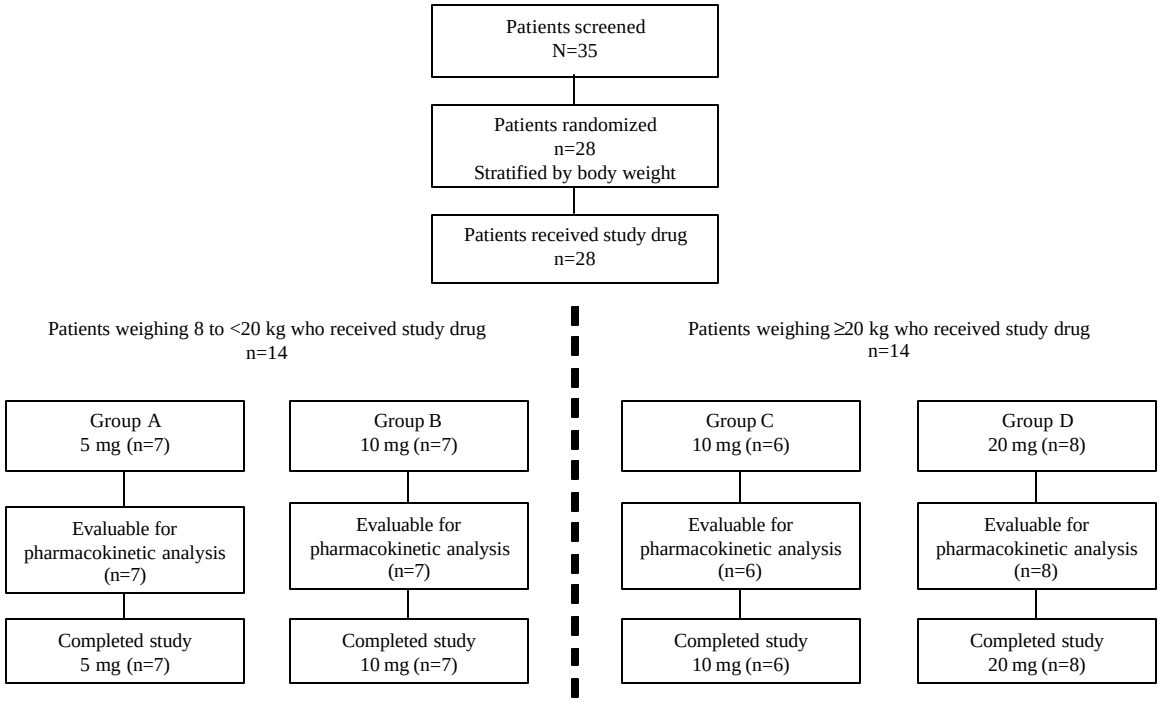
Statistical methods

The aim of this study was to determine the AUC of esomeprazole after a single oral dose of 5 mg, 10 mg, or 20 mg esomeprazole. Plasma concentration data, pharmacokinetic data, and safety information obtained from laboratory assessments and adverse events were summarized using descriptive statistics by weight group and dose.

Subject population

All 28 patients who were randomized to study drug were included in the safety and pharmacokinetic analysis sets (Figure S1). Treatment groups A, B, and C each contained more males than females by at least 2:1; overall most (57.1%) patients were males; most (67.9%) patients were Caucasian.

Figure S1 Patient disposition



Summary of pharmacokinetic results

Exposures of single-dose esomeprazole, as measured by AUC and C_{max}, were approximately 1.8- and 2.2-fold higher, respectively, in patients weighing from 8 to <20 kg who received 10-mg doses (0.71 mg/kg) than in patients who received 5-mg doses (0.35 mg/kg). In patients weighing ≥20 kg who received 20-mg (0.68 mg/kg) and 10-mg (0.35 mg/kg) doses of esomeprazole, AUC and C_{max} were approximately 4.4- and 2.4-fold higher, respectively, in patients who received 20-mg doses than in patients who received 10-mg doses (Table S1). Corresponding exposures of esomeprazole metabolites 5-hydroxy esomeprazole and

esomeprazole sulphone were higher by the same order of magnitude. There were no clinically meaningful differences between treatment groups in t_{max} for the parent compound or its metabolites. Median t_{max} of esomeprazole and 5-hydroxy esomeprazole ranged from 1.00 to 2.00 hours independent of treatment group; the range of median t_{max} for esomeprazole sulphone was comparable, from 1.50 to 2.00 hours in each treatment group. Median values of $t_{1/2?z}$ for esomeprazole, 5-hydroxy esomeprazole, and esomeprazole sulphone ranged across treatment groups from 0.42 to 0.99 hour, 0.59 to 0.95 hour, and from 0.85 to 2.52 hours, respectively, but did not appear to vary between treatment groups. Geometric mean (coefficient of variation) weight-normalized apparent clearance of esomeprazole in patients who received a single 10-mg dose of study drug was comparable between weight strata, 1.53 (61.1%) L/h/kg among patients weighing from 8 to <20 kg and 1.40 (49.1%) L/h/kg among patients weighing ≥20 kg.

Table S1 Esomeprazole pharmacokinetic parameters (pharmacokinetic population)

Parameter	8 to <20 kg		³20 kg	
	Group A 5 mg (N=7)	**Group B 10 mg (N=7)**	**Group C 10 mg (N=6)**	**Group D 20 mg (N=8)**
AUC, µmol·h/L				
n	6[a]	7	5[a]	7[a]
Geometric mean	0.73	1.32	0.69	3.06
CV (%)	93.3	54.1	67.1	98.3
$AUC_{(0-t)}$, µmol·h/L				
n	7	7	6	8
Geometric mean	0.66	1.3	0.67	2.31
CV (%)	87.0	53.1	59.5	140.2
C_{max}, µmol /L				
n	7	7	6	8
Geometric mean	0.62	1.39	0.64	1.54
CV (%)	79.4	30.5	44.1	125.4
t_{max}, h				
n	7	7	6	8
Median (range)	1.52 (1.00, 2.02)	1.00 (0.98, 1.50)	1.75 (1.50, 3.00)	2.00 (1.50, 3.00)
$t_{1/2?z}$, h				
n	6	7	5	7
Geometric mean	0.75	0.52	0.40	0.86
CV (%)	91.2	48.6	23.1	44.5
CL/F/kg, L/h/kg				
n	—	7	5	—
Geometric mean	—	1.53	1.40	—
CV (%)	—	61.1	49.1	—

[a] Insufficient numbers of blood specimens had measurable plasma concentrations in 1 patient in this treatment group to determine the area under the esomeprazole plasma concentration-time curve from time zero to infinity.

$AUC_{(0-t)}$ Area under the plasma concentration-time curve from time zero to the last measurable concentration; CI Confidence interval; CL/F Apparent oral clearance; C_{max} Maximum plasma concentration; CV Coefficient of

variation; Gmean Geometric mean; SD Standard deviation; $t_{1/2?z}$ Elimination half-life; t_{max} Time of maximum plasma concentration; $V_{?z}/F$ Apparent volume of distribution.

Summary of safety results

There were no deaths, serious adverse events, discontinuations attributed to adverse events, or other significant adverse events in this study. One patient experienced treatment-related constipation that resolved with no action taken. Another patient experienced acute cytomegalovirus infection with corresponding elevated liver enzymes that was not considered serious or treatment-related by the investigator. There were no clinically important findings or trends in hematology, clinical chemistry, urinalysis, or vital signs.