Drug Substance(s)	Esomeprazole	**SYNOPSIS**	(For national authority use only)
Study Code	SH-NEC-0002		
Date	10 January 2007		

An Open Single-centre Study on the Pharmacokinetics and Pharmacodynamics of Esomeprazole After Once Daily Oral Administration for 7 Days in Preterm Infants and Neonates

Study dates		**Phase of development**
First patient enrolled	2 June 2004	Therapeutic exploratory
Last patient completed	8 March 2006	

Objectives

The primary objective was to assess the pharmacokinetics of esomeprazole and its effect on intragastric pH in preterm infants and neonates.

The secondary objectives were:

- to assess the effect of esomeprazole on esophageal acid exposure secondary to gastroesophageal reflux (GER) using 24 hour pH monitoring and intraluminal impedance measurements
- to assess the safety and tolerability of esomeprazole in preterm infants and neonates
- to assess the ability of esomeprazole to reduce symptoms suggestive of gastroesophageal reflux disease (GERD) in preterm infants and neonates

Study design

This was an open study conducted at 1 centre, where the investigational product, ie, esomeprazole 0.5 mg/kg, was administered once daily (od) for 7 days.

Target patient population and sample size

The patient population comprised pre-term infants and neonates (gestational age ≥32 weeks and <1 month post-term, where term is 38 gestational weeks[*]) with symptoms of gastroesophageal reflux disease (GERD) and the diagnosis confirmed by a 24-hour pH-monitoring. The patient's weight had to be ≥1.8 kg and ≤6.5 kg if the patient was to participate in the study.

The aim was to have 24 evaluable patients for the pharmacokinetics in the study. In order to achieve this, and compensate for potential dropouts, it was estimated that 28 patients should be randomised. However, the study was to be terminated as soon as 24 evaluable patients had been reached. The patients were both in- and outpatients.

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

The target dose of the investigational product was 0.5 mg/kg to the patients, with as little deviation as possible using the available strengths of esomeprazole capsules, ie, 1 mg, 1.5 mg and 2.5 mg. Depending on the patient's bodyweight, measured at the pre-entry visit, 3 different strengths of the esomeprazole capsule were given. The investigational products consisted of pellets that were administered od for 7 days orally via a specially designed funnel pan with a black adaptor attached and positioned within a teat.

Batch numbers were H 1692-01-01-01, H 1539-01-01-02 and H 1538-01-01-02 for the 1 mg, 1.5 mg and 2.5 mg esomeprazole capsules, respectively.

Duration of treatment

One treatment period of 7 days.

Variables

- **Pharmacokinetic**

  Area under the plasma concentration versus time curve within a dosing interval at steady-state (AUC_{τ}, in the protocol referred to as AUC, ie, area under the plasma concentration versus time curve) *(primary variable)*, apparent clearance, ie, oral clearance (CL/F), apparent volume of distribution, ie oral volume of distribution (V/F), plasma elimination half-life ($t_{½}$)

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[*] 38 gestational weeks = 38 weeks after conception, ie, conception is defined as 2 weeks after the first day of the mother's last menstruation. Hence, the upper age limit for inclusion in the study was a corrected age of <44 complete weeks after the first day of the mother's last menstruation.

The maximum plasma concentration at steady state ($C_{ss,max}$, in the protocol referred to as C_{max}, ie, the maximum plasma concentration at steady-state) and the time at which $C_{ss,max}$ occurs (t_{max}) were evaluated as well as covariate relationships between pharmacokinetic parameters and patient demographics.

- **Pharmacodynamic**

Intragastric pH measurement

- The percentage of time with intragastric pH>4 during the 24-hour period *(primary variable)*
- Median intragastric pH during the 24-hour period

Esophageal pH measurement

- The percentage of time with esophageal pH<4 during the 24-hour period
- Number of acid reflux episodes during the 24-hour period
- Number of acid reflux episodes longer than 5 minutes during the 24-hour period
- GER score (number of acid reflux episodes + 4 x number of acid reflux episodes longer than 5 min) during the 24-hour period

Intraluminal impedance measurement

- Number and percentage of acid GER episodes (pH<4) during the 24-hour period
- Number and percentage of weak acidic GER episodes (4<pH>7) during the 24-hour period
- Number and percentage of non acid GER (pH>7) during the 24-hour period
- Number and percentage of liquid GER episodes during the 24-hour period
- Number and percentage of gas GER episodes during the 24-hour period
- Number and percentage of mixed gas/liquid GER episodes during the 24-hour period
- Mean bolus clearance time (sec) during the 24-hour period
- Mean acid clearance time (sec) during the 24-hour period
- Mean proximal extent of GER (cm) during the 24-hour period

- **Safety**

Adverse events, laboratory variables, blood pressure, pulse, respiratory rate, head circumference, weight and length.

Efficacy

Frequency of GERD symptoms from symptom assessment charts.

Statistical methods

A Per Protocol approach was used for the statistical analysis.

Pharmacokinetic variables

Empirical Bayes' estimates of the individual pharmacokinetic parameters were generated based on the final structural and variance parameter estimates, the individual covariates and the individual plasma concentration measurements, using NONMEM. The secondary pharmacokinetic variable AUC_τ was calculated based on the individual estimates of oral clearance (CL/F) according to AUC_τ = F x Dose/CL. In addition, individual $C_{ss,max}$ and t_{max} were obtained from simulated individual concentration-time curves. The data were not sufficiently informative regarding individual terminal $t_{1/2}$ and the inter-individual variability in this parameter could therefore not be estimated.

