Drug Substance(s)	Esomeprazole	**SYNOPSIS**	(For national authority use only)
Study Code	SH-NEC-0001		
Date	15 February 2006		

A Single-Blind, Randomised, Parallel-Group, Single-Centre Pharmacokinetic and pH-Monitoring Study of Esomeprazole in Infants up to 24 Months of Age

Study dates		**Phase of development**
First subject enrolled	6 June 2002	Therapeutic exploratory
Last subject completed	23 March 2005	

Objectives

The primary objective of this study was to assess the pharmacokinetics of esomeprazole and its efficacy in controlling intragastric pH in infants.

The secondary objectives were:

- to assess the efficacy of esomeprazole in controlling esophageal acid exposure
- to assess the safety and tolerability of esomeprazole in infants
- to assess the ability of esomeprazole to reduce gastroesophageal reflux disease (GERD) symptoms in infants.

Study design

A single-centre, randomised, single blind, two-arm parallel, repeated dose design was used in this study. Subjects were given a 1 week regimen of esomeprazole 0.25 mg/kg or esomeprazole 1.0 mg/kg administered orally once daily (od).

Target subject population and sample size

The subject population comprised outpatient infants up to 24 months of age with symptoms of GERD where the diagnosis was confirmed by 24-hour pH-monitoring.

The aim was to have about 30 evaluable subjects for the pharmacokinetics (PK) in the study of which at least 24 subjects (12/treatment arm) had to be <12 months, including at least 2 subjects aged between 1to 3 months. Thus, taking into account a dropout from the PK evaluation of some subjects, 40-50 subjects were estimated to be randomised. However, if infants eligible for inclusion were difficult to recruit, the study was to be terminated when 24 (12/treatment arm) PK evaluable subjects <12 months had been reached with at least 2 subjects aged between 1 to 3 months.

Investigational product: dosage, mode of administration and batch numbers

Each subject was randomised to receive 1 of 2 possible doses of the study drug (hereafter referred to as investigational product), ie esomeprazole 0.25 mg/kg or esomeprazole 1.0 mg/kg orally once daily (od) in the morning for a period of 7 or 8 days (hereafter referred to as 7/8 days). The pellets were dispersed in approximately 1 teaspoon of apple sauce (subjects ≥3 months of age) or emptied into a funnel pan and administered through a specially designed adapter (subjects ≥1 month to <3 months of age). Four different capsules (1.5 mg, 2.5 mg, 5 mg and 10 mg) were used in combination to achieve a dose as accurate as possible.

Batch numbers were H1539-01-01-01, H1538-01-01-01, H1504-01-01-02 and H1221-02-01-05 for the 1.5 mg, 2.5 mg, 5 mg and 10 mg esomeprazole capsules, respectively.

Duration of treatment

Once daily oral doses of the investigational product were given during 7/8 days.

Variables

- **Pharmacokinetic**

- AUC_τ the area under the plasma concentration versus time curve during a dosage interval (24 hours) (*primary variable*)

- AUC_t the area under the plasma concentration versus time curve from zero to the last quantifiable concentration, calculated by log/linear trapezoidal method (*primary variable*)

- C_{SSmax} the observed maximum plasma concentration (*primary variable*)

- t_{max} the time to reach C_{max}
- $t_{½}$ the plasma elimination half-life, calculated by ln2/λ

- **Pharmacodynamic**

- The percentage of time with intragastric pH >4 during the 24-hour period (*primary variable*)
- Median intragastric pH during the 24-hour period
- The percentage of time with intra-esophageal pH <4 during the 24-hour period
- Number of reflux episodes during the 24-hour period. The reflux episode is defined as an intra-esophageal pH <4 lasting longer than 5 seconds, or if pH is already below 4, a further drop of at least 1 pH unit
- Number of reflux episodes longer than 5 minutes during the 24-hour period
- Gastroesophageal reflux (GER) score (number of reflux episodes + 4 x number of reflux episodes longer than 5 min)
- Symptom scores for vomiting, crying and gagging, respectively and combined
- Visual analogue scale for overall symptom intensity
- Weight

- **Safety**

Adverse Events (AEs), laboratory measurement, weight, height, head circumference, pulse and breathing rate

Statistical methods

The conclusions of the pharmacodynamic and pharmacokinetic analyses are based on the intention to treat (ITT) population.

Pharmacokinetic variables

The log transformed variables AUC , AUC_t, C_{max} and $t_{½}$ were analysed using an ANOVA model. The estimates, ratios (difference between treatments) and 95% confidence intervals for the true geometric means are presented.

The metabolites were analysed in the same way as the main compound and the ratios between esomeprazole and its metabolites are also given.

The relationship between exposure (AUC_t and C_{max}) and age, weight, intragastric pH and dose as well as the relationship between the ratio of esomeprazole and its metabolites and age and weight were investigated.

