OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA 21-957 / (b) (4)	Submission Date(s): December 18, 2008
Brand Name	Nexium®
Generic Name	Esomeprazole
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OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	AstraZeneca
Submission Type; Code	Supplements
Formulation; Strength(s)	NDA 21-153 Nexium® (esomeprazole) Delayed-Release Capsules NDA 21-957 Nexium® (esomeprazole) For Delayed-Release Oral Suspension NDA 22-101 Nexium® (esomeprazole) For Delayed-Release Oral Suspension 10 mg base / packet
Indication	(b) (4) Gastroesophageal Reflux Disease (GERD)

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1 Executive Summary

Regulatory History: The Agency issued a Pediatric Written Request (PWR) for esomeprazole to AstraZeneca on December 31, 2001. There were six studies requested in the PWR, of which the studies for ages 1 to 16 years have previously been reviewed by the Agency. For the age group 12 to 16 years, AstraZeneca submitted studies D9614C00094 and D9614C00098 for the evaluation of PK and safety, respectively. AstraZeneca submitted three studies for the age group 1 to 11 years; Study D9614C00007 for single-dose PK, D9614C00099 for multiple-dose PK, and D9614C00097 for the exposure/response component.

Current Submission: For this supplement, AstaZeneca submitted three studies; SH-NEC-0001 assessed the PK/PD in infants 1 to 11 months, D9614C00096 assessed the safety and efficacy in infants 1 to 11 months, and SH-NEC-0002 which assessed the PK/PD in neonates less than 44 weeks of corrected age. The Pediatric Exclusivity Board meeting for NDA 22-101, 21-153, & 21-957 was held April 6, 2009 and it was concluded that the submitted studies met the PWR requirements. It should be noted that pediatric exclusivity was granted for Prilosec® (racemate omeprazole) in 2001 for use in pediatric patients 2 years and up. As such, any additional exclusivity for Nexium can only be granted for use in patients under 2 years of age if safety and efficacy are found to be acceptable for the corresponding age range.

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective. The sponsor is not requesting the GERD indication for neonates or infants (b) (4) however, OCP recommends language to be inserted in the label regarding the PK/PD results.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Study Formulation: The product used in the infant and neonate PK studies was identical to the enteric-coated esomeprazole pellets used in commercially available Nexium Delayed-Release Capsules and Oral Suspension in the US. Capsules containing different fill weights of esomeprazole pellets were used in all three studies; however, the capsules served only to package the esomeprazole pellets. For administration, the capsules were opened up and the esomeprazole pellets were emptied into a funnel pan and mixed with either applesauce (for patients > 3 months of age) or a mixture of 5 mL of water and excipient granules (for patients ≤ 3 months of age). In the clinical study

(D9614C00096) the esomeprazole pellets were always mixed with a sachet of excipient granules in the funnel pan before use.

(A) Neonates

Pharmacokinetics: The PK of esomeprazole was evaluated in 24 neonates who received 0.5 mg/kg/day for 7 days. Study SH-NEC-0002 was designed to study repeat doses of esomeprazole; therefore, no blood samples were drawn for PK assessment following a single oral dose. The oral clearance for esomeprazole in neonates was approximately 1.9 L/h (range 0.52 to 21 L/h) with a large CV of 98%. When corrected for weight, clearance in neonates was approximately 0.6 L/h/kg. **(b) (4)**

The geometric mean AUC_{tau} was 2.5 µmol*h/L (range 0.2 to 6.6 µmol*h/L). Mean esomeprazole exposure in neonates who received 0.5 mg/kg/day is less than the exposure in infants who received 1 mg/kg/day (3.51 µmol*h/L), children 1 to 11 years who received 10 or 20 mg/day (3.7 to 6.28 µmol*h/L), adolescents who received 20 or 40 mg/day (3.65 to 13.9 µmol*h/L), and adults who received 20 or 40 mg/day (4.21 to 12.8 µmol*h/L).

Note that the approved doses for GERD in adults and pediatric patients aged 1 year and up are as follows: 1-11 years: 10 or 20 mg
12-17 yrs: 20 or 40 mg
Adults: 20 or 40 mg

Esomeprazole exposure across age groups.

	<1 month[a]	1 to 11 months[b]		1 to 5 years[c]		6 to 11 years[c]		12 to 17 years[d]		Adults[e]	
	0.5 mg/kg (n=24)	0.25 mg/kg (n=13)	1.0 mg/kg (n=16)	5 mg (n=6)	10 mg (n=8)	10 mg (n=7)	20 mg (n=6)	20 mg (n=14)	40 mg (n=14)	20 mg (n=36)	40 mg (n=36)
Mean dose (mg/kg)	0.48	0.27	0.99	0.26	0.71	0.34	0.71	0.37[f]	0.62[f]	0.25[f]	0.49[f]
Median BW (kg)	2.9	6.5	7.8	19.6	14.5	30.0	29.1	53.4	64.1	81.0	81.0
Geomean (range) AUC (µmol*h/L)	2.45[g] (0.21-6.57)	0.87[gh] (0.09-4.55)	3.51[gh] (0.82-16.7[j])	0.74[i] (0.42-1.39)	4.83 (2.60-10.9)	3.70 (1.36-6.86)	6.28 (3.80-10.7)	3.65 (1.75-9.24)	13.9 (6.72-26.7)	4.21 (0.89-14.9)	12.8 (3.97-25.6)
Geomean (range) C_{SSmax} (µmol/L)	0.74 (0.10-1.50)	0.16 (0.01-1.69)	0.87 (0.22-9.32*)	0.62 (0.34-1.25)	2.98 (2.23-4.04)	1.77 (0.59-3.20)	3.73 (2.49-5.75)	1.45 (0.18-4.13)	5.13 (1.89-8.32)	2.11 (0.51-4.78)	4.74 (1.59-9.61)

[a] Data derived from SH-NEC-0002 (Module 2.5.4.2).
[b] Data derived from SH-NEC-0001 (Module 3.5.4.1).
[c] Data derived D9614C00099.
[d] Data derived from D9614C00094.
[e] Data derived from SH-QBE-0008.
[f] Calculated as Dose (mg)/Median BW.
[g] AUC_{τ}.
[h] n=7.
[i] n=5.
[j] The maximum value was observed for patient No. 33 (see Section 3.1.1).
BW = Body weight.
Geomean = Geometric mean.

Exposure/pharmacodynamic relationship: Among subjects with an AUC > 1 µmol*h/L, **(b) (4)**

(b) (4)

(B) Infants

Pharmacokinetics: The PK of esomeprazole was evaluated in 13 infants who received 0.25 mg/kg/day and in 16 infants who received 1.0 mg/kg/day for 7 days. The study included infants from one month to 24 months of age, inclusive. Like the neonate study, study SH-NEC-0001 was designed to study repeat doses of esomeprazole; therefore, no blood samples were drawn for PK assessment following a single oral dose. There was a large interindividual variability in the AUC_{tau}, AUC_t and C_{SSmax} for both the 0.25 and 1.0 mg/kg dose groups. The geometric mean AUC_{tau} was 0.65 µmol*h/L (95% CI 0.27 to 1.57 µmol*h/L) and 3.51 µmol*h/L (95% CI 1.28 to 9.59 µmol*h/L) for the 0.25 and 1.0 mg/kg dose groups, respectively.

Mean esomeprazole exposure in infants who received 1.0 mg/kg/day is similar to children 1 to 11 years who received 10 mg/day (3.7 to 4.83 µmol*h/L), adolescents who received 20 mg/day (3.65 µmol*h/L), and adults who received 20 mg/day (4.21 µmol*h/L). Infants who received 0.25 mg/kg/day had exposures that were significantly less than those in all other groups except children 1 to 5 years of age who received 5 mg/day (0.74 µmol*h/L), a dose that is lower than the approved dose in children weighing < 20kg. See table above for exposure across different age groups. Modeling shows that esomeprazole CL in this age group is a function of both age and weight (see Appendix 2, page 11). (b) (4)

Exposure and Pharmacodynamic Relationship

The percentage of time intragastric pH exceeds 4 over the 24-hour dosing interval is significantly higher in the high-dose group relative to the low-dose group (69.25% vs 47.91%; p=0.0009). The change in percentage of time intragastric pH > 4 from baseline to Day 7/8 was also significantly higher in the high-dose group (increase of 40.6%) relative to the low-dose group (increase of 14%). The increase in the high-dose groups is similar to pharmacodynamic effect seen in adults. The percentage of time esophageal pH < 4 during the 24-hour dosing interval decreased in both dose groups; however, the difference between the two groups was only significant if infants older than 12 months were excluded from the analysis. (b) (4)

Dose / Exposure and Efficacy

In the infant PK/PD study, the proportion of subjects improving after 7 days of treatment (assessed by the parent) was 76.9% and 62.5% in the 0.25 and 1.0 mg/kg/day dose groups, respectively. Therefore, despite the clear difference in pharmacodynamic effect between the two dose groups, a dose-response effect cannot be identified in this 7-day PK/PD study. In the efficacy study (D9614C00096), there was only one dose per weight group and there was no PK component to the study from which to draw exposure/response conclusions. (b) (4)

Conclusions from Pharmacometrics regarding combined data from neonates and infants

(b) (4)

2 Question Based Review

2.1 General Attributes

What is the regulatory background?

The Agency issued a Pediatric Written Request (PWR) for esomeprazole to AstraZeneca on December 31, 2001. There were six studies requested in the PWR, of which the studies for ages 1 to 16 years have previously been reviewed by the Agency.

For this supplement, AstaZeneca submitted three studies; SH-NEC-0001 assessed the PK/PD in infants 1 to 11 months, D9614C00096 assessed the safety and efficacy in infants 1 to 11 months, and SH-NEC-0002 which assessed the PK/PD in neonates less than 44 weeks of corrected age. With the submission of these three studies, the sponsor has fulfilled the requirements of the PWR and an additional period of exclusivity may be granted.

The formulations of Nexium® Delayed-Release Capsules and Nexium® Delayed-Release Oral Suspension are approved in adults and pediatric patients 1-17 years of age for the treatment of GERD, risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

What were the esomeprazole dosage and route of administration studied in neonates and infants?

Neonates were administered a dose of 0.5 mg/kg/day orally via a funnel pan attached to a teat for ingestion. Infants received a dose of either 0.25 or 1 mg/kg/day administered orally by mixing with either applesauce (for patients > 3 months of age) or a mixture of 5 mL of water and excipient granules (for patients ≤ 3 months of age). The product used in the infant and neonate PK studies was identical to the enteric-coated esomeprazole pellets used in commercially available Nexium Delayed-Release Capsules and Oral Suspension in the US. Capsules containing different fill weights of esomeprazole pellets were used in all three studies; however, the capsules served only to package the esomeprazole pellets.

What is the proposed mechanism of action and indication for esomeprazole in infants and neonates?

Esomeprazole irreversibly inhibits the gastric proton pump, which reduces gastric acid production resulting in an increase in gastric pH. The clinical trial in infants (b) (4)

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Both of the PK/PD studies performed in infants and neonates were multiple-dose studies; however, infants were randomized to one of two dose groups (0.25 or 1.0 mg/kg) while all neonates received the same dose (approximately 0.5 mg/kg). The infant study was designed to be able to obtain full PK profiles for each infant while the neonate study was designed to collect sparse PK data that would then be incorporated into a population model. The efficacy study was a double-blind, treatment-withdrawal design in infants with clinical diagnosis of GERD. As opposed to the standard dose in the PK study, infants in the clinical study were assigned to one of three doses by weight group. On average, the infants in the efficacy study received a lower dose than the infants in the PK study (0.88 vs. 1.0 mg/kg in the efficacy and PK studies, respectively).

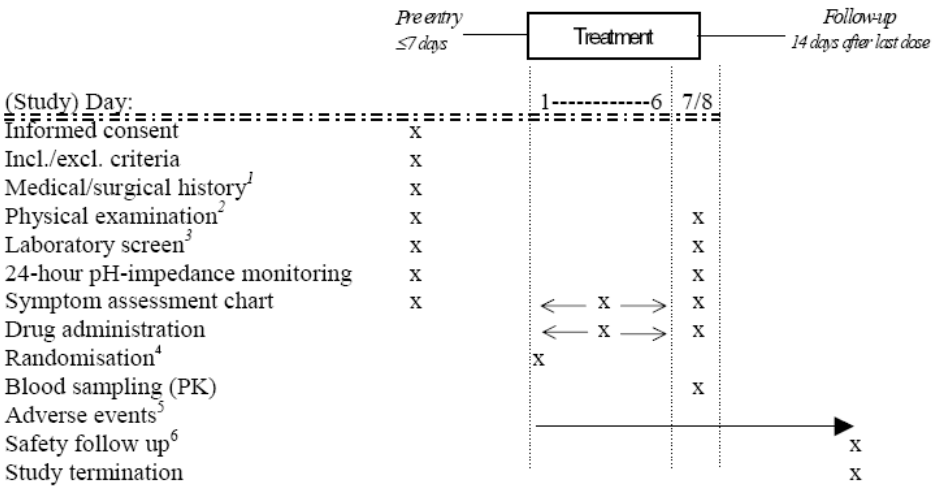
(b) (4)

A more detailed description of each of the studies is included below.