The pharmacokinetic (PK) variables AUC_τ, $C_{ss,max}$ and CL/F were log-transformed. The means were calculated together with symmetric 95% confidence intervals, based on Student's t-distribution. Applying the antilogarithm transformation on the confidence intervals thus obtained, confidence intervals for the geometric means were generated. For the PK variables, lag time (t_{lag}), V/F, t_{max} and absorption rate constant (k_a), the means were calculated together with symmetric 95% confidence intervals based on Student's t-distribution.

Pharmacodynamic variables

The percentage of time with intragastric pH>4 during the 24-hour period following drug administration (or any other pH level and time period) was analysed using a linear mixed model ANOVA (ANalysis Of VAriance) with a fixed factor for Day and patient being treated as a random effect. The mean for each day and the mean difference between Day 7/8 and baseline (pre-entry visit) were estimated together with symmetric 95% confidence intervals, based on Student's t-distribution. The sums of squares of the residuals in the linear model were used to estimate the variance, which was assumed to be equal for both days. P-values for the corresponding tests are also reported.

Median intragastric pH, the percentage of time with esophageal pH<4, the mean bolus clearance time (sec), the mean acid clearance time (sec) and the mean proximal extent of GER (cm) during the 24-hour period were analysed in the same way.

The number of acid reflux episodes, the number of acid reflux episodes longer than 5 minutes during the 24-hour period, GER score (number of acid reflux episodes + 4 x number of acid reflux episodes longer than 5 min), the number and percentage of acid GER episodes (pH<4), the number and percentage of weak acidic GER episodes (4<pH<7), the number and percentage of non-acid GER (pH>7), the number and percentage of liquid GER episodes, the number and percentage of gas GER episodes and the number and percentage of mixed

gas/liquid GER episodes during the 24-hour period are presented as medians and ranges for each day and for the difference between days. The Wilcoxon signed rank sum test has been used to test if there is a statistically significant difference between Day 7/8 and baseline. P-values for the corresponding tests are reported.

Pharmacokinetic/pharmacodynamic relationships

The relationship between PK and PD variables are depicted graphically.

Efficacy

Frequency of GERD symptoms from bedside symptom assessment charts are presented descriptively at baseline and on Day 7/8.

Safety

Adverse events (AEs), laboratory variables, blood pressure, pulse, respiratory rate, head circumference, weight and length are presented descriptively.

Patient population

Number of patients:

- enrolled 38
- randomized: 26 (11 males, 15 females)
- discontinued: 1 (male)
- completed: 25 (10 males, 15 females)
- All randomized patients were Caucasians except 1 who was Oriental.

Summary of pharmacokinetic results

The estimated geometric mean for AUC_{τ} of esomeprazole was 2.5 µmol*h/L (median 3.4 µmol*h/L) and the individual estimates ranged between 0.2 µmol*h/L and 6.6 µmol*h/L.

The model for esomeprazole pharmacokinetics predicts the maximum concentration ($C_{ss,max}$) to occur approximately 1.5 hours after dose administration. The oral clearance (CL/F) for esomeprazole was estimated to 1.9 L/h, which corresponds to 0.6 L/h/kg, when corrected for the median body weight in the pharmacokinetic study population (n=24). The inter-individual variability (IIV) in CL/F was estimated to 98% (given as coefficient of variation), and the individual CL/F-estimates ranged between 0.52 and 21 L/h. None of the studied covariates were found to be predictive for the variability in CL/F between individuals.

Summary of pharmacodynamic results

The mean percentage of time with intragastric pH>4 during the 24-hour recording was 45.1% at baseline and 84.7% on Day 7/8, and the increase was statistically significant. A statistically

significant increase was also observed for the 24-hour median intragastric pH, from a mean value of 3.7 at baseline to 6.1 on Day 7/8.

The mean percentage of time with esophageal pH<4 during 24-hour baseline recording was 15.7% and there was a statistically significant decrease in the mean value to 7.1% on Day 7/8.

There was a significant reduction from baseline to Day 7/8 in both the number of acid reflux episodes and the acid clearance time during the 24-hour pH-impedance monitoring. On the other hand, there was no major change in the number and type (liquid, gas, mixed) of reflux episodes during the 24-hour pH-impedance monitoring. In addition, no major change in the proximal extent of the refluxate and the bolus clearance time during the 24-hour pH-impedance monitoring was observed.

Symptoms associated with GERD were reported for all patients at baseline as well as after repeated treatment with esomeprazole. However, frequent symptom reporting occurred for substantially fewer patients on Day 7/8 compared with baseline (11 times or more during the 24 hour observation period).

Summary of pharmacokinetic/pharmacodynamic correlations

The percentage of time with intragastric pH >4 seems to be positively related to AUC_τ of esomeprazole

Summary of safety results

Esomeprazole 0.5 mg/kg was well tolerated throughout the study. The occurrence of AEs reported was within an acceptable level (10 of the 26 patients had in total 17 AEs) and none of the AEs were judged by the investigator to have any relation to the investigational product. There were no discontinuations due to AEs or any AEs classified as Other Significant AEs (OAEs).

No SAEs occurred during the treatment period. However, 1 SAE was reported during the follow-up period, which was 10 days after end of treatment, when a hospital visit was made by 1 patient after developing an acute respiratory illness (diagnosis=pertussis). Despite this incident the patient completed the study. In addition, 1 SAE (respiratory illness) was also reported post-study.

There were no findings in vital signs, physical exam and laboratory variables, vital signs that raised any safety concerns.