Individual values and descriptive statistics are given for all pharmacokinetic variables.

Pharmacodynamic variables

The percentage of time with intragastric pH >4 during the 24-hour period following drug administration was analysed using an ANOVA model.

The change in percentage of time with intragastric pH>4 during the 24-hour period from pre-entry to that after 1 week of treatment was analysed using an ANOVA model, with the pre-entry values used as a covariate.

The percentage of time with esophageal pH <4 during the 0 to 24-hour period following drug administration was analysed in the same way as intragastric pH.

Symptoms recorded on the diary cards are presented descriptively.

The results of the parent's assessment of the global severity of the child's symptoms are presented as the proportion of subjects with improved health.

Individual values and descriptive statistics are given for all pharmacodynamic variables.

Safety evaluation

Adverse events, laboratory variables, weight, height, head circumference, pulse and breathing rate are presented descriptively for the safety population.

Subject population

Number of subjects:

- enrolled = 107
- randomised = 50 (43 were ≤12 months of age [9 were <3 months of age], 7 were >12 months of age)
- completed = 45 (39 were ≤12 months of age, 6 were >12 months of age)
- discontinued = 5

The baseline demographics for randomised subjects in the 2 dosage groups were comparable.

Summary of pharmacokinetic results

The median time to reach the maximum plasma concentration (t_{max}) of esomeprazole was approximately 2 hours for the 0.25 mg/kg dose and 3 hours for the 1.0 mg/kg dose group. There was a large interindividual variability in $AUC_{t,}$ AUC_{τ} and C_{SSmax} of esomeprazole for both the 0.25 mg/kg and 1.0 mg/kg doses, and the variability seemed to be larger in the younger children. Numerically there was a larger than proportional increase in AUC_t, AUC_{τ} and C_{SSmax} with dose, even though not statistically significant (Table S 1). The geometric mean half-life was similar for the 2 dose-groups, 0.8 and 1 hours for the 0.25 mg/kg and 1.0 mg/kg dose, respectively.

Table S 1 Estimated geometric mean and 95% CI for pharmacokinetic variables, esomeprazole, ITT

Variable		Estimated	95% confidence interval	
		Mean	Lower	Upper
AUC_t (µmol*h/L)*	Esomeprazole 0.25 mg/kg (n=17)	0.24	0.12	0.48
	Esomeprazole 1.0 mg/kg (n=18)	1.79	0.90	3.56
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	7.62	2.85	20.40
AUC_{τ} (µmol*h/L)	Esomeprazole 0.25 mg/kg (n=9)	0.65	0.27	1.57
	Esomeprazole 1.0 mg/kg (n=7)	3.51	1.28	9.59
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	5.42	1.42	20.73
C_{SSmax} (µmol/L)	Esomeprazole 0.25 mg/kg (n=17)	0.17	0.09	0.31
	Esomeprazole 1.0 mg/kg (n=17)	0.85	0.45	1.60
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	5.08	2.09	12.35
$t_{½}$ (h)	Esomeprazole 0.25 mg/kg (n=9)	0.77	0.55	1.08
	Esomeprazole 1.0 mg/kg (n=8)	0.95	0.66	1.35
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	1.23	0.75	2.00

*In the 0.25 mg/kg dose group there is 1 subject with all samples below LOQ and therefore no PK-variables could be calculated. This subject is therefore not included in the calculation of the estimated geometric means or ratios between doses.

Summary of pharmacodynamic results

The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group on Day 7/8. Statistically, the increase was significantly higher with the esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg dose.

At baseline, the mean percentage of time with intra-esophageal pH <4 was 11.6% in the esomeprazole 0.25 mg/kg dose group and 12.5% in the 1.0 mg/kg dose group. After 7/8 days of treatment with esomeprazole 0.25 mg/kg or 1.0 mg/kg, these values decreased to 8.4% and 5.5%, respectively. There was no statistically significant difference in the decrease in the percentage of time with intra-esophageal pH<4 between the 2 dosage groups.

The proportion of subjects improving after 1 week´s treatment (as assessed by the parent) was 77% and 62% in the 0.25 mg/kg and 1.0 mg/kg group, respectively.

Summary of pharmacokinetic/pharmacodynamic correlations

A positive correlation between both AUC_t and C_{SSmax} of esomeprazole and the percentage of time with an intragastric pH>4 could be seen in the study.

Summary of safety results

Esomeprazole in doses of 0.25 mg/kg and 1.0 mg/kg was well tolerated. The occurrence of adverse events was similar in the treatment groups. One subject discontinued use of the investigational product due to an adverse event (DAE), irritabillity. No serious adverse events (SAEs) were reported. There were no clinically important trends within or between treatment groups with respect to laboratory variables, vital signs or physical findings.