<u>Neonate study (SH-NEC-0002)</u>

This study was an open-label study in preterm infants and neonates (gestational age ≥32 weeks and < 1 month post-term) with symptoms of GERD. To participate, neonates had to weigh from 1.8 kg to 6.5 kg. Subjects received approximately 0.5 mg/kg of esomeprazole orally once daily for 7 days. All subjects were followed for 14 days after the last dose as a safety follow-up. Investigators drew blood for PK assessment on Day 7 only. Neonates had blood drawn at 4 time points following esomeprazole administration on Day 7/8. Population PK was utilized to assess the data collected from these neonates.

Neonate study flow chart.



1) = Including past and current medication
2) = Including weight, length, head circumference, blood pressure (BP), pulse and respiratory rate. The second physical examination may have been carried out after last PK blood sample on Day 7 or on Day 8 at the time the pH probe was removed.
3) = Including haematology, serum chemistry and urine dipstick. The laboratory screen on Day 7 was performed in connection with the collection of the first PK blood sample.
4) = Allocation to PK schedule
5) = AEs in patients were collected during the whole study after the first administration of esomeprazole. Any unresolved AE at the time the patient completed or discontinued the study were followed up by the investigator for as long as medically indicated
6) = Safety follow-up of all patients was made 14 days after the last dose of investigational product.

Infant study (SH-NEC-0001)

This study was similar to the neonate study but included two dose groups. No minimum or maximum weight was specified in the protocol. Subjects received either 0.25 or 1.0 mg/kg esomeprazole orally once daily for 7 days. Esomeprazole was administered by the parent/guardian for subjects ≥ 3 months of age but was administered by study personnel for subjects 1 to < 3 months of age. Parents assessed symptoms throughout the study period including the two days prior to the first dose of esomeprazole. Blood was collected at 6-8 time points and a standard PK approach was used in the analysis.

Infant study flow chart.

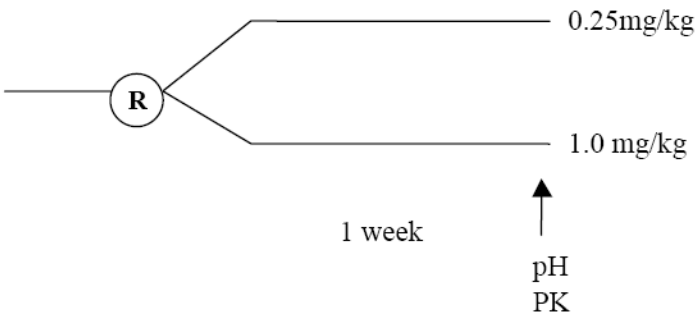


Table 1 Study Procedures

Study Day	Pre-entry	-2	1-6	7/8
Visit number	1	2		3
Informed consent	X			
Medical/surgical history[a]	X			
Routine lab tests[b]	X			X
Physical examination[c]	X			X
24-hour pH-monitoring study	X			X
Drug dispensed		X		
Drug dosing			X	X
PK blood samples				X
Adverse Event recording				X
Symptom diary	X[d]	X[d]	X	
Visual analogue scale		X		X

a Including past and current medication.
b Including haematology, serum chemistry and urine dip stick.
c Including weight, height, head circumference, pulse and breathing rate.
d Start of symptom assessments at least 2 days before first dose.

The safety and efficacy study (D961400096) was a double-blind, placebo-controlled, treatment-withdrawal study of infants with signs and symptoms of GERD. Only subjects who responded to treatment in the 2-week open-label phase were eligible for the 4-week double-blind treatment-withdrawal phase. The primary efficacy variable was the time from randomization to discontinuation due to symptom worsening. Based upon the results of the infant PK/PD study, a variation of the 1.0 mg/kg dose was chosen for the efficacy study; however, the regimen was simplified by stratifying the infants by weight group; those weighing 3-5 kg were given 2.5 mg of esomeprazole, those > 5 kg to 7.5 kg received 5 mg, and those > 7.5 kg to 12 kg received 10 mg per day. This regimen results in a dosing range of 0.5 mg/kg to 1.33 mg/kg in contrast to the fixed, weight-based dose utilized in the PK/PD studies. On average, the infants in the efficacy study received 0.88 mg/kg compared to 1.0 mg/kg in the PK study. This difference in dosing between the PK study and the clinical study is not likely to have had a significantly negative impact on the clinical study results.

2.2.2 What is the basis for selecting the pharmacodynamic and clinical endpoints and how are they measured in the clinical pharmacology studies?

The parameters evaluated for both the PK/PD studies were the AUC_{tau}, AUC_t (infant only), $C_{ss,max}$ (infant only), and the % time intragastric pH > 4 during the 24-hour dosing interval on Day 7/8 relative to baseline. The primary PD variable has been shown to be correlated with clinical efficacy in the treatment of GERD in adults[1]. Secondary variables included median intragastric pH, % time esophageal pH < 4 over the 24-hour dosing interval, number of reflux episodes during the 24-hour period, number of reflux episodes lasting longer than 5 minutes, GER score, global severity, weight, and symptom scores for vomiting, crying, and gagging.

For PD parameters, intraluminal impedance (intragastric and esophageal) monitoring was performed for 24-hours at baseline and on Day 7/8. The pH probe was positioned with the esophageal sensor 3 cm above the lower esophageal sphincter (estimated by body length) which was confirmed by X-ray. In addition, symptom assessment charts were completed at baseline and throughout the 7-day study.

[1]Burget DW, *Gastroenterology* 1990;99(2):345-51.

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess the pharmacokinetic parameters?

Yes, refer to 2.6, Analytical Section.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-pharmacodynamic relationships in neonates and infants?

(A) Neonates

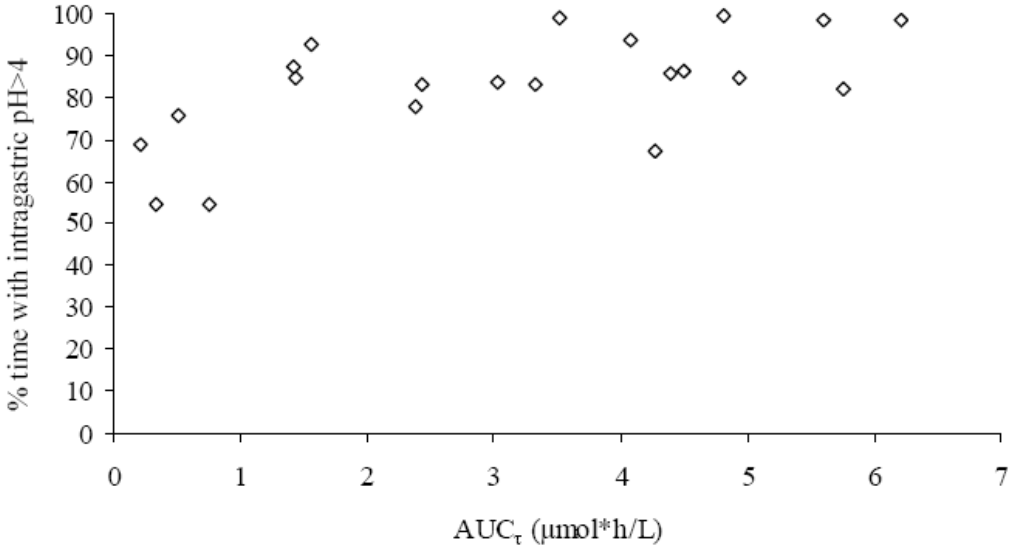
Esomeprazole exposure was characterized in neonates on Day 7 of treatment. Subjects were randomized to one of two PK sampling schemes having blood drawn at four time points each. Due to the limited number of samples from each subject, investigators used population modeling to estimate PK parameters and interindividual variance. This includes the assessment of the primary pharmacokinetic variable, AUC_{tau}. The primary pharmacodynamic variable was the percentage of time intragastric pH>4 over the 24-hour dosing interval. Investigators measured this and other PD variables via intraluminal impedance monitoring for 24 hours at baseline and on Day 7/8. The sensor measured the potential difference between the recording and reference sensors every four seconds. The impedance equipment malfunctioned in several patients but operated successfully in 21 other patients.

Estimated means and 95% CI for percentage of time intragastric pH>4 at baseline and on Day 7/8 in neonates.

Day	Estimate	95% CI		p-value
		Lower	Upper	
Baseline	45.1	37.5	52.7	
Day 7/8	84.7	77.1	92.3	
Day 7/8 - Baseline	39.6	28.9	50.3	<0.0001

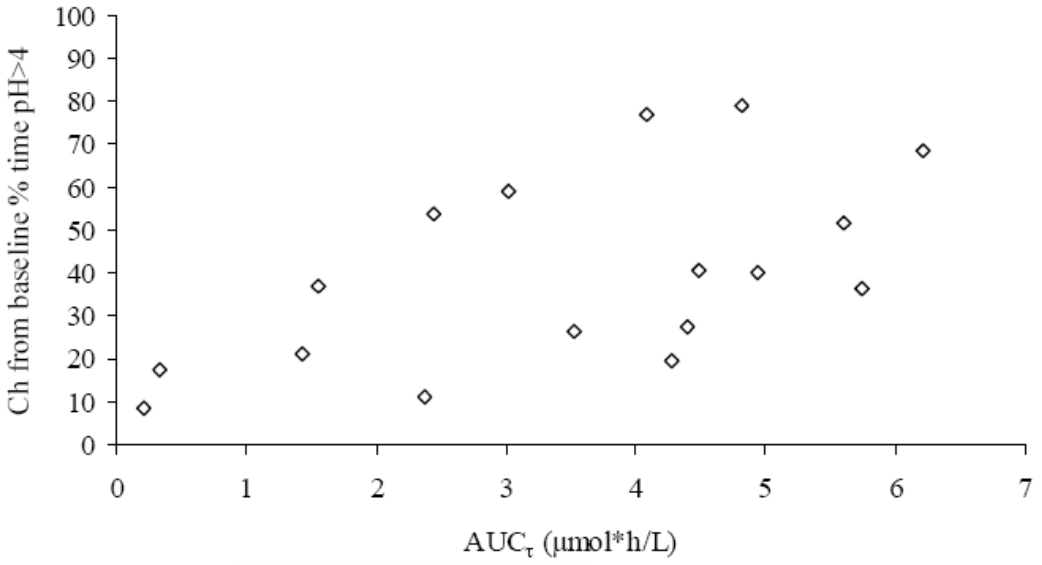
The percentage of time that intragastric pH>4 increases by approximately 40% following 7 days of treatment and the difference (b) (4) . Neonates have a higher pH at baseline compared to other age groups.

The individual percentage of time with intragastric pH>4 during the 24-hour dosing interval on Day 7/8 versus individual AUC_{tau} of esomeprazole in neonates.



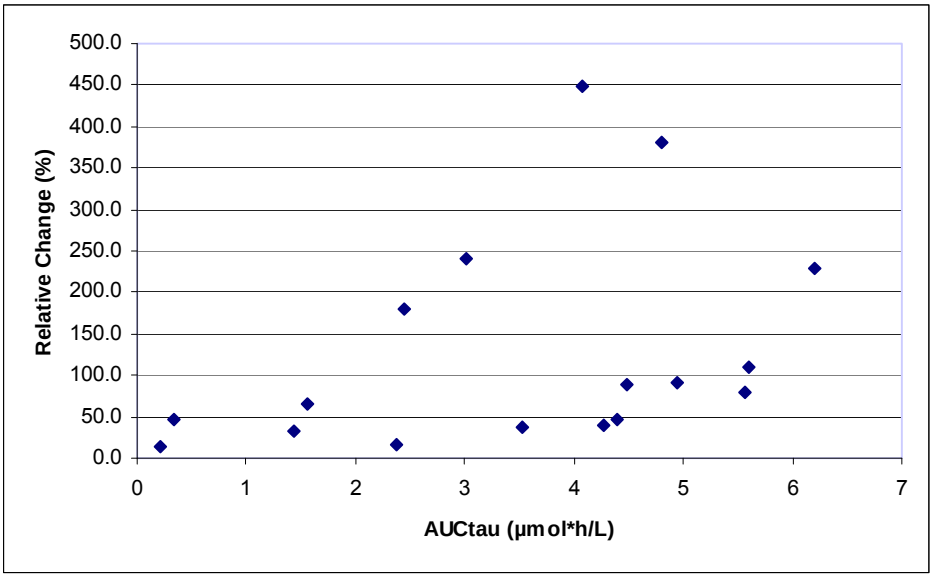
These data show that 16 of 17 neonates with esomeprazole exposure above 1 µmol*h/L have an intragastric pH>4 for approximately 75% or more of the 24-hour dosing interval. Only one of four subjects with an AUC_{tau} <1 µmol*h/L has an intragastric pH>4 for 75% of the 24-hour dosing interval, while the range for the other three subjects is approximately 55 to 70%. There appears to be a flattening of the response curve above 1 µmol*h/L with very little additional benefit amongst the neonates with the highest exposures. This is consistent with combined exposure-response data from neonates and infants (see Appendix 2, Figure 7 on page 15).

The individual *absolute* change from baseline in percentage of time with intragastric pH>4 during the 24-hour dosing interval on Day 7/8 versus individual AUC_{tau} of esomeprazole in neonates.



These data show a (b) (4) between exposure and the change in percentage of time intragastric pH>4 relative to baseline; however, the figure does not differentiate between subjects with high or low baseline values. All subjects experiencing a large increase (>50% change from baseline) had an AUC_{tau} > 2 µmol*h/L. Among the subjects with a change of approximately 20% or less, the AUC_{tau} ranged from 0.21 to 4.81 µmol*h/L. The two subjects with the smallest improvement by Day 7/8 had high baseline values (60.3% and 66.6%). Conversely, the two subjects with the largest improvement by Day 7/8 had very low baseline values (17.1% and 20.7%). When the data is reanalyzed to show the change in percentage from baseline rather than the absolute percentage increase, the relationship between exposure and response is less apparent. See below.

The individual *relative* change from baseline in percentage of <u>time with intragastric pH>4</u> during the 24-hour dosing interval on Day 7/8 versus individual AUC_{tau} of esomeprazole in neonates.



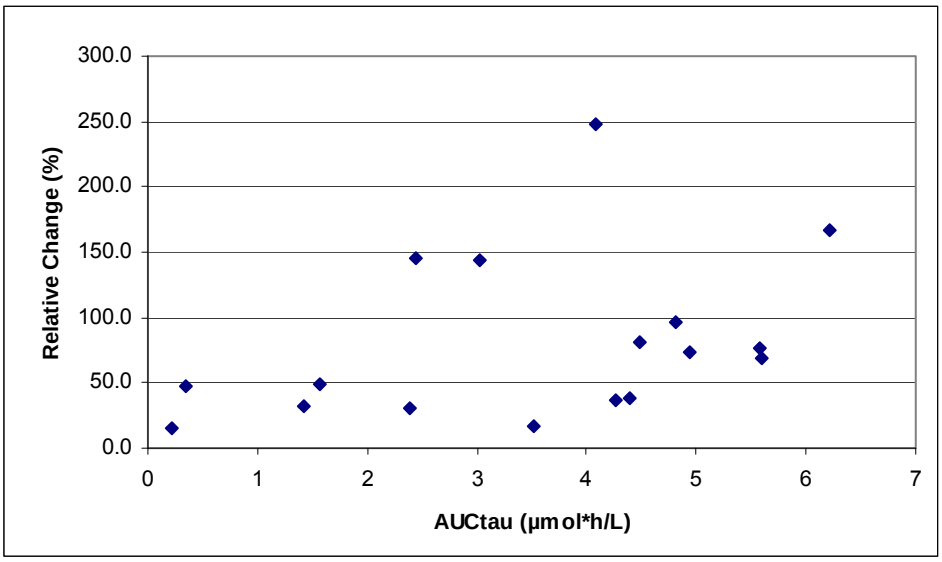
Means and 95% CIs for percentage of time with esophageal pH<4 at baseline and on Day 7/8 in neonates.

Day	Estimate	95% CI		p-value
		Lower	Upper	
Baseline	15.7	12.7	18.8	
Day 7/8	7.1	4.0	10.1	
Day 7/8 - Baseline	-8.6	-11.8	-5.5	<0.0001

Neonates who received 0.5 mg/kg for 7 days spent approximately half as much time with an esophageal pH<4 relative to baseline and the difference [redacted] (b) (4)

Intragastric pH was measured for 24 hours at baseline and on Day 7/8 in 17 neonates. Baseline pH values ranged from 1.9 to 5.5 (median 3.6) while Day 7/8 values ranged from 4.0 to 6.7 (median 5.9). All subjects experienced an increase in the median intragastric pH on Day 7/8 relative to baseline.

The individual *relative* change from baseline in percentage median intragastric pH during the 24-hour dosing interval on Day 7/8 versus individual AUC_{tau} of esomeprazole in neonates.



The relationship between esomeprazole exposure and median intragastric pH is not clear. Neonates who experienced the largest increases from baseline had esomeprazole exposures exceeding 2 µmol*h/L. [redacted] (b) (4)

(B) Infants

Esomeprazole exposure was characterized in infants on Day 7 of treatment. Investigators drew blood samples at 1, 2, 3, 4, & 6 hours post-dose in infants aged 1 to <3 months and at 0.5, 1, 1.5, 2, 3, 4, & 6 hours post-dose in infants aged 3 to 11 months. In contrast to the neonate study, the samples drawn in the infant study allow for complete PK characterization without the need for population modeling. The primary pharmacodynamic variable was the percentage of time intragastric pH>4 over the 24-

hour dosing interval. Like the neonate study, investigators measured this and other PD variables via intraluminal impedance monitoring for 24 hours at baseline and on Day 7/8.

Mean percentage of time with intragastric pH>4 after one week of treatment in both dose groups.

	Estimated Mean	95% confidence interval Lower	Upper	p-value
Esomeprazole 0.25 mg/kg	47.91	39.35	56.47	.
Esomeprazole 1.0 mg/kg	69.25	60.69	77.82	.
Esomeprazole 1.0 mg/kg-Esomeprazole 0.25 mg/kg	21.34	9.23	33.45	0.0009

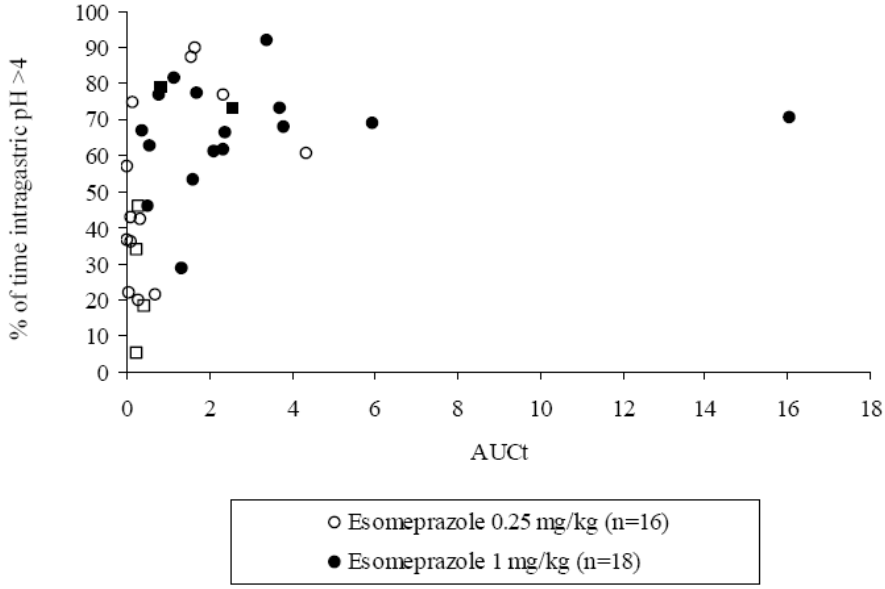
The 0.25 mg/kg group had an intragastric pH<4 for significantly less time than the 1.0 mg/kg group. Baseline values were 33% and 29% for the 0.25 and 1.0 mg/kg groups, respectively; therefore, **(b) (4)**

Change in % time intragastric pH>4 from baseline to Day 7/8 in infants.

	Estimated Mean	95% confidence interval Lower	Upper	p-value
Esomeprazole 0.25 mg/kg	14.00	7.25	20.74	.
Esomeprazole 1.0 mg/kg	40.60	33.86	47.35	.
Esomeprazole 1.0 mg/kg-Esomeprazole 0.25 mg/kg	26.61	17.02	36.20	<0.0001

The 1.0 mg/kg group had an increase in the percentage of time intragastric pH>4 that was significantly higher than the low-dose group. The increase of 40% is similar to the increase seen in neonates who received 0.5 mg/kg.

Percentage of time with intragastric pH>4 versus AUC_t in infants.



o: infants up to 12 months; □: infants older than 12 months

There appears to be wide variability in response for subjects whose AUC on Day 7 was < 2 µmol*h/L while a flattening of the response curve is apparent at or above 2 µmol*h/L.

Although four subjects in the 0.25 mg/kg dose group have AUCs ≥ 2 µmol*h/L by Day 7, the majority (13 of 17, 76%) have an AUC < 1 µmol*h/L. The percent time pH>4 is ≥ 60% in 15 of 18 (83%) of subjects in the 1.0 mg/kg dose group but only 5 of 17 (29%) of the 0.25 mg/kg dose group. The percent time pH>4 is < 30% in 5 of 17 (29%) of the 0.25 mg/kg group but only 1 of 18 (6%) of the 1.0 mg/kg group. In addition, all four of the infants older than 12 months who received 0.25 mg/kg had a percent time pH>4 of < 50%. (b) (4)

For many subjects, AUC_{tau} could not be calculated due to the inability to collect all planned samples, too few samples in the terminal phase, or if ≥ 40% of the AUC was extrapolated. Therefore, the calculation of AUC_t (from 0 to 6 hours) may be misleading as approximately half of the subjects did not meet the criteria for calculation of AUC_{tau}.

Means and 95% CIs for percentage of time with esophageal pH<4 on Day 7/8 in infants by dose group.

	Estimated Mean	95% confidence interval Lower	Upper	p-value
Esomeprazole 0.25 mg/kg	8.42	5.50	11.34	.
Esomeprazole 1.0 mg/kg	5.54	2.55	8.52	.
Esomeprazole 1.0 mg/kg-Esomeprazole 0.25 mg/kg	-2.89	-7.06	1.29	0.1709

Although subjects in the 1 mg/kg group had a lower percentage of time esophageal pH<4 relative to the 0.25 mg/kg group, (b) (4).

Change in percentage of time esophageal pH<4 at baseline and on Day 7/8 per dose group.

	Estimated Mean	95% confidence interval Lower	Upper	p-value
Esomeprazole 0.25 mg/kg	-3.46	-5.83	-1.09	.
Esomeprazole 1.0 mg/kg	-6.72	-9.20	-4.25	.
Esomeprazole 1.0 mg/kg-Esomeprazole 0.25 mg/kg	-3.26	-6.69	0.16	0.0615

Although there was a larger decrease in the percentage of time esophageal pH<4 following 7 days of treatment in the 1 mg/kg group relative to the 0.25 mg/kg group, the difference (b) (4). (b) (4).

Intragastric pH was measured in the 0.25 mg/kg dose group at baseline and on Day 7/8 in 25 and 22 infants, respectively. In the 1.0 mg/kg dose group, intragastric pH was measured at baseline and on Day 7/8 in 23 and 22 infants, respectively. Not all subjects had data available for both time periods. For the 0.25 mg/kg group, median pH at baseline was 2.3 and increased to 3.6 following 7 days of treatment. Of the 21 subjects for whom data is available on both days, 5 did not experience an increase in their median pH. For the 1.0 mg/kg group, median pH at baseline was 2.2 (similar to the 0.25 mg/kg dose group) and increased to 5.6 following 7 days of treatment. The increase in the high-dose group is significantly more than the low-dose group. Although a direct comparison of AUC and change in median intragastric pH was not performed, subjects in the high-dose group had exposures up to 7.6 times that of the low-dose group on average. (b) (4)

Overall Conclusions: (b) (4) [redacted]

2.2.4.2 What are the characteristics of the exposure-safety relationship in neonates and infants?

The medical officer has reviewed the clinical study. There were no safety issues apparent in infants that were not previously observed in other studies in adults. However, the small number of subjects included in these studies precludes a thorough assessment of the safety of this product in children less than one year of age.

(A) Neonate

There is no clear relationship between esomeprazole exposure and adverse events (AEs) or serious adverse events (SAEs) in neonates. Esomeprazole was well tolerated in neonates receiving 0.5 mg/kg for 7 days. Of the 26 subjects, 10 experienced a total of 17 AEs and investigators did not consider these to be related to esomeprazole treatment. Three of these AEs and one SAE occurred during the follow-up period and not on active treatment. The mean AUC_{tau} in 9 (data for one neonate was not available) of the subjects who experienced an AE or SAE was 2.83 µmol*h/L; however, when data from the three subjects who only experienced an AE in the follow-up period is excluded, the mean AUC_{tau} is 4.07 µmol*h/L compared to a mean of 3.65 µmol*h/L in the 15 neonates without any reported AEs.

The most common AEs in neonates were gastrointestinal events, infections of the respiratory tract and skin, followed by other disorders of the respiratory tract. No serious adverse events occurred during the treatment period but one SAE did occur in the 2-week follow-up period. The subject developed an acute respiratory illness and was ultimately diagnosed with pertussis.

Number of neonates with any AE during the treatment period and during follow-up.

System Organ Class Preferred Term	Esomeprazole (n=26)	Follow-up (n=25)
Total no. of patients with AE:	8	4
Cardiac disorders	**2**	**0**
Bradycardia	1	0
Tachycardia	1	0
Eye disorders	**0**	**1**
Eye discharge	0	1
Gastrointestinal disorders	**4**	**0**
Constipation	2	0
Diarrhoea	1	0
Vomiting	1	0
General disorders and administration site conditions	**1**	**0**
Oedema	1	0

Infections and infestations	**0**	**3**
Pertussis	0	1
Respiratory tract infection	0	1
Skin candida	0	1
Investigations	**1**	**0**
Blood urine present	1	0
Respiratory, thoracic and mediastinal disorders	**3**	**0**
Apnoea	2	0
Choking	1	0
Cyanosis neonatal	1	0
Skin and subcutaneous tissue disorders	**1**	**0**
Dermatitis contact	1	0

AEs presented by system organ class, a patient is counted once within the system organ class total and once for each AE belonging to that particular class.

(B) Infants

There does not appear to be a relationship between exposure and the occurrence of AEs in infants; however, no PK data is available for 4 of the 12 subjects who experienced an AE. The 12 subjects who experienced an AE were evenly split between the two dose groups. Furthermore, only two subjects had an AUC_t (4.33 & 5.94 µmol*h/L in the low- and high-dose groups, respectively) that exceeded the mean AUC_t in the 1.0 mg/kg group (2.83 µmol*h/L).

The most common AEs were classified as infections, psychiatric disorders, and gastrointestinal disorders. One subject who received 0.25 mg/kg had moderate neutropenia noted during the follow-up period. Another subject in the 0.25 mg/kg group experienced irritability on the day he started treatment and the symptoms stopped when the subject was withdrawn from the study following four days of treatment. Two subjects in the 1.0 mg/kg group also experienced irritability which started following 2-3 days of treatment but ceased within 1-3 days despite ongoing esomeprazole treatment.

Number of infants with any AE during the treatment period and during follow-up.

System Organ Class Preferred Term	Esomeprazole 0.25 mg/kg (n=26)	Esomeprazole 1.0 mg/kg (n=24)
Total no. of subjects with AE:	***6***	***6***
Infections and infestations	**2**	**2**
Nasopharyngitis	1	2
Urinary tract infection	1	0
Blood and lymphatic system disorders	**1**	**0**
Neutropenia	1	0
Psychiatric disorders	**1**	**2**
Irritability	1	2
Respiratory, thoracic and mediastinal disorders	**0**	**1**
Nasal congestion	0	1
Gastrointestinal disorders	**1**	**2**
Constipation	0	1
Regurgitation of food	0	1
Vomiting	1	1
Skin and subcutaneous tissue disorders	**1**	**1**
Eczema	1	0
Rash	0	1

Overall conclusions: There is no apparent relationship between exposure and the incidence or severity of adverse events in infants and neonates.

2.2.5 What were the demographics of the neonates and infants who participated in the PK/PD studies?

(A) Neonates

Summary of baseline characteristics of the pre-term infants and neonates in study SH-NEC-0002

Statistic	Age (weeks)	Gestational age at birth (weeks)	Weight (g)	Height (cm)	Head circumference (cm)
N	26	26	26	25	26
Mean	7.8	32.1	3018.8	47.4	34.4
SD	4.5	5.0	602.9	4.0	2.0
Min	1.0	23.0	1910.0	40.2	31.0
Median	7.5	31.0	3012.5	48.0	34.5
Max	15.9	41.0	4145.0	54.0	38.0

There were 19 pre-term infants and 7 term infants randomized in the PK study. Subjects ranged in gestational age from 23 to 41 weeks. The corrected age for all pre-term infants was < 43 weeks. All term infants were ≤ 4 weeks of age except one who was 6 weeks old (gestational age 37 weeks at birth). Of the 26 randomized subjects, there were 15 females and 11 males. In addition, 25 were Caucasian and one subject was Asian.

(B) Infants

Summary of baseline characteristics of infants in study SH-NEC-0001

		Esomeprazole 0.25 mg/kg n=26	Esomeprazole 1.0 mg/kg n=24	All n=50
Gender	Male	17(65.4%)	14(58.3%)	31(62.0%)
	Female	9(34.6%)	10(41.7%)	19(38.0%)
Race	Caucasian	25(96.2%)	24(100.0%)	49(98.0%)
	Oriental	1(3.8%)	0(0.0%)	1(2.0%)
Age (months)	≤12 months	22(84.6%)	21(87.5%)	43(86.0%)
	>12 months	4(15.4%)	3(12.5%)	7(14.0%)
	Mean	6.9	7.0	7.0
	SD	5.2	5.5	5.3
	Min	2.3	2.2	2.2
	Max	22.2	23.8	23.8
Height (cm)	Mean	66.5	67.8	67.1
	SD	7.8	8.2	7.9
	Min	56.5	56.0	56.0
	Max	88.0	91.5	91.5
Weight (kg)	Mean	7.4	8.0	7.7
	SD	1.9	2.7	2.3
	Min	4.5	5.2	4.5
	Max	12.0	18.0	18.0
BMI (kg/m^2)	Mean	16.5	17.1	16.8
	SD	1.5	2.0	1.8
	Min	13.4	12.1	12.1
	Max	18.7	21.5	21.5
Head circumference (cm)	Mean	43.1	43.7	43.4
	SD	2.6	3.4	3.0
	Min	38.5	38.5	38.5
	Max	48.5	52.5	52.5

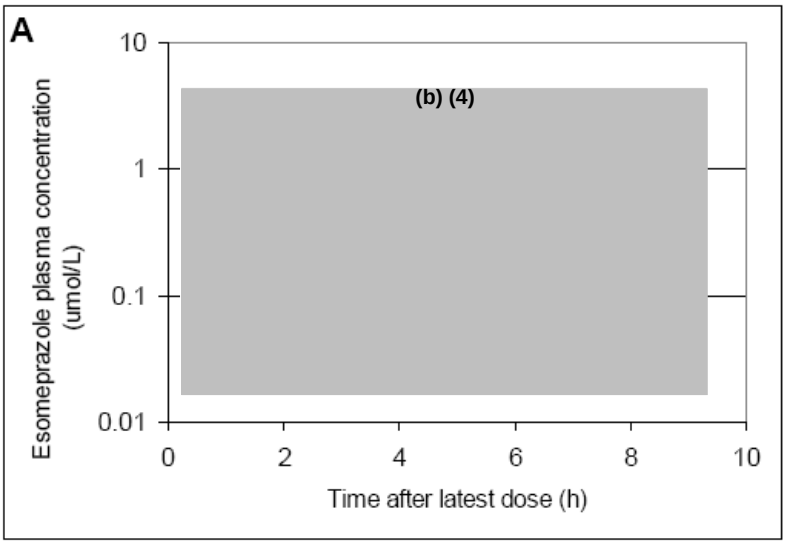
The dose groups were very similar with regard to ethnicity, age, height, weight, BMI, and head circumference. There were slightly more males than females in the 0.25 mg/kg dose groups compared to the 1.0 mg/kg dose group.

2.2.5 What are the PK characteristics of esomeprazole and its metabolites in neonates and infants?

(A) Neonates

Pharmacokinetic data was available from 24 neonates following 7 days of treatment with esomeprazole at a dose of 0.5 mg/kg. Neonates were randomized to one of two blood sampling schedules; 1, 3, 5, & 7 hours post-dose (schedule 1), or 2, 4, 6, & 8 hours post-dose (schedule 2). Population modeling was utilized for the PK evaluation via NONMEM software. The primary PK variable was AUC_{tau} while secondary PK variables were CL/F and V/F.

Observed esomeprazole plasma concentration vs time following 7 days of treatment in neonates. The model prediction for a typical individual is shown by the dark line.



There is wide variability in plasma esomeprazole concentrations in neonates. The estimated geometric mean for AUC_{tau} was 2.5 µmol*h/L (median 3.4 µmol*h/L) with a range of 0.2 to 6.6 µmol*h/L. When compared to infants who received 1.0 mg/kg (AUC 3.51 µmol*h/L), the geometric mean AUC in neonates is approximately 30% lower. The geometric mean $C_{ss,max}$ was 0.74 with a range of 0.10 to 1.50 µmol/L. This is approximately 15% lower than the $C_{ss,max}$ observed in infants receiving 1.0 mg/kg (0.87 µmol*h/L).

Estimated geometric means and 95% CIs for AUC_{tau} (µmol*h/L), estimated $C_{SS,max}$ (µmol/L), CL/F (L/h), t_{max} (h), V/F (L), and t_{lag} (h) of esomeprazole in neonates.

Variable	N	Estimate	95% CI	
			Lower	Upper
AUC_{τ}	24	2.45	1.63	3.68
$C_{ss,max}$	24	0.74	0.54	1
CL/F	24	1.89	1.25	2.85
t_{max}	24	1.65	1.43	1.86
V/F	24	0.99	0.87	1.11
t_{lag}	24	0.61	0.52	0.71

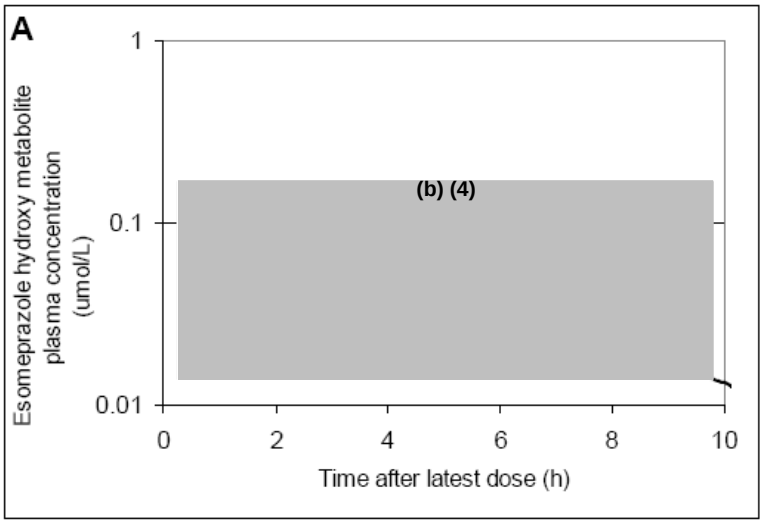
The geometric mean oral clearance for esomeprazole was estimated to be 1.9 L/h (range 0.52 to 21 L/h) with an interindividual variability of 98%. There were two subjects with an estimated CL/F more than two standard deviations above the mean. These subjects were both pre-term, Caucasian females; both with a corrected age of approximately 38 weeks. One of these subjects only had one sample that contained esomeprazole concentration above the lower limit of quantitation (LOQ) and the other only had two samples above the LOQ. These results may indicate that esomeprazole was not ingested properly, poorly absorbed, or rapidly cleared in these two subjects. The estimated V/F of 0.99 L corresponds to approximately 0.33 L/kg when corrected for the mean body weight in the study population. In comparison, adults have a lower V/F of approximately 0.20-0.25 L/kg.

Estimated geometric means and 95% CIs for esomeprazole *5-hydroxy metabolite* PK parameters in neonates.

Variable	N	Estimate	95% CI	
			Lower	Upper
AUC_τ	23	0.44	0.4	0.47
CL/F	23	10.66	9.42	12.07

The esomeprazole 5-hydroxy metabolite is formed via cytochrome P450 2C19. The oral clearance was estimated to be 10.7 L/h with an interindividual variability of 32%. However, this variability may be underestimated as two subjects were found to have no samples above the LOQ and were therefore not included in the analysis. The effect of 2C19 polymorphisms on the formation of the 5-hydroxy metabolite in these patients was not studied; however, 2C19 expression is low for several weeks following birth making it unlikely that a difference in metabolite formation would be identified.

Observed plasma concentration vs time of the *5-hydroxy metabolite* in preterm infants and neonates.



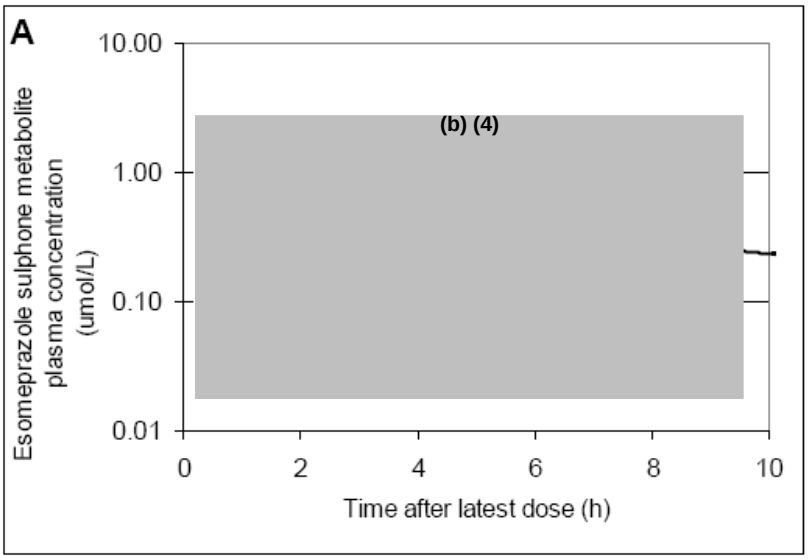
The maximum concentration of the 5-hydroxy metabolite occurred approximately 2 hours post-dose with an estimated $t_{1/2}$ of 3 hours.

Estimated geometric means and 95% CIs for esomeprazole *sulphone metabolite* PK parameters in neonates.

Variable	N	Estimate	95% CI	
			Lower	Upper
AUC_τ	23	4.87	3.23	7.34
CL/F	23	0.95	0.63	1.45

The esomeprazole sulphone metabolite is formed via CYP 3A4. The oral clearance was estimated to be 0.96 L/h with an interindividual variability of 96% and the geometric mean AUC_{tau} was 4.87 µmol*h/L.

Observed plasma concentration vs time of the *sulphone metabolite* in preterm infants and neonates.

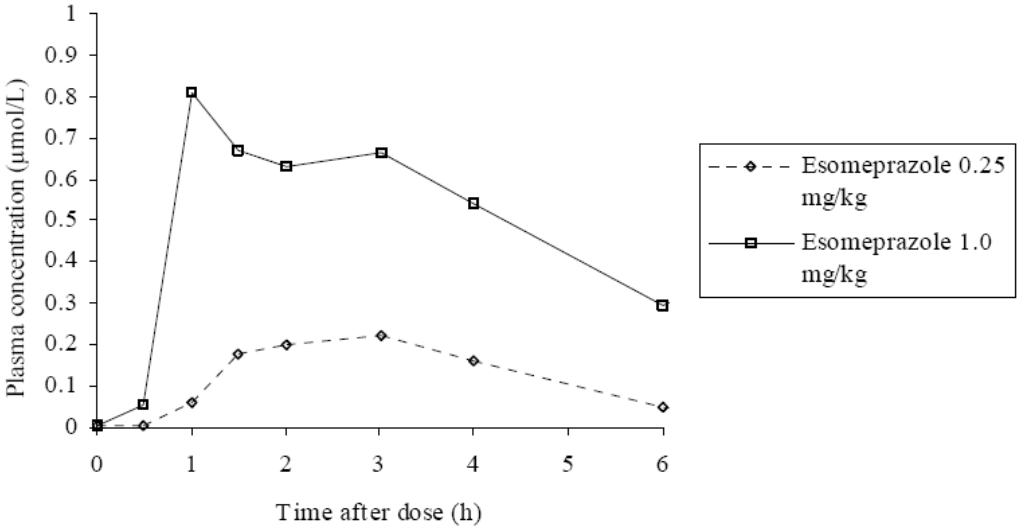


From the plot of individual plasma concentrations it is apparent that formation of the sulphone metabolite is still occurring at 8-hours, the end of the sampling window. Therefore, accurate characterization of the PK of the sulphone metabolite may not be possible within 8 hours of dosing.

(B) Infants

Pharmacokinetic data was available following 7 days of treatment in 17 infants in the 0.25 mg/kg group and in 18 infants from the 1.0 mg/kg group. Subjects 1 to <3 months of age had blood drawn for PK assessment at 1, 2, 3, 4, & 6 hours post-dose while subjects ≥3 months of age had blood drawn at 0.5, 1, 1.5, 2, 3, 4, & 6 hours post-dose.

Mean esomeprazole plasma concentration vs time following 7 days of treatment in infants.



The prominent peak observed in the plasma concentration vs time curve for the 1.0 mg/kg group is strongly driven by one subject (Caucasian male, 8 months old), whose concentration at one-hour was approximately 9 µmol/L. In both groups t_{max} occurred 2-3 hours post-dose.

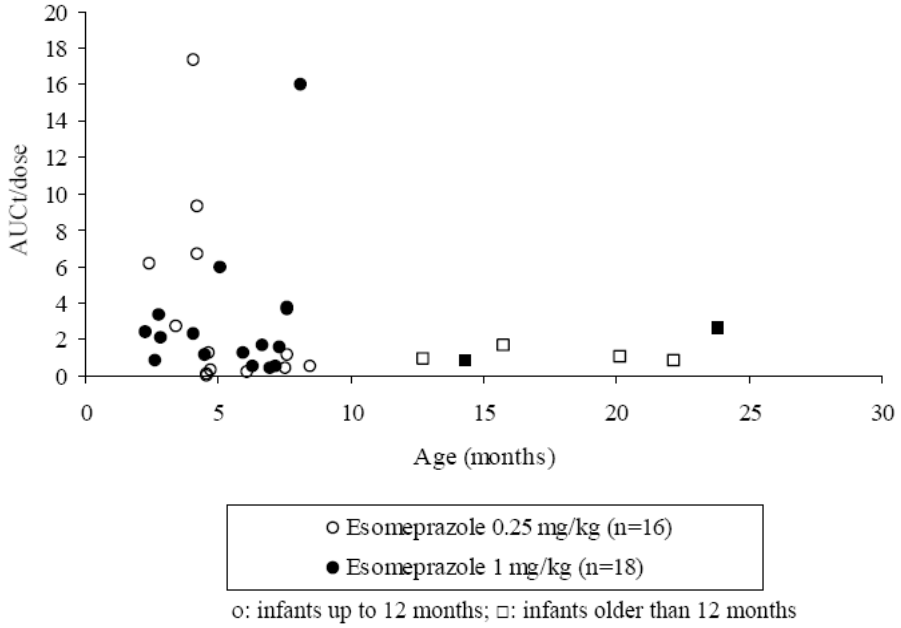
Estimated geometric mean and 95% CI for esomeprazole PK parameters.

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 (Subject 62) 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.

There is a greater than dose-proportional increase in AUC_t, AUC_{tau}, and C_{SSmax} in the high-dose group relative to the low-dose group; however, the differences are not statistically significant. The $t_{1/2}$ is similar between the two groups. Plasma concentrations were below the LOQ for one subject but at least one value above the LOQ was measurable in all others. Geometric mean AUC_{tau} is higher in infants who received 1.0 mg/kg (3.51 µmol*h/L) compared to neonates who received 0.5 mg/kg (2.45 µmol*h/L).

Dose-normalized AUCt of esomeprazole vs age (months) in infants.

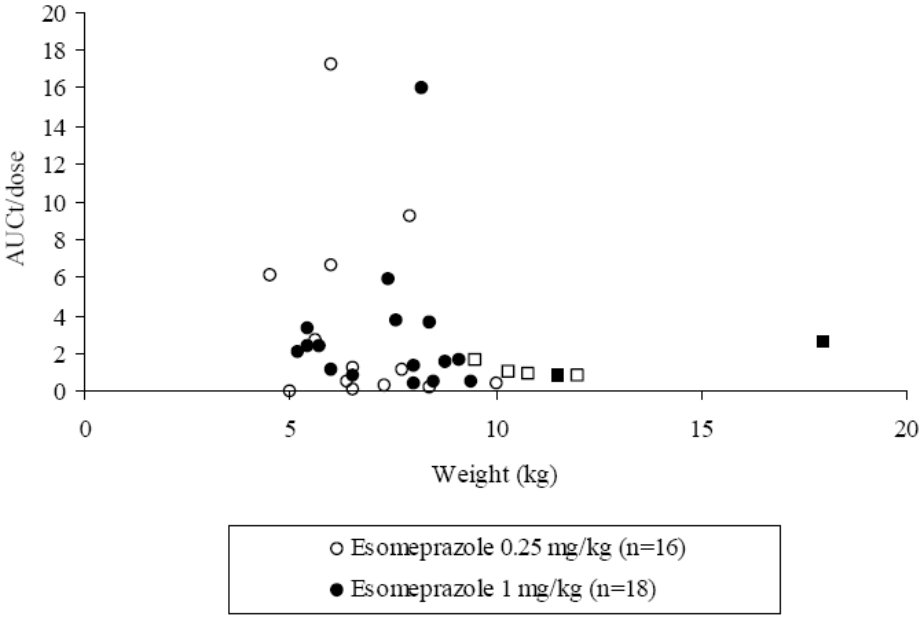


o: infants up to 12 months; □: infants older than 12 months

There is no apparent relationship between esomeprazole exposure and age in infants less than 12 months old. In those infants older than 12 months, however, the AUC

appears constant despite age. The results for C_{SSmax} were similar (data not shown). The two subjects with the highest esomeprazole exposure may be described as poor metabolizers phenotypically (no genotyping was performed in this study) with mean AUCs approximately 5 times the mean AUC. In these same two subjects, the hydroxy and sulphone metabolite concentrations were approximately 3-fold and > 5-fold higher than the mean, respectively.

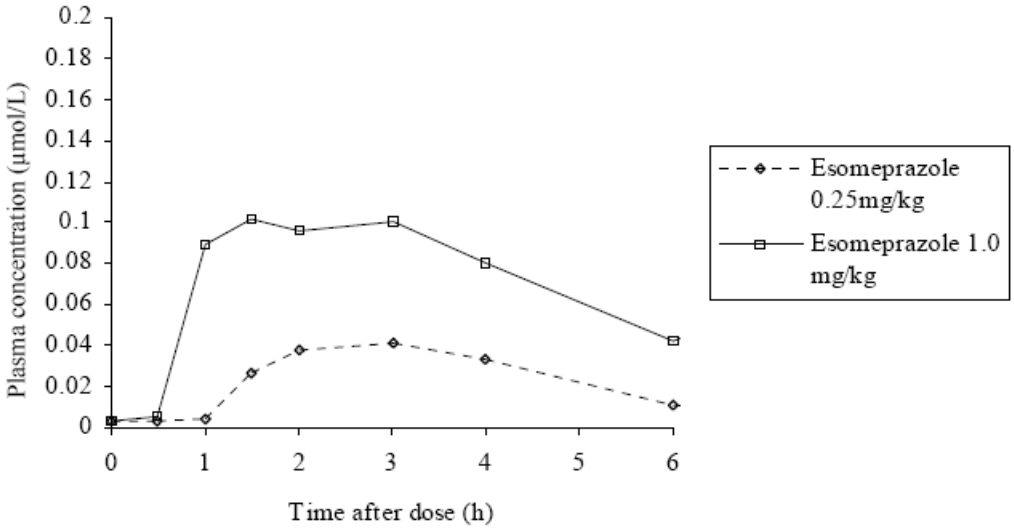
Dose-normalized AUC_t vs weight (kg) in infants from 1 to 24 months of age.



○: infants up to 12 months; □: infants older than 12 months

As observed with age in the previous figure, there is a poor correlation between esomeprazole exposure and weight in infants weighing less than approximately 10 kg. In those infants weighing 10 kg or more, however, the AUC appears constant with increasing weight.

The plasma concentration of the 5-hydroxy metabolite was evaluated in 8 infants in the 0.25 mg/kg group and 11 infants in the 1.0 mg/kg group.



Similar to the esomeprazole concentration vs time curve, the peak for the 5-hydroxy metabolite observed in the 1.0 mg/kg group is driven by one subject. In both groups t_{max} occurred 2-3 hours post-dose. Formation of this metabolite appears similar in neonates receiving 0.5 mg/kg and infants who receive 1.0 mg/kg.

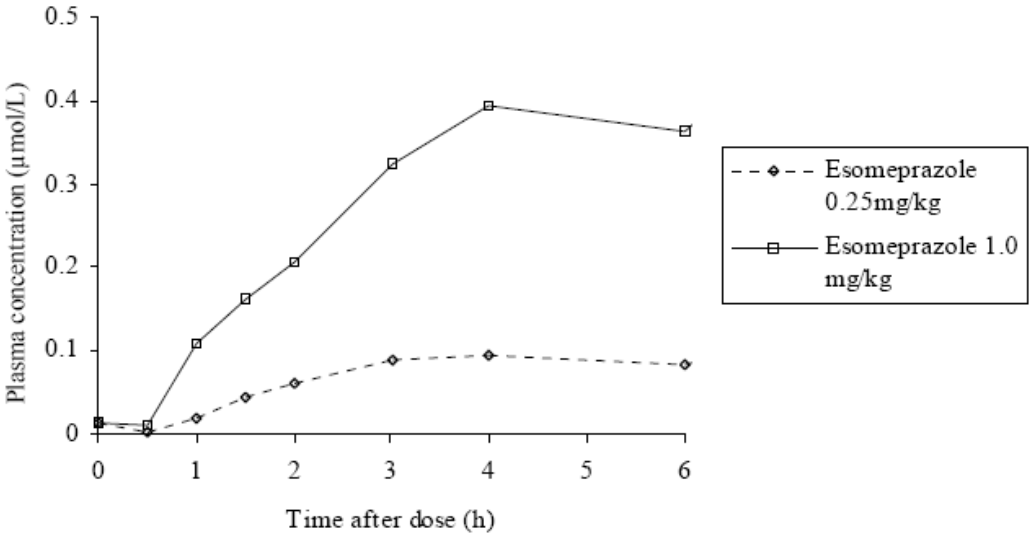
Estimated geometric means and 95% CIs for esomeprazole *5-hydroxy metabolite* PK parameters in infants.

Variable		Estimated	95% confidence interval	
		Mean	Lower	Upper
AUC_t (µmol*h/L)*	Esomeprazole 0.25 mg/kg (n=8)	0.09	0.05	0.17
	Esomeprazole 1.0 mg/kg (n=11)	0.34	0.20	0.58
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	3.80	1.66	8.71
AUC_τ (µmol*h/L)	Esomeprazole 0.25 mg/kg (n=6)	0.16	0.07	0.37
	Esomeprazole 1.0 mg/kg (n=4)	0.60	0.22	1.61
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	3.65	1.03	12.99
C_{SSmax} (µmol/L)	Esomeprazole 0.25 mg/kg (n=8)	0.05	0.03	0.09
	Esomeprazole 1.0 mg/kg (n=10)	0.13	0.08	0.20
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	2.39	1.24	4.59
$t_{½}$ (h)	Esomeprazole 0.25 mg/kg (n=6)	1.30	0.83	2.03
	Esomeprazole 1.0 mg/kg (n=5)	1.32	0.81	2.15
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	1.02	0.52	1.97

*In the 0.25 mg/kg dose group there are 3 subjects (Subjects 3, 35, and 62) with all samples below LOQ and therefore no PK -variables could be calculated. These subjects are therefore not included in the calculation of the estimated geometric means or ratios between doses.

In contrast to the parent compound, the AUC_t, AUC_{tau}, and C_{SSmax} for the 5-hydroxy metabolite is proportional to less than dose-proportional in the 1.0 mg/kg group relative to the 0.25 mg/kg group. The t_{max} for the 5-hydroxy metabolite is the same in both dose groups. There were three subjects in the low-dose group for whom all samples were below the LOQ. The AUC_{tau} in infants who received 1.0 mg/kg (0.6 µmol*h/L) is higher than neonates who received 0.5 mg/kg (0.44 µmol*h/L).

The plasma concentration of the sulphone metabolite was evaluated in 16 infants in the 0.25 mg/kg group and 18 infants in the 1.0 mg/kg group.



From this figure of the mean concentration of the sulphone metabolite, it is apparent that formation is still occurring at 6-hours, the end of the sampling window. Therefore, accurate characterization of the PK of the sulphone metabolite may not be possible within 6 hours of dosing. Relative to neonates, infants appear to produce the sulphone metabolite more slowly and have lower exposures on average.

Estimated geometric means and 95% CIs for esomeprazole *sulphone metabolite* PK parameters in infants.

Variable		Estimated	95% confidence interval	
		Mean	Lower	Upper
AUC_t (µmol*h/L)*	Esomeprazole 0.25 mg/kg (n=16)	0.19	0.10	0.36
	Esomeprazole 1.0 mg/kg (n=18)	0.98	0.55	1.77
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	5.12	2.18	12.00
AUC_τ (µmol*h/L)	Esomeprazole 0.25 mg/kg (n=5)	0.20	0.05	0.79
	Esomeprazole 1.0 mg/kg (n=3)	1.29	0.22	7.43
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	6.37	0.69	58.50
C_{SSmax} (µmol/L)	Esomeprazole 0.25 mg/kg (n=15)	0.09	0.05	0.14
	Esomeprazole 1.0 mg/kg (n=17)	0.39	0.25	0.61
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	4.56	2.38	8.73
$t_{½}$ (h)	Esomeprazole 0.25 mg/kg (n=7)	1.52	0.74	3.13
	Esomeprazole 1.0 mg/kg (n=4)	1.56	0.60	4.05
	Esomeprazole 1.0 mg/kg/Esomeprazole 0.25 mg/kg	1.02	0.31	3.39

*In the 0.25 mg/kg dose group there are 2 subjects (Subjects 24 and 35) with all samples below LOQ and therefore no PK-variables could be calculated. These subjects are therefore not included in the calculation of the estimated geometric means or ratios between doses

Similar to the parent compound, there is a greater than dose-proportional increase in AUC_t, AUC_{tau}, and C_{SSmax} in the high-dose group relative to the low-dose group; however, the differences are not statistically significant. The $t_{1/2}$ is similar between the two groups. Plasma concentrations were below the LOQ for two subjects in the low-dose group but at least one value above the LOQ was measurable in all others. In contrast to exposure of the parent compound and the 5-hydroxy metabolite, the AUC_{tau} of the sulphone metabolite in infants who received 1.0 mg/kg (1.29 µmol*h/L) is *lower* than neonates who received 0.5 mg/kg (4.87 µmol*h/L). This data may suggest that CYP3A4 plays a more prominent role in the metabolism of esomeprazole in neonates compared to infants.

Overall conclusions: (b) (4)

[redacted]

2.2.6 What is the effect of protein binding on the PK of esomeprazole in infants and neonates?

In the neonate study, plasma from 5 subjects was pooled and used in an in vitro study to assess the impact of protein binding. Investigators used two concentrations of esomeprazole, 5 and 50 µM, and replicated the measures six times. The protein binding was 93.8% ± 0.3% at 5 µM and 93.4% ± 0.6% at 50 µM. Investigators performed a similar study with the plasma of healthy adults in order to determine the effect of repeated freeze-thaw cycles and storage at -20ºC & -80ºC on the plasma protein binding of esomeprazole. The results were consistent; approximately 96.1% to 96.9% protein binding, indicating prolonged storage (up to 12 months) at either 20ºC or 80ºC and repeated freeze-thaw cycles had no effect in adults. No protein binding study was performed in the infant study.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure?

The effect of CYP 2C19 polymorphisms on the metabolism of esomeprazole in this population was not explored. However, there is very little activity of either CYP 2C19 or CYP 3A4 in the first few weeks after birth and the impact of such a 2C19 polymorphism in neonates is not clear. The effect of 2C19 polymorphisms in infants may be greater; however, esomeprazole exposure is highly variable even among those expressing the wild-type enzyme and elevated exposure is not correlated with adverse outcomes in adults.

2.4 General Biopharmaceutics

2.4.1 How does the formulation used in this NDA submission compare to those approved previously?

The product used in the infant and neonate PK studies was identical to the enteric-coated esomeprazole pellets used in commercially available Nexium Delayed-Release Capsules and Oral Suspension in the US. Capsules containing different fill weights of esomeprazole pellets were used in all three studies; however, the capsules served only to package the esomeprazole pellets and were opened up and mixed with water or applesauce for administration. (b) (4)

(b) (4)

(b) (4)

2.5 Analytical Section

2.5.1 What analytical methods were used to assess concentrations?

The plasma concentrations of esomeprazole, the sulphone metabolite, and the 5-hydroxy metabolite were determined by LC/MS/MS. Different methods were used in the neonate and infant PK studies to allow for the smaller samples drawn from neonates. However, the methods only differ by sample volume and concentration range. Accordingly, the LLOQ for the neonate study was 20 nmol/L and 5 nmol/L for the infant study. The assays were performed at DMPK & Bioanalytical Chemistry AstraZeneca R& D Mölndal, Sweden.

2.6.2 Are the analytical assay methods adequately validated?

Yea, the analytical assay methods were adequately validated.

Infant study: The range of the standard curve for esomeprazole and both metabolites was (b) (4) nmol/mL. The plasma standard at one concentration level was used and 4-8 replicates were analyzed in each run. The intra-day repeatabilities (%CV) for esomeprazole were (b) (4) % for the 5-hydroxy metabolite, and (b) (4) (b) (4) % for the sulphone metabolite. The linearity of the method was estimated from eight experiments and the results demonstrated acceptable accuracy and precision at all concentration levels. Two QC samples at two concentration levels were analyzed in each run and found to be accurate within (b) (4) %.

Neonate study: The range of the standard curve for esomeprazole and the 5-hydroxy (b) (4) . The range of the standard curve for the sulphone The plasma standards at two concentration levels (LLOQ and ULOQ) were used and six replicates at each concentration level were analyzed in each run. The precision for plasma standards for all analyses and compounds was < (b) (4) % (%CV). The linearity of the method was estimated from six experiments and the results demonstrated acceptable accuracy and precision at all concentration levels. Two QC samples at three concentration levels were analyzed in (b each run and found to be accurate within 1 (b) (4) .

3 Detailed Labeling Recommendations

(b) (4)

OCP will provide appropriate language to describe the PK/PD results (b) (4) The description of esomeprazole PK/PD in neonates and infants up to 1 year will be included in Section 8.4 Pediatric Use.

Sponsor's Proposed Label (information proposed in Section 12.3 will be edited and moved to Section 8.4).

(b) (4)

(b) (4)

Reviewer's Proposed Label (Section 8.4)

The following pharmacokinetic and pharmacodynamic information was obtained in pediatric patients with GERD aged birth to less than one year of age. In neonates (< 1 month old) given NEXIUM 0.5 mg/kg once daily, the percent time with intragastric pH > 4 over the 24-hour dosing period increased from 44% at baseline to 83% on Day 7. In infants (1 to 11 months old, inclusive) given NEXIUM 1.0 mg/kg once daily, the percent time with intragastric pH > 4 increased from 29% at baseline to 69% on Day 7, which is similar to the pharmacodynamic effect in adults *[see Clinical Pharmacology (12.2)]* . Apparent clearance (CL/F) increases with age in pediatric patients from birth to 2 years of age.

4 Appendix 1: Individual Study Reports

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

Investigator

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Study centre

This was a single-centre study conducted in Adelaide Australia at the Centre for Paediatric and Adolescent Gastroenterology, Women's and Children's Hospital, Child Youth & Women's health Service.

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).

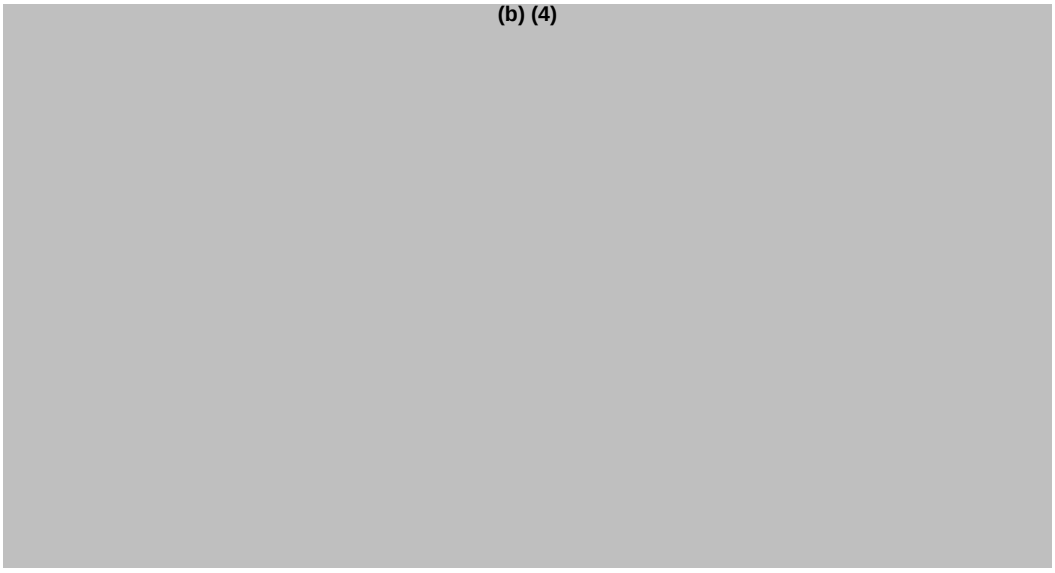
No SAEs occurred during the treatment period. However, 1 SAE was reported during the follow-up period, which was 10 days after end of treatment, when a hospital visit was made by 1 patient after developing an acute respiratory illness (diagnosis=pertussis). Despite this incident the patient completed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

Conclusions

- (b) (4)
-

(b) (4)



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

Investigator

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Study centre

This was a single-centre study conducted in Australia at the Centre for Paediatric and Adolescent Gastroenterology, Women's and Children's Hospital, North Adelaide, Australia.

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 $\ln 2/\lambda$

- **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.

Conclusions

(b) (4)

[redacted]

Appendix 2: Office of Clinical Pharmacology Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY
PHARMACOMETRICS REVIEW

Table of Contents

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The following key questions were addressed in this pharmacometrics review.

1.1.1 Does the proposed dosing regimen in pediatrics 0-11 month of age produces exposures similar to older pediatrics (1-17 years) and adults?

(b) (4)

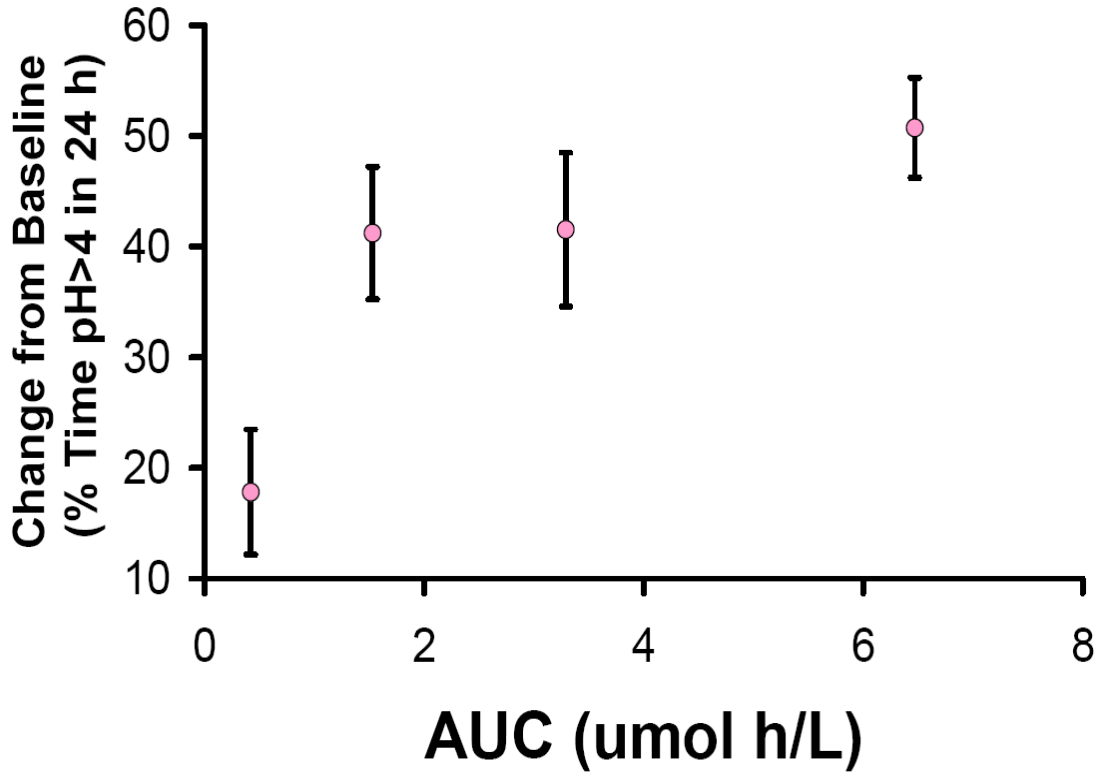
(b) (4)

1.1.2 Is there an evidence of exposure-response relationship for effectiveness for esomeprazole?

(b) (4)

The time for which the intragastric pH is greater than pH 4 during a 24 h period (change from baseline) was one of the key pharmacodynamic endpoints evaluated in the clinical trials NEC-0001 and NEC-0002, a (b) (4)

Figure 2: AUC (Mean ± SE) in each quartile vs time for which pH>4 in a 24 hour period (Change from baseline) in birth-11 month pediatrics.



1.2 Recommendations

None

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

12.3 Pharmacokinetics

Pediatric

(b) (4)

(b) (4)

The following text will replace the text in Section 8.4 of the Label:

Section 8.4

(b) (4)

2 Pertinent Regulatory Background

Esomeprazole, a proton pump inhibitor, is approved for the treatment of GERD and also for eradication of *H. Pylori* in peptic ulcer in combination with other antibacterial regimens. Esomeprazole is approved in adults and in pediatrics 1 year and older in US and Europe. Sponsor seeks indication for the treatment of GERD in birth-11 month pediatrics. Sponsor has three studies which include a pivotal safety efficacy trial to support the same. Study 96 is a pivotal efficacy safety trial to support GERD indication in 1-11 month pediatrics. (b) (4) Study NEC-0001 and NEC-0002 are other two studies in 1-24 month and birth-1 month pediatrics respectively to support the proposed indication.

3 Results of Sponsor's Analysis

3.1 Population PK analysis

Sponsor performed population PK modeling utilizing data from four studies, SH-NEC-0002 (<1 month post term where term is 38 gestational weeks), SH-NEC-0001 (1-24 months), D9614C00099 (1-11 years) and D9614C00094 (12-17 years). The objective of the analysis was to develop a pharmacokinetic model that describes the steady state pharmacokinetics of esomeprazole across birth-17 years which could be used to support dose recommendation in pediatrics birth-11 months. 117 subjects with 596 samples at steady state constituted the PK population. Non-linear mixed effects modeling, using the software NONMEM (version V, GloboMax, Hannover, MD) run with PsN (PsN Toolkit), was used for analysis of the data. Excel (Microsoft Excel 2000) was used for statistical and exploratory analysis and graphics. R (GNU General Public License) and Excel (Microsoft Excel 2000) were used for data handling. The program Xpose (version 4), which is an R-based model building aid for NONMEM analysis, was used for data set check-out, exploration and visualization, model diagnostics and model comparison. At first, a suitable structural model was identified with adequate model for random effects. Allometric scaling of CL and V were scaled with weight a priori according to the following relationships:

$$\text{Clearance} = \theta_{CL}(w/70)^{0.75}$$

$$\text{Volume} = \theta_{V}(w/70)$$

where: θ_{CL} = Population estimate of clearance term (L/h).
θ_{V} = Population estimate of distribution volume term (L).
w = Body weight (kg).

Dose and age were the main covariates evaluated and stepwise covariate modeling approach was utilized. A reasonably good fit was found for a 1-compartment model with first-order absorption, transit lag time and linear CL. However, the linear CL was dose dependent, and so attempts to describe CL using saturable Michaelis-Menten elimination and mixed linear and saturable Michaelis-Menten were made. The latter approach (linear and saturable Michaelis-Menten) is most physiologically plausible based on the known esomeprazole pharmacokinetics in adults, whereby the formation of 5-hydroxyesomeprazole becomes saturated within the usual dosing range. However, these attempts were unsuccessful and it was concluded that the data available were unable to support such CL models.
The final basic model therefore estimated a dose-dependent relative bioavailability according to the following relationship:

$F = F_{MAX}*\text{Dose}/(\text{Dose}+D_{50})$ where:
F = Estimated bioavailability.
F_{MAX} = Maximum bioavailability.
Dose = Dose in mg/kg.
D_{50} = Dose in mg/kg to reach half the maximum bioavailability.

As differences in F, CL/F and V/F cannot be separated using oral data, inter-individual variability was assumed to be only from the bioavailability component. The final population pharmacokinetic model is a one-compartment model with a chain of transit compartments to capture the absorption behavior of esomeprazole. The model well describes the data from the pediatric population included in the analysis. The results of the analysis indicate that the pharmacokinetics of esomeprazole is dose, weight and age dependent. Whereas CL/F (oral clearance) and V/F (oral volume of distribution) in the model is allometrically scaled according to CL/F ~ (body weight/70)$^{0.75}$ and V/F ~ body weight/70, bioavailability (F) is a function of dose and age, with F increasing with increase in dose and increase in age.

The details of the analysis can be found in population PK report submitted by the sponsor. The model was successfully evaluated using predictive check and the precision on parameters was tested using bootstrap procedure. The final population PK parameter estimates are presented in **Table 2**.

Table 2: Parameter values from sponsor's population pharmacokinetic model.

		Parameter	Estimate (%CV)	Interindividual Variability (%CV)	Covariate Effect
Final model	Pharmaco-kinetic parameters	CL/F (L/h/70kg$^{0.75}$)	5.67(10.4)	NE	
		V/F (L/70kg)	0.63(7.3)	NE	
		F_{MAX}	0.28(17.8)	1.16[£](3.0)	1.64(18.1)
		D_{50} (mg/kg)	0.25(12.0)		
		MTT (h)	1.22(1.8)	54(16.2)	
		N	16.5(1.9)	105(28.6)	
		ka (h^{-1})	0.66(1.9)	48(23.7)	
	Residual error	Proportional (%)	19.3(3.6)	19.4(58.5)	
		Additive (µmol/L)	0.054(2.4)		

(Source: Population PK report, Table 5, Pg 23*)*
MTT: Mean transit time

Reviewer's comments: *Sponsor's population PK model reasonably described the data. However, the reviewer does not completely agree with the clearance model chosen by the sponsor. Sponsor did not evaluate interindividual variability on CL/F or V/F and rather chose it to be on F. Esomeprazole is primarily eliminated by liver therefore status of hepatic function (partially dictated by age) is likely to explain variability in clearance among pediatrics and adults. Therefore*

it makes physiological sense to model age as a covariate on clearance as opposed to modeling F as a function of age. Moreover, there has been debate over use of fixed power coefficients in allometric scaling as standard vs estimating them. It has been argued by several experts in the field that fixing the allometric exponents to 0.75 and 1 for clearance and volume respectively, may not always be appropriate. Rather, these exponents should be estimated if suitable data is available. The reviewer developed a simple pharmacokinetic model which reasonably described the data with weight and age as primary covariates on clearance. The power coefficients on weight were estimated for both clearance and volume of distribution. The model was then used it to predict exposures in pediatrics following the proposed dosing regimen (See Section 4.1 for details).

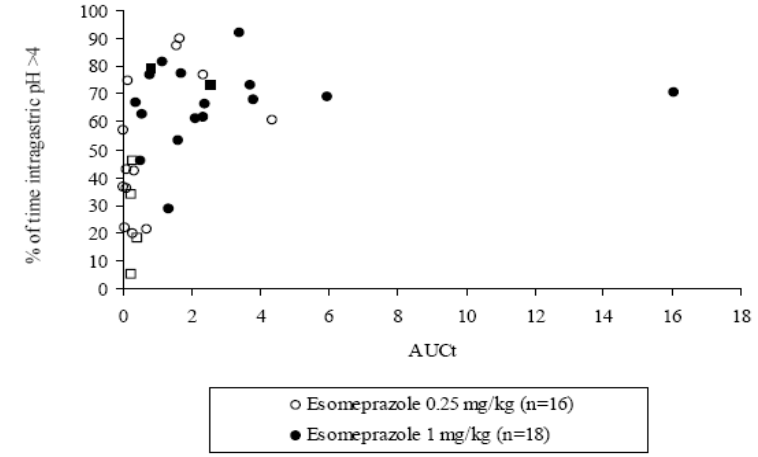
3.2 Pharmacodynamic Analysis

PK data was not available for the pivotal efficacy trial (Study 96). Therefore, sponsor utilized PK-PD information collected in the two supporting trials (NEC-0001 and NEC-0002) to explore PK-PD correlations. Two important PD variables assessed in these trials were:

- Time that Intragastric pH >4 over a 24 hr period, at baseline (Pre-entry visit) and on Day 7/8.
- Median intragastric pH over a 24 h period, at baseline (Pre-entry visit) and on Day 7/8.

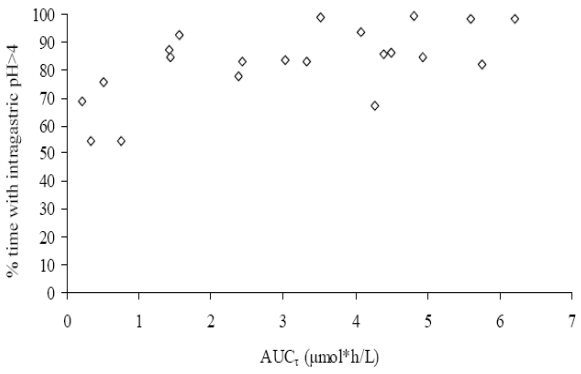
Sponsor found positive correlation between steady state AUC and time that Intragastric pH >4 (**Figure 3** and **Figure 4**).

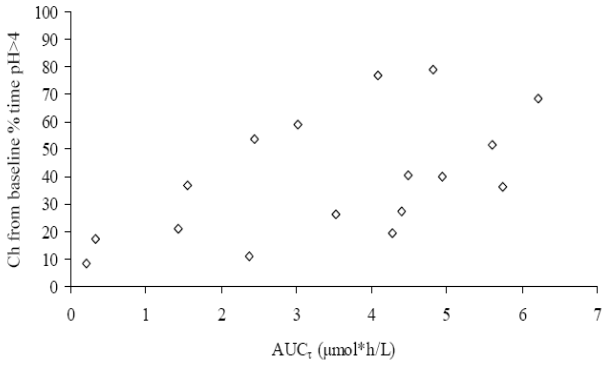
Figure 3: Percentage of time with intragastric pH>4 (after one week of treatment) versus AUCt (µmol*h/L) in study NEC-0001 (*Source: Study report NEC-0001, Figure 15, Pg 82*).



: infants up to 12 months; □: infants older than 12 months

Figure 4: The individual percentage of time (left) and change from baseline in percentage of time (right) with intragastric pH>4 during the 24-hour period following drug administration versus individual AUC_τ of esomeprazole in study NEC-0002 *(Source: Study report NEC-0002, Figure 8, Pg 76)*.





Reviewer's comments: *In study NEC-0001 there were some subjects who did not have complete plasma concentration profiles and therefore $AUC_{(0-t)}$ could be misleading. Most of the subjects had plasma samples collected up to 6 h, therefore only these subjects were used in the PK-PD exploratory analysis. Moreover, absolute value of PD biomarker at steady state may be misleading, therefore change from baseline was explored.*

PD markers were assessed both at baseline (screening visit) and at Day 7/8 after one week dosing of esomeprazole. Change from baseline was calculated as:

Change from baseline= PD biomarker on Day7/8 - PD biomarker at baseline.

Furthermore, median pH over 24 h period was also explored in support of the exposure response relationship.

4 Reviewer's Analysis

4.1 Population PK Analysis

4.1.1 Objectives

1. To determine major intrinsic factors affecting pharmacokinetics of esomeprazole.
2. To use the results derived from first objective to compare exposures produced by the proposed dosing regimen with older pediatrics and adults.

4.1.2 Methods

FOCE estimation with interaction was used for parameter estimation.

4.1.3 Datasets

The dataset eso-bv29.xpt (\\cdsesub1\evsprod\NDA021957\0018\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\population-pk-report-december-2008\crt\datasets\eso-bv29.xpt) was utilized for running the model.

4.1.4 Software

NONMEM VI was used for analysis. SAS was used for data refinement and S-Plus for graphical evaluations.

4.1.5 Model

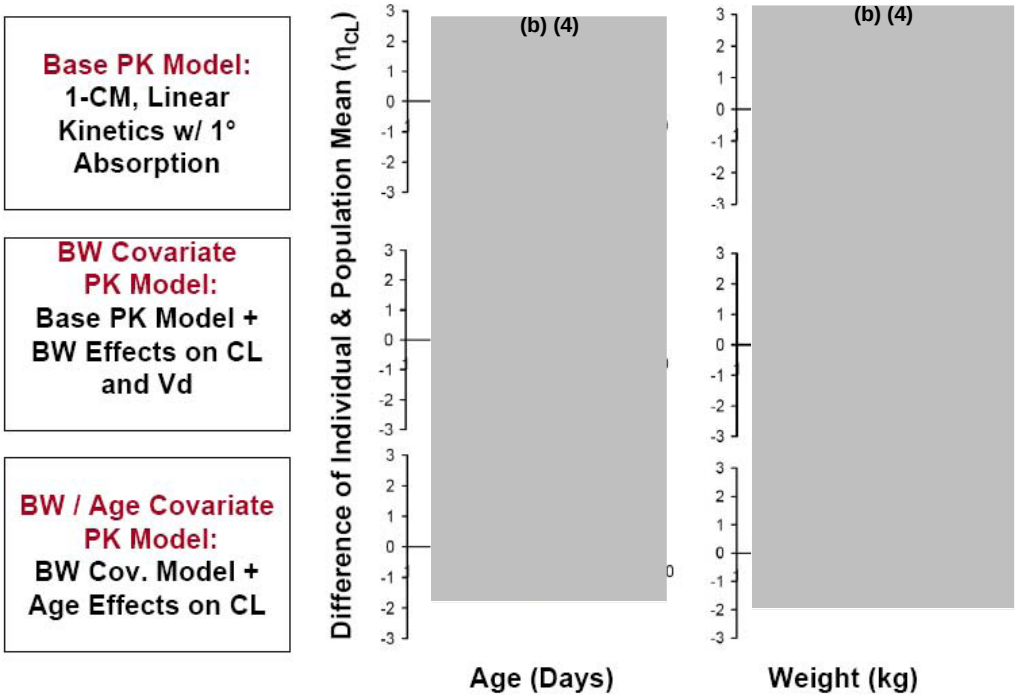
Base model (one compartment) was similar to sponsor's base model. Final model was constructed sequentially using the available covariates. Plots of interindividual variability estimates of clearance (ETA_{CL}), reduction in interindividual variability, decrease in objective function and physiological plausibility were the guiding factors for the selection of covariates. The power coefficients on weight for CL and V_d were estimated.

Table 3: Decrease in interindividual variability in CL after inclusion of weight and age as covariates on CL.

Model	Description	Interindividual variability in CL (CV%)	Objective function
Base-Wt	No covariate on CL and Vd	105.8	-258
Base	BWT on CL and Vd	55.4	-323
Final	Base + Age factor on CL (Age/(Age+A_{50}))	52.9	-336

Figure 5 shows the reduction in the inter-individual variability of esomeprazole clearance (CL) as a function of age and body weight (BW) after 1) the inclusion of body weight as a covariate and 2) the subsequent inclusion of age as a covariate compared to the base model without covariates. Visual inspection of the difference between the base model (**Figure 5**, 1st row, 3rd column) and body weight covariate model by weight (**Figure 5**, 2nd row, 3rd column) indicates that the BW model corrects the under-prediction of the clearance in lower weight individuals. Inclusion of weight also reduces the bias in the prediction of clearance for younger individuals as well (**Figure 5**, 2nd row, 2nd column).

Figure 5: Body weight and age significantly explain interindividual variability in Clearance.



Weight and age were the key covariates on clearance with increase in clearance with increasing weight (see Figure 6 Left). Pediatrics less than two years of age had lower clearance due to immature hepatic function (see Figure 6 Right).

Figure 6: (Left) Body weight is the key covariates affecting clearance of esomeprazole. **(Right)** Hepatic maturation factor (Age/(Age+A_{50}) vs. age. Age does not significantly influence clearance for pediatric patients older than two years of age.

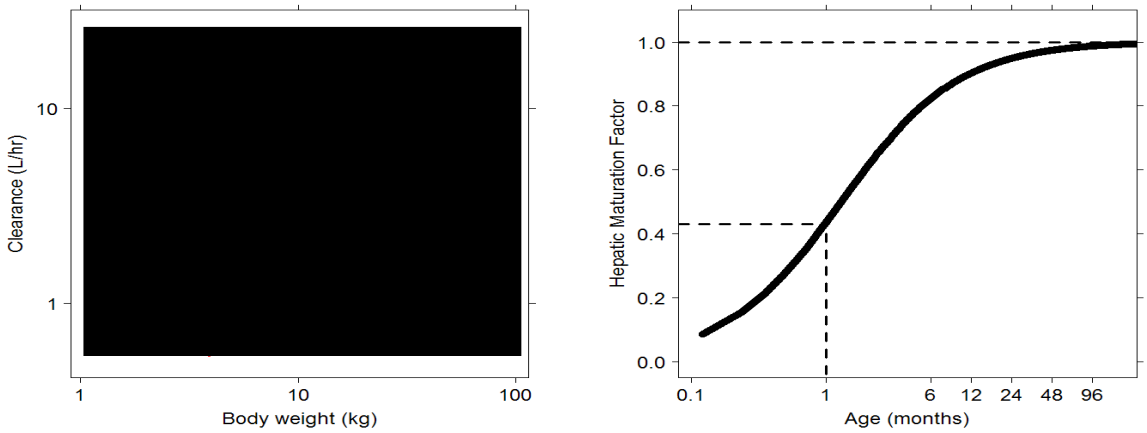


Table 4 shows the comparison of sponsor's and reviewer's final covariate model.

Table 4: Comparison of parameter estimates of sponsor's and reviewer's final covariate model.		
Parameter	**Parameter Estimate**	
	Sponsor's Model	**Reviewer's Model**
CL (L/h/70 kg)	5.67	-
CL (L/h/10 kg)	-	6.1
V_d (L/70 kg)	0.63	
V_d (L/10 kg)	-	5.4
F_{max}	0.28	-
D_{50}	0.25	-
MTT	1.22	-
N (Number of Transit compartments)	16.5	-
Power coefficient of weight on CL	0.75 Fixed	0.41
Power coefficient of weight on V_d	1.0 Fixed	0.58
MAT (h)	-	1.11
ALAG(h)	-	0.49
A_{50}	-	0.11
Residual Error		
Proportional (%)	19.3 (19%)*	53.7
Additive (umol/l)	0.05	0.09

** Sponsor's model included interindividual variability on proportional error and was estimated to be 19%. Hence, proportional error in sponsor's model is much less than that of reviewer's.*

4.1.6 Results

(b) (4)

(b) (4)

Table 5: Geometric means and range of predicted AUC at proposed and approved dosing regimens in pediatrics and adults.

Group	N	GeometricMean AUC (umol h/L)	Range
Birth-1 month	**6**	**4.7**	**2.5-9.4**
1-11 month (Wt < 5 kg, 2.5 mg)	**20**	**3.8**	**1.6-9.4**
1-11 month (Wt 5-7.5 kg, 5 mg)	**17**	**4**	**2.3-13.1**
1-11 month (7.5-12 kg)	**14**	**5.4**	**2.6-12.3**
1-11 years (Wt < 20 kg, 10 mg)	**17**	**3.9**	**2-10**
1-11 years (Wt > 20 kg, 10 mg)	**17**	**2.9**	**1.9-4.6**
1-11 years (Wt > 20 kg, 20 mg)	**17**	**5.8**	**3.8-9.3**
12-17 years (20 mg)	**28**	**4.6**	**2.4-10.2**
12-17 Years (40 mg)	**28**	**9.3**	**4.7-20.4**
Adults (20 mg) [+]		**4.2**	**59% CV**
Adults (40 mg) [+]		**12.6**	**42% CV**

[+] The information comes from the current label of esomeprazole.

4.2 Pharmacokinetic-Pharmacodynamic Analysis

4.2.1 Objectives

To evaluate if there is a relationship between exposure and intragastric pH in pediatrics birth-11 months utilizing two pharmacodynamic endpoints:

- Time for which Intragastric pH >4 over a 24 hr period, at baseline (Pre-entry visit) and on Day 7/8.
- Median intragastric pH over a 24 h period, at baseline (Pre-entry visit) and on Day 7/8.

4.2.2 Methods

Subjects less than 12 months were included from the NEC-0001 and NEC-0002 studies. For study NEC-0001 only subjects who had AUC (0-6h) were included in the analysis.

4.2.3 Datasets

The following datasets were utilized for the PK-PD analysis:

Study Number	Name	Link to EDR
NEC-0001	Pat.xpt	\\cdsesub1\evsprod\NDA021957\0022\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\sh-nec-0001\crt\datasets\pat.xpt
NEC-0001	Kinetik.xpt	\\cdsesub1\evsprod\NDA021957\0022\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\sh-nec-0001\crt\datasets\kinetic.xpt
NEC-0001	Phmon.xpt	\\cdsesub1\evsprod\NDA021957\0022\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\sh-nec-0001\crt\datasets\phmon.xpt
NEC-0002	Dem.xpt	\\cdsesub1\evsprod\NDA021957\0022\m5\53-clin-stud-rep\534-rep-human-pd-stud\5341-healthy-subj-pd-stud-rep\sh-nec-0001\crt\datasets\dem.xpt

NEC-0002	Kinetik.xpt	\\cdsesub1\evsprod\NDA021957\0007\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\sh-nec-0002\crt\datasets\kinetik.xpt
NEC-0002	Phmon.xpt	\\cdsesub1\evsprod\NDA021957\0007\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\sh-nec-0002\crt\datasets\phmon.xpt
NEC-0002	Vit.xpt	\\cdsesub1\evsprod\NDA021957\0007\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\sh-nec-0002\crt\datasets\vit.xpt

4.2.4 Software

SAS 9.1 was utilized for data refinement and S-PLUS was used for graphical evaluations.

4.2.5 Model

There was no formal statistical analysis conducted. Mean exposure-pH curves were constructed to evaluate if there is increase in time pH>4 or median intragastric pH with AUC.

PD markers were assessed both at baseline (screening visit) and at Day 7/8 after one week dosing of esomeprazole. Change from baseline was calculated as:

Change from baseline= PD biomarker on Day7/8 - PD biomarker at baseline.

The AUCs were divided into quartiles and mean of the AUC in each quartile was plotted against mean PD variable.

4.2.6 Results

Drug is supposed to increase the intragastric pH by proton pump inhibition. **Figure 7** depicts a clear evidence of a PK/PD relationship for pH in birth-11 month pediatrics. (b) (4)

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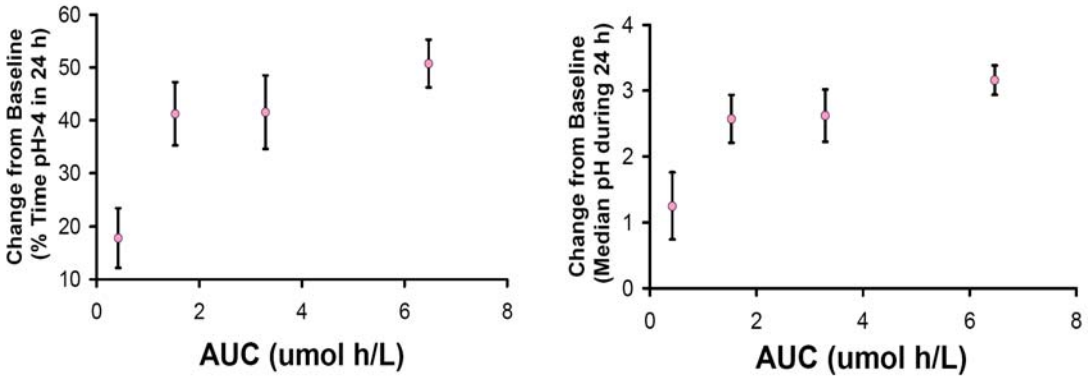
Figure 7: AUC (Mean ± SE) in each quartile vs % time intragastric pH>4, change from baseline (left) and median intragastric pH, change from baseline (right) over 24 hr period showing evidence of a PK/PD relationship.



Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		**Information**
NDA Number	**21-957**	**Brand Name**	**Nexium**
OCP Division (I, II, III)	**III**	**Generic Name**	**Esomeprazole**
Medical Division	**GI**	**Drug Class**	**PPI**
OCP Reviewer	**Kris Estes**	**Indication(s)**	**GERD**
OCP Team Leader	**Sue Chih Lee**	**Dosage Form**	**Delayed Release Oral Suspension / Capsules**
Date of Submission	**18 DEC 2009**	**Proposed Dosing Regimen**	**(b) (4)**
Estimated Due Date of OCP Review	**11 JUN 2009**	**Route of Administration**	**PO**
Medical Division Due Date		**Sponsor**	**AstraZeneca**
PDUFA Due Date	**18 JUN 2009**	**Priority Classification**	

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**	**2**	
Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**2**	**2**	
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**X**	**2**	**2**	
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**1**	**1**	

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
QT study				
Simulations				
Reference Articles				
Total Number of Studies		**5**	**5**	

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	**X**	**Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?**
Comments sent to firm		**Comments have been sent to firm (or attachment included). FDA letter date if applicable.**
QBR questions (key issues to be considered)	**Is the dosing regimen supported by data from the PK/PD studies in infants and neonates?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**Kristina Estes, Pharm.D. 11 JUN 2009**	
Secondary reviewer Signature and Date	**Dennis Bashaw, Pharm.D. 11 JUN 2009**	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kristina E Estes
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