

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as amended**

**Nexium
(esomeprazole)**

SE/W/006/pdWS/001

Rapporteur:	Sweden
Start of the procedure (day 0):	18 Jan 2010
Finalisation of the procedure (day 120)	11 Oct 2010
Date of this report	09 Dec 2010

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Nexium
INN (or common name) of the active substance(s):	Esomeprazole
MAH:	AstraZeneca
Currently approved Indication(s)	Treatment of endoscopically proven erosive reflux oesophagitis
Pharmaco-therapeutic group (ATC Code):	A02B C05
Pharmaceutical form(s) and strength(s):	gastro-resistant granules for oral suspension/ sachet

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I. EXECUTIVE SUMMARY

In March 2009, AstraZeneca was informed by the EMEA/CMDh of the upcoming work-sharing procedure for assessment of paediatric data according to Article 46 of the Regulation (EC) No 1901/2006 as amended for esomeprazole.

At the time of notification, AstraZeneca had an ongoing study in neonatal patients and therefore requested that the procedure should be postponed, which was accepted.

This is the public assessment report of the article 46 procedure. The report starts by giving the concluded labelling proposed for inclusion in the SPC through a variation procedure. Thereafter the first assessment is given followed by the questions raised (RSI) and the response assessment. In the end of the report, the conclusions are presented.

II. RECOMMENDATION

It is suggested that the agreed paediatric changes in the SPC sections 4.2 and 5.1 is harmonised in a type IB variation after finalising this procedure. The following wording is suggested:

Section 4.2

Paediatric patients

The experience of treatment with esomeprazole in infants < 1year is limited and treatment is therefore not recommended. See section 5.1.

Section 5.1

Paediatric patients

In a placebo-controlled study (98 patients aged 1-11 months) efficacy and safety in patients with signs and symptoms of GERD were evaluated. Esomeprazole 1 mg/kg once daily was given for 2 weeks (open-label phase) and 80 patients were included for an additional 4 weeks (doubleblind, treatment-withdrawal phase). There was no significant difference between esomeprazole and placebo for the primary endpoint time to discontinuation due to symptom worsening.

In a placebo-controlled study (52 patients aged <1 month) efficacy and safety in patients with symptoms of GERD were evaluated. Esomeprazole 0.5 mg/kg once daily was given for a minimum of 10 days. There was no significant difference between esomeprazole and placebo in the primary endpoint, change from baseline of number of occurrences of symptoms of GERD.

Results from the paediatric studies further show that 0.5 mg/kg and 1.0 mg/kg esomeprazole in <1 month old and 1 to 11 month old infants, respectively, reduced the mean percentage of time with intra-oesophageal pH<4.

The safety profile appeared to be similar to that seen in adults.

III. INTRODUCTION

Esomeprazole (Nexium®) is available as 20 and 40 mg enterocoated tablets, powder for solution for injection/infusion 40 mg as well as 10 mg gastro-resistant granules for oral suspension, sachet. The granule formulation is approved for GERD in 1-11 year-old children. The approved dose is:

Gastroesophageal Reflux Disease (GERD)

- Treatment of endoscopically proven erosive reflux esophagitis

Weight ≥10- <20 kg: 10 mg once daily for 8 weeks.

Weight ≥20 kg: 10 mg or 20 mg once daily for 8 weeks.

- *Symptomatic treatment of gastroesophageal reflux disease (GERD)
10 mg once daily for up to 8 weeks.*

The MAH submitted 5 completed paediatric studies for esomeprazole (one Phase I/PK/safety, two PK/PD/safety, two Phase III, efficacy and safety), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use. A short critical expert overview was also provided.

IV. SCIENTIFIC DISCUSSION

Gastroesophageal reflux (GER) is defined as passage of gastric content into the oesophagus with or without regurgitation and vomiting. This is a normal physiological process occurring several times a day in healthy children, causing few or no symptoms. When the gastric contents reflux produce symptoms gastroesophageal reflux disease (GERD) is present. The diagnosis of GERD can be concluded when tests show excessive frequency or duration of reflux events, oesophaitis, or a clear association of symptoms in the absence of alternative diagnoses.

IV.1 Information on the pharmaceutical formulation used in the studies

The pharmaceutical formulation used in study D9614C00007, SH-NEC-0001, SH-NEC-0002 and study D9614C00096 were capsules either administered intact or as opened capsules (pellets). The pharmaceutical formulation used in study D9614C0004 was a solution of esomeprazole sodium diluted with a sodium bicarbonate solution at time of administration.

<p>Assessors comment: 10 mg as an oral gastro-resistant granule formulation is the presently lowest approved strength in EU. Capsules are not available on the EU market. The iv formulation is not suitable for oral use.</p>

IV.2 Clinical aspects

1. Introduction

The MAH submitted final report(s) for the 5 studies included in the Table 1.

Study SH-NEC-0001 was also included in MR Procedure for 1 to 11 year-olds (SE/H/0211/004) that was concluded in April 2008.

Table 1. Overview of the paediatric studies submitted

Study code	Study title	Type of study	Study population
D9614C00007	A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)	Phase I, PK, safety and tolerability	Paediatric patients 1 to 11 years old, inclusive, with endoscopically proven GERD
SH-NEC-0001	A Single-Blind, Randomised, Parallel-Group, Single-Centre Pharmacokinetic and pH-Monitoring Study of Esomeprazole in Infants up to 24 Months of Age	PK/PD/safety	Outpatient infants (up to 24 months old) who had symptoms of GERD where the diagnosis was confirmed by 24-hour pH-monitoring
SH-NEC-0002	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	PK/PD/safety	Preterm infants and neonates (gestational age ≥ 32 weeks and < 1 month post-term) who had symptoms of GERD where the diagnosis was confirmed by 24-hour pH-monitoring
D9614C00096	A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group, Treatment-withdrawal Study to Evaluate the Efficacy and Safety of Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Infants Aged 1 to 11 Months, Inclusive	Phase III, efficacy and safety	Infants aged 1 to 11 months, inclusive, with GERD. This included subjects with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD.
D9614C00004	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Esomeprazole Once Daily for the Treatment of Gastroesophageal Reflux Disease (GERD) in Neonatal Patients, Including Premature and up to 1 Month Corrected Age	Phase III, efficacy and safety	Preterm infants and neonates up to 1 month corrected age, with clinically suspected GERD and occurrence of predefined clinical findings that were reproducible in an 8-hour video

2. Clinical studies

2.1 Studies of esomeprazole pharmacokinetics and pharmacodynamics

➤ Introduction

Esomeprazole is acid labile and is administered orally as enteric-coated granules. *In vivo* conversion to the R-isomer is negligible. Absorption of esomeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. The absolute bioavailability is 64% after a single dose of 40 mg and increases to 89% after repeated once-daily administration. For 20 mg esomeprazole the corresponding values are 50% and 68%, respectively. Esomeprazole is 97% plasma protein bound.

Food intake both delays and decreases the absorption of esomeprazole but this has no clinical relevance at the recommended doses. The major part of the metabolism (formation of the hydroxy- and desmethyl metabolites) catalysed by the polymorphic CYP2C19. The remaining part (formation of esomeprazole sulphone) is catalysed by CYP3A4.

The parameters below relates to 2C19 EMs (extensive metabolisers) unless otherwise specified. The area under the plasma concentration-time curve increases with repeated administration of esomeprazole. This increase is dose-dependent and results in a more than dose proportional increase in AUC after repeated administration. This time - and dose-dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by esomeprazole and/or its sulphone metabolite. The major metabolites of esomeprazole have no effect on gastric acid secretion.

Approximately 2.9 \pm 1.5% of the population lack a functional CYP2C19 enzyme and are called poor metabolisers. In these individuals the metabolism of esomeprazole is probably mainly catalysed by CYP3A4. After repeated once-daily administration of 40 mg esomeprazole, the mean area under the plasma concentration-time curve was approximately 100% higher in poor metabolisers than in subjects having a functional CYP2C19 enzyme (extensive metabolisers).

D9614C00007A Randomized, Open-Label Study to Evaluate the Pharmacokinetics of Single Oral Doses of Esomeprazole Magnesium in Pediatric Patients 1 to 11 Years-Old Inclusive with Endoscopically-Proven Gastroesophageal Reflux Disease (GERD)

➤ **Methods**

• **Objectives**

The objective of the study was to determine the pharmacokinetics of esomeprazole and metabolites after single oral doses of 5 mg, 10 mg, or 20 mg esomeprazole in pediatric patients 1 to 11 years old, inclusive, with endoscopically proven GERD. The safety and tolerability was assessed as secondary objective.

• **Study design**

This was a randomized, open-label study designed to evaluate the pharmacokinetics, safety, and tolerability of esomeprazole 5 mg, 10 mg, and 20 mg when given as a single oral dose to pediatric patients 1 to 11 years old, inclusive, with endoscopically-proven GERD. The study was conducted at 7 study centers in the US. The first subject was enrolled on the 14th of August 2006 and the last subject completed on the 8th of May 2008.

• **Study population /Sample size**

The target was to enroll approximately 40 male and female patients from 1 to 11 years of age, inclusive, with endoscopically-proven GERD in order to obtain at least 24 evaluable patients. In table 2 below, the demographics of the included patients is presented.

Table 2 Demographics of patients included in study D9614C00007

Demographic or baseline characteristic	Treatment group				Total (N=28)
	8 to <20 kg		≥20 kg		
	Group A 5 mg (N=7)	Group B 10 mg (N=7)	Group C 10 mg (N=6)	Group D 20 mg (N=8)	
Sex, n (%)					
Male	5 (71.4)	5 (71.4)	4 (66.7)	2 (25.0)	16 (57.1)
Female	2 (28.6)	2 (28.6)	2 (33.3)	6 (75.0)	12 (42.9)
Race, n (%)					
Caucasian	3 (42.9)	7 (100.0)	3 (50.0)	6 (75.0)	19 (67.9)
Black	2 (28.6)	0	3 (50.0)	1 (12.5)	6 (21.4)
Oriental	1 (14.3)	0	0	1 (12.5)	2 (7.1)
Other ^a	1 (14.3)	0	0	0	1 (3.6)
Age (yr)					
n	7	7	6	8	28
Mean	3.14 (1.773)	3.00 (2.082)	8.00 (1.673)	8.50 (2.390)	5.68 (3.278)
Range	1.0–5.0	1.0–6.0	6.0–10.0	5.0–11.0	1.0–11.0
Median	4.00	3.00	7.50	8.50	5.50
Weight (kg)					
n	7	7	6	8	28
Mean (SD)	15.13 (3.293)	14.66 (3.380)	30.98 (9.370)	31.49 (9.838)	23.08 (10.766)
Median	16.10	13.30	27.35	28.90	20.75
Range	10.4–19.6	10.2–18.8	21.9–46.4	22.3–49.9	10.2–49.9

Diagnosed with esophagitis, n (%)	0	1 (14.3)	0	1 (12.5)	2 (7.1)
LA classification of EE, n (%)					
A	0	0	0	1 (12.5)	1 (3.6)
B	0	1 (14.3)	0	0	1 (3.6)
C	0	0	0	0	0
D	0	0	0	0	0
Barrett's esophagus					
Absent	7 (100.0)	7 (100.0)	6 (100.0)	8 (100.0)	28 (100.0)
Present	0	0	0	0	0
Stricture					
Absent	7 (100.0)	7 (100.0)	6 (100.0)	8 (100.0)	28 (100.0)
Present	0	0	0	0	0
Hiatus Hernia					
Absent	7 (100.0)	6 (85.7)	6 (100.0)	8 (100.0)	27 (96.4)
Present	0	1 (14.3)	0	0	1 (3.6)
Malignancy					
Absent	7 (100.0)	7 (100.0)	6 (100.0)	8 (100.0)	28 (100.0)
Present	0	0	0	0	0
Other abnormal ^b					
Absent	3 (42.9)	3 (42.9)	1 (16.7)	1 (12.5)	8 (28.6)
Present	4 (57.1)	4 (57.1)	5 (83.3)	7 (87.5)	20 (71.4)

- **Treatments**

Patients were randomized into the study based on weight. Patients who weighed from 8 kg to <20 kg were randomized into 1 of 2 dosing groups (Group A or Group B). Patients randomized to Group A received a single, 5-mg oral dose of esomeprazole. Patients randomized to Group B received a single, 10-mg oral dose of esomeprazole. Patients who weighed \geq 20 kg were randomized into 1 of 2 dosing groups (Group C or Group D). Patients randomized to Group C received a single, 10-mg oral dose of esomeprazole. Patients randomized to Group D received a single, 20-mg oral dose of esomeprazole. Esomeprazole magnesium blue, clinical-image capsules, formulated as 5 mg, 10 mg, and 20 mg, were used for oral administration as either intact with water or as an opened capsule mixed with up to 1 tablespoon of applesauce followed by water (batch numbers 2000095328 [5 mg], 2000095327 [10 mg], 2000095326 [20 mg]).

- **Outcomes/endpoints**

Single-dose pharmacokinetic parameters of esomeprazole and metabolites

- **Results**

- **Pharmacokinetics**

Exposures of single-dose esomeprazole, as measured by AUC and C_{max}, were approximately 1.8- and 2.2-fold higher, respectively, in patients weighing from 8 to <20 kg who received 10-mg doses (0.71 mg/kg), than in patients who received 5-mg doses (0.35 mg/kg). In patients weighing \geq 20 kg who received 20-mg (0.68 mg/kg) and 10-mg (0.35 mg/kg) doses of esomeprazole, AUC and C_{max} were approximately 4.4- and 2.4-fold higher, respectively, in patients who received 20-mg doses than in patients who received 10-mg doses. Corresponding exposures of 5-hydroxy esomeprazole and esomeprazole sulphone were higher by the same order of magnitude. Geometric mean (CV) weight-normalized apparent clearance of esomeprazole in patients who received a single 10-mg dose of study drug was comparable between weight strata, 1.53 (61.1%) L/h/kg among patients weighing from 8 to <20 kg and 1.40 (49.1%) L/h/kg among patients weighing \geq 20 kg.

Table 3 Pharmacokinetics of esomeprazole in young paediatric patients (D9614C00007)

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

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

The pharmacokinetics of the hydroxyl and sulphone metabolites were measured. They are mainly relevant for comparative purposes although these are single-dose data in contrast to the other studies submitted.

Assessors comment: The study illustrates the nonlinear pharmacokinetics of esomeprazole. In this study it is visible even at single-dose conditions while usually it has been observed at multiple-dose conditions. If comparing these data with multiple dose data it should be remembered that there is accumulation at multiple dose conditions.

• **Safety results**

Of the 28 patients included, 7 received a single dose of 5 mg, 13 received 10 mg and 20 mg was administered to 8 patients.

Two patients experienced adverse events (AEs). One was considered related to the study drug (constipation) and one was not treatment-related (acute virus infection).

There were no serious adverse events (SAEs) or deaths during the study. There were no clinically important findings or trends in haematology, clinical chemistry, urinalysis, or vital signs.

SH-NEC-0001 A Single-Blind, Randomised, Parallel-Group, Single-Centre Pharmacokinetic and pH-Monitoring Study of Esomeprazole in Infants up to 24 Months of Age (study already included in the application for the granule formulation)

➤ **Methods**

• **Objective(s)**

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**

The study was a single centre, randomized, single-blind, 2-arm parallel, repeated dose PK/PD study in 1-24 month old outpatient infants with symptoms of GERD (diagnosis confirmed by 24-hour pH-monitoring). Study SH-NEC-0001 was performed at the Centre for Paediatric Adolescent Gastroenterology, Womens and Children hospital, North Aderlaine, Australia between 02-06-01 and 05-03-23.

• **Study population /Sample size**

The study was performed in 1-24 month old outpatient infants with symptoms of GERD (diagnosis confirmed by 24-hour pH-monitoring). The demographic characteristics of the included patients are presented below. Fifty patients were included in the ITT population. Forty-five patients completed the study, 39 of these were <12 months of age.

Table 4 Demographic and baseline characteristics, ITT population

		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

- **Treatments**

Subjects were given a 7 or 8 days regimen of esomeprazole 0.25 mg/kg or esomeprazole 1.0 mg/kg administered orally once daily.

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. Pellets from the capsules 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). If the child missed the last dose at home on day 6, the dose regimen was prolonged by one day. The doses were administered in the morning. There was no information on drug intake in relation to food. Blood samples were drawn for 6 hours after the last dose. Five subjects aged > 3 months had samples also drawn at 8 hours post-dose.

- **Results**

- **Pharmacokinetics**

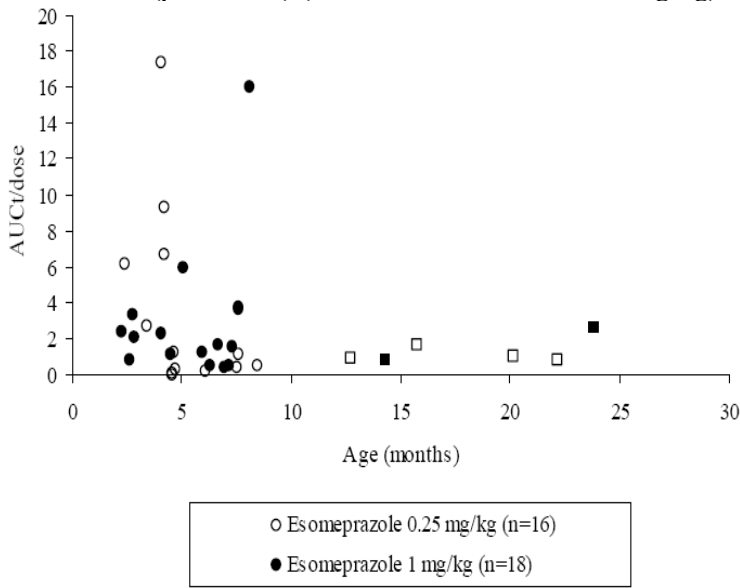
There was a large interindividual variability in AUC_t, AUC_τ and C_{SSmax} of esomeprazole for both the 0.25 mg/kg and 1.0 mg/kg doses, and the variability seemed to be larger in the younger children (see figure 1). Numerically there was a larger than proportional increase in AUC_t, AUC_τ and C_{SSmax} with dose, even though not statistically significant. The 5-OH metabolite increased proportionally with dose while the sulphone metabolite increased more than doseproportional when comparing 0.25 mg/kg with 1 mg/kg, see Table 5 and Figure 1 showing the PK results below.

Table 5 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 _{1/2} (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.

Figure 1 AUCt ($\mu\text{mol}\cdot\text{h/L}$) (dose normalisation to 1.0 mg/kg) of esomeprazole versus age (months)



Assessors comment: AUC of the sulphone metabolite was not that well estimated. The residual area was very large.

• **Pharmacodynamics**

A positive correlation between both AUCt and CSSmax of esomeprazole and the percentage of time with an intragastric pH>4 could be seen in the study.

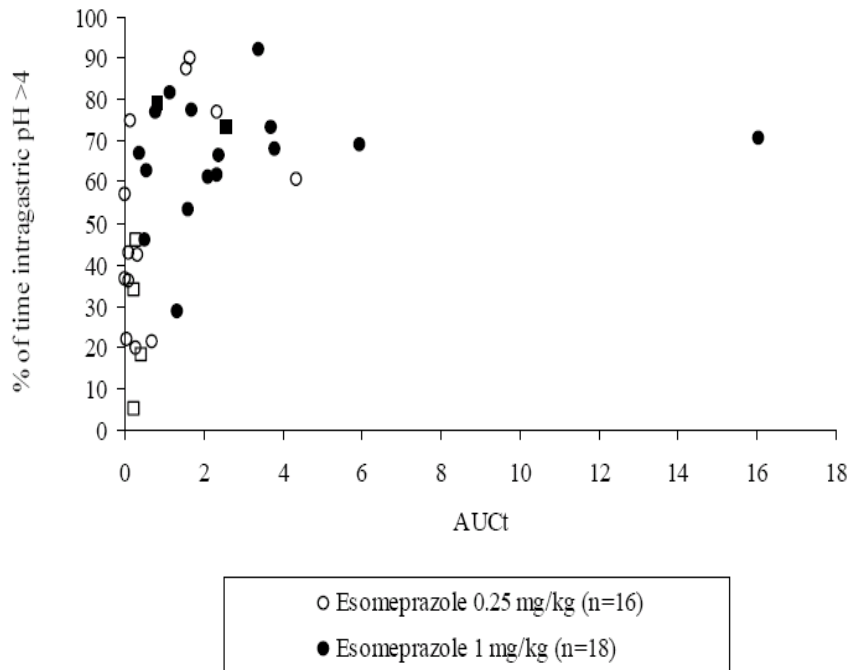
The mean percentage of time with intragastric pH >4 increased from 30.5% at baseline to 47.9% in the 0.25 mg/kg dose group and from 28.6% to 69.3% in the 1.0 mg/kg dose group on Day 7/8. Statistically, the increase was significantly higher with the esomeprazole 1.0 mg/kg dose compared with the 0.25 mg/kg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

Change in percentage of time with intra-esophageal pH <4 from preentry to after one week of treatment is shown below (the pre-entry measurement is used as a covariate). Estimates, 95% confidence intervals and p-values for test of equal means (0.25 mg/kg n=23, 1.0 mg/kg n=21)

	Estimated Mean	95% confidence interval		p-value
		Lower	Upper	
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

The relationship between AUC and time with intragastric pH>4 is shown below.

Figure 2 Percentage of time with intragastric pH>4 (after one week of treatment) versus AUCt ($\mu\text{mol}\cdot\text{h/L}$)



Efficacy results

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. Data on the effect of esomeprazole on symptoms of GERD were inconclusive.

Safety results

The safety population consisted of all patients who had received at least 1 dose of the study medication, i.e. 50 subjects. Of patients younger than 1 year (n=43), 22 were randomized to treatment with 0.25 mg/kg and 21 to 1.0 mg/kg. Seven patients were between 1 and 2 years old, 4 of them were randomized to receive 0.25 mg/kg and 3 to 1.0 mg/kg. Six patients did not complete the whole study period. The numbers of AEs is shown in Table 6.

Table 6. Number of AEs in subgroups by age (SA population)

Category of adverse events ^a	Esomeprazole 0.25 mg/kg	Esomeprazole 1.0 mg/kg	Esomeprazole 0.25 mg/kg	Esomeprazole 1.0 mg/kg
	$\leq 1\text{Year}$	$\leq 1\text{Year}$	$> 1\text{Year}$	$> 1\text{Year}$
	(n=22)	(n=21)	(n=4)	(n=3)
Any AE	4	7	2	2
Serious AEs	0	0	0	0
Discontinuation AEs	1	0	0	0
Other significant AEs	0	0	0	0
Severe AEs	0	0	0	0

^a Events are counted by preferred term i.e. for subjects with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

Data derived from Appendix 12.2.7

The majority of AEs occurred in the youngest age-group. The events were of mild to moderate intensity. The numbers of patients with any AEs is shown in Table 7.

Table 7. Number of patients with any AEs (SA population)

System Organ Class Preferred Term	Esomeprazole 0.25 mg/kg (n=26)	Esomeprazole 1.0 mg/kg (n=24)
<i>Total no. of subjects with AE:</i>	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

Subjects were counted once within the SOC total and once for each AE belonging to that particular class.

One 3-month-old discontinued the study after experiencing irritability that stopped when treatment was withdrawn. Concerning the patient with neutropenia, additional results from the screening at the pre-entry visit showed that this patient had a low neutrophil count already at baseline. There were no SAEs or deaths occurring in the safety population. No clinically relevant findings were observed regarding haematology, clinical chemistry, urinalysis, or vital signs.

SH-NEC-0002 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

➤ **Description**

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. The first patient was enrolled and last patients completed on 2 June 2004 and 8 March 2006, respectively.

➤ **Methods**

• **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**

The pharmacokinetic parameters were determined through a sparse sampling approach using population PK (NONMEM) analysis. Blood samples for determination of esomeprazole and its metabolites in plasma were taken on Day 7 according to 2 different blood-sampling schedules as follows:

- * 1, 3, 5 and 7 hours post-dose (schedule 1)
- * 2, 4, 6 and 8 hours post dose (schedule 2)

- **Study population /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 pHmonitoring. The patient's weight had to be ≥ 1.8 kg and ≤ 6.5 kg if the patient was to participate in the study. The patients were both in- and outpatients. (*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). Twenty-six patients were included in the study. The demographics is shown below.

Table 8. Demographics of patients evaluated as potential covariates in the pharmacokinetic analyses of esomeprazole (n=24)

Patient	Dose (mg)	Age (weeks)	Gestational age at birth (weeks)	Postconceptional age ^a (weeks)	Weight ^b (g)	Height ^b (cm)	Body surface area ^b (m ²)	S-Albumin ^b (g/L)
N	24	24	24	24	24	23	23	21
Mean	1.6	8	31	39.9	3209	47	0.195	34
SD	0.4	4.5	5	2.3	627	3	0.027	3
Min	1	1	23	35.6	2120	40	0.144	28
Median	1.5	7.5	31	39.4	3177	48	0.193	33
Max	2.5	15.9	41	44	4500	54	0.245	42
Geom.mean	1.6	6.5	31	39.8	3150	47	0.193	33

^a Postconceptional age, calculated as postnatal age + gestational age at birth

^b On Day 7/8

- **Treatments:**

Esomeprazole 0.5 mg/kg, was administered once daily (od) for 7 days. The dose was administered as pellets or capsules prefilled with low doses of esomeprazole. The pellets were administered through a funnelpan with an adaptor.

- **Outcomes/endpoints**

In total, 86 samples from 24 patients (on average 3.6 samples per individual, range 1-4) were used in the analysis for esomeprazole. Somewhat smaller number of samples was used for the metabolites. A separate pharmacokinetic model was developed for each analyte (esomeprazole, the hydroxyl metabolite and the sulphone) and for all of these the data supported one-compartment models with first order absorption and a lag time. A covariate analysis was carried out for esomeprazole only. The following patient characteristics were evaluated as potential covariates of the pharmacokinetic parameters; post-natal age

(AGE, days), gestational age at birth (GeAGE, days), postconceptional age (PcAGE, days, calculated as AGE + GeAGE), body weight (WT, kg), body height (HT, cm), body surface area (m²) and s-albumin. Steady state pharmacokinetic parameters for esomeprazole. 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. The relationship between PK and PD variables are depicted graphically. During the study, the investigator added measurement of free versus protein bound fractions of esomeprazole in plasma. Surplus plasma remaining from the completed esomeprazole analyses in study SH-NEC-0002 was pooled and used for *in vitro* protein binding determinations of plasma spiked with radiolabelled esomeprazole.

➤ Results

• Pharmacokinetics

The PK of esomeprazole and its metabolites were described by one-compartment models with first order absorption and a lag time. Whereas the time window for PK sampling was satisfactory for esomeprazole and the 5-hydroxy metabolite 8 hours seemed too short a time to capture the main part of the concentration-time curve for the sulphone metabolite. The estimated geometric mean for AUC_τ of esomeprazole was 2.5 μmol*h/L (median 3.4 μmol*h/L) and the individual values ranged between 0.2 μmol*h/L and 6.6 μmol*h/L. The oral clearance (CL/F) for esomeprazole was estimated to 1.9 L/h, which corresponds to 0.6 L/h/kg, if corrected for the median body weight in the study population (3.2 kg). The inter-individual variability (IIV) in CL/F was estimated to 98%. None of the investigated covariates were shown to be predictive for the inter-individual variability in CL/F of esomeprazole. The results are described below. In addition, the main results for the metabolites are given but here it is mainly of interest to see the general exposure level in comparison with approved age groups. The fraction bound of esomeprazole was 93-94%.

Figure 3 Observed plasma concentration (μmol/L) versus time (h) on Day 7 for esomeprazole after once daily administration esomeprazole 0.5 mg/kg in preterm infants and neonates, given on logarithmic scale (A) and on linear scale (B). Shown are also model predictions for the typical individual (given by the dark line).

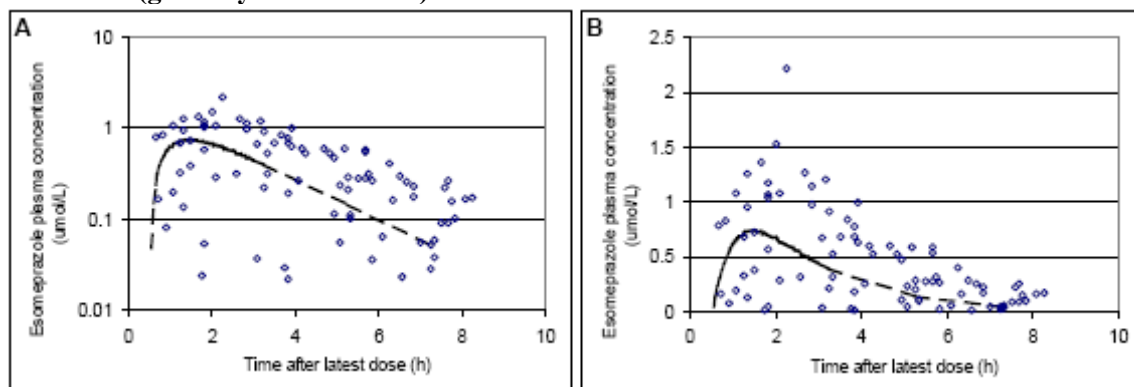


Table 9. Estimated population pharmacokinetic parameters for esomeprazole in the final model

Analyte	Parameter ^a	Estimate ^b (CV ^c %)	IIV ^d % (CV %)	Covariate effect ^e
				WT %/kg (CV%)
Esomeprazole	Pharmacokinetic parameters	CL/F (L/h)	1.89 (21)	98 (34)
		V/F (L)	1.01 (23)	46 (28)
		k _a (h ⁻¹)	0.52 (13)	
		t _{lag} (h)	0.53 (35)	59 (94)
	Residual error	Proportional (%)	21 (32)	
	Additive (µmol/L)	0.04 (37)		

^a CL/F, oral clearance; V/F, oral volume of distribution; k_a, absorption rate constant; t_{lag}, lag time.

^b The values for the parameter estimates presented in the table represent estimates for the typical individual in the studied population.

^c CV%, relative standard deviation, given in %.

^d IIV, inter-individual variability, given in %.

^e WT, total body weight in kg. The covariate effect is centered around the median body weight, ie, 3.18 kg.

Table 10. Estimated geometric means and 95% CIs for AUC_τ (µmol*h/L), estimated C_{ss,max} (µmol/L) and CL/F (L/h) and estimated means and 95% CIs for estimated t_{max} (h), V/F (L) and t_{lag} (h) for esomeprazole after once daily oral administration for 7 days in preterm infants and 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

Assessors comment: The population PK model development is very briefly described and it is difficult to judge how well the model describes the data and whether model development has been adequate and a more complete description would have been appreciated. Possibly Appendix 12.2.5 (not submitted) to the study report contains that information. The exposure measures have been calculated based on empirical Bayes estimates and to conclude that these are of good quality, the shrinkage toward the population mean needs to be presented (eta-shrinkage). Furthermore, epsilon-shrinkage is needed to assess the quality of individual predictions interpreted to be used for estimation of C_{ss,max}.

No covariates were included on CL/F. Quite commonly, allometric body weight is included a priori on clearance and volume terms when modelling paediatric data, and this could have been a reasonable approach, and thereafter explore further covariates. No relationship between age and CL/F was found. This is very surprising as a quite marked maturation of the liver takes place the first month after birth. Possibly this could have been due to the quite narrow age range of the data and/or a changing protein binding, assuming the degree of binding increased over the first month.

The reduced protein binding observed in the (five) patients (fu 6-7% vs fu 3% in adults) should be remembered when looking at the exposure data. The free drug exposure may also covary with age in the 0-1 month old patients, the youngest having the lowest binding.

Assessors comment: The exposure of the 5-OH metabolite seems similar to the exposure in the population 2 months to 2 years. The mean sulphone exposure is ca 2-fold higher.

- **Pharmacodynamics**

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.

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.

Estimated means and 95% CIs for percentage of time with esophageal pH <4 during the 24-hour period at baseline and on Day 7/8 and for the difference between days, after once daily oral administration for 7 days in preterm infants and neonates (n=23) is shown below.

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

- **Relationship between exposure and pharmacodynamic effect**

Figure 4. The individual percentage of time with intragastric pH>4 during the 24-hour period following drug administration versus individual AUC_τ of esomeprazole

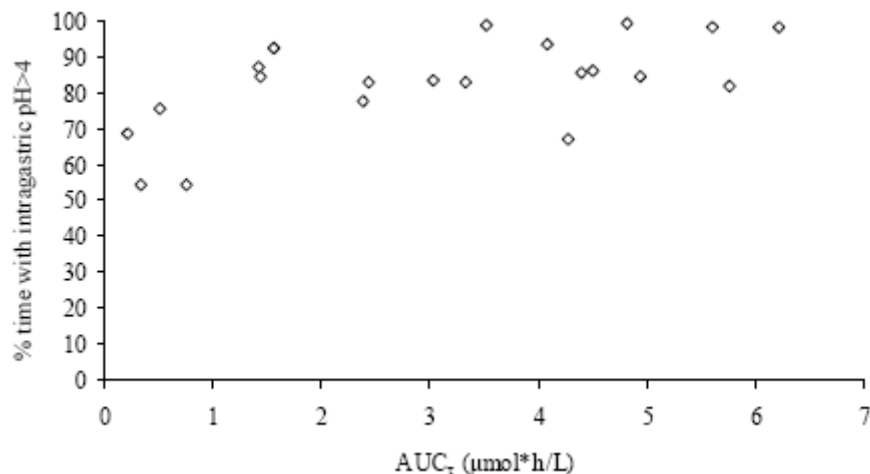
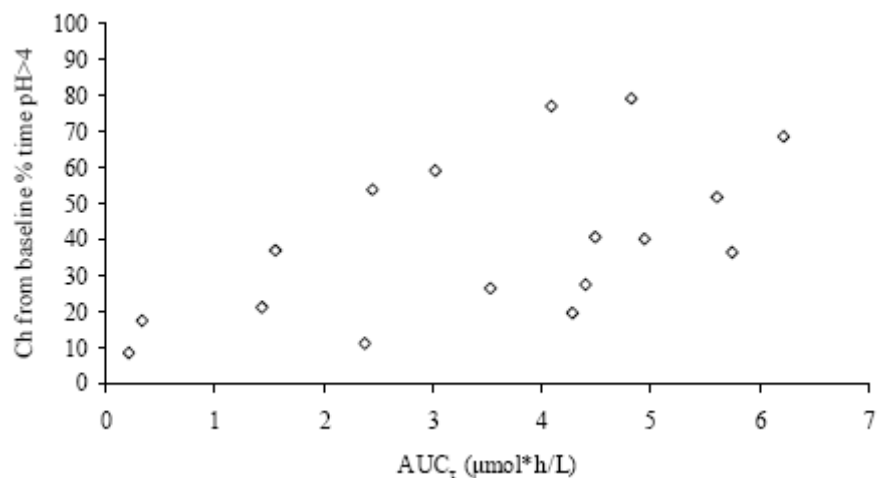


Figure 5. The individual change from baseline in percentage of time with intragastric pH>4 during the 24-hour period following drug administration versus individual AUC_τ of esomeprazole



Assessors comment: A maximum effect was roughly observed at $AUC_{0-24} > 4$. It is noted that the effect on Ph was mainly visible when presented as % change of time with $pH > 4$. The reason for this appears to be that the majority of patients had intragastric $pH > 4$ during a major part of the time at baseline, However, they were still suffering from symptoms of GERD.

- **Safety**

All patients that were randomized ($n=26$) received the same treatment, i.e. 0.5 mg/kg. Twenty-five completed the 7 days treatment.

Seventeen AEs occurred in 10 patients, none of them were considered to be related to the study drug. There were no discontinuations due to AEs. There were no SAEs occurring during the treatment but 2 SAEs were reported during the follow-up period (pertussis, respiratory illness). There were no clinically relevant findings in laboratory variables, physical exams or vital signs.

- **Efficacy**

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 pharmacokinetics

The applicant has submitted a table with systemic exposures of esomeprazole observed in different age groups. It is noted that the results from NEC-002 is not used in this comparison, besides for children below 1 month of age. This seems appropriate as NEC-001 includes full plasma concentration-time curves. The listed data in this age group are not summarised in the NEC-002 study report but originates from the results. It is unclear whether the data is multiple-dose data. Esomeprazole has a short half-life but accumulated due to the time-dependent 2C19 inhibition. Thus, multiple-dose data should be used for the comparison as the NEC-001 is multiple-dose data.

Table 11. Esomeprazole exposure - Comparison 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)	2.45 ^g	0.87 ^{gh}	3.51 ^{gh}	0.74 ⁱ	4.83	3.70	6.28	3.65	13.9	4.21	12.8
AUC (µmol*h/L)	(0.21-6.57)	(0.09-4.55)	(0.82-16.7)	(0.42-1.39)	(2.60-10.9)	(1.36-6.86)	(3.80-10.7)	(1.75-9.24)	(6.72-26.7)	(0.89-14.9)	(3.97-25.6)
Geomean (range)	0.74	0.16	0.87	0.62	2.98	1.77	3.73	1.45	5.13	2.11	4.74
C _{SSmax} (µmol/L)	(0.10-1.50)	(0.01-1.69)	(0.22-9.32)	(0.34-1.25)	(2.23-4.04)	(0.59-3.20)	(2.49-5.75)	(0.18-4.13)	(1.89-8.32)	(0.51-4.78)	(1.59-9.61)

a Data derived from SH-NEC-0002.

b Data derived from SH-NEC-0001.

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.

BW = Body Weight, Geomean = Geometric mean.

Nevertheless, for clarity, the AUC at approved doses and age/weight-groups are the following using data from the table: (geom. mean and range)

Adults (20 mg) 4.21 (0.89-14.9)

Children 12-17 years (20 mg) 3.65 (1.75-9.24) µM*h

Children 1-11 years (20 mg) weight ≥20 kg approx 6.28 (3.80-10.7) µM*h

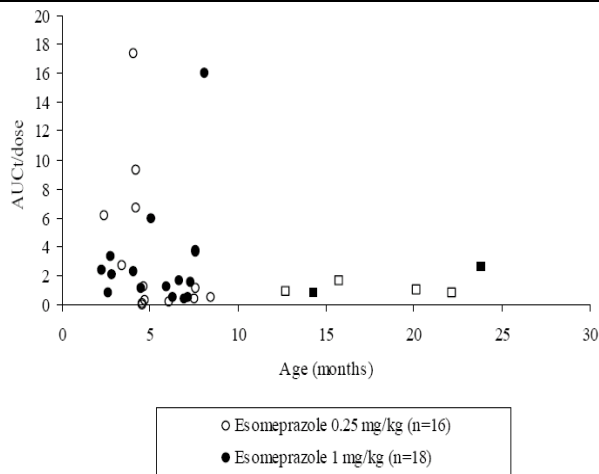
Children 1-11 years (10 mg) weight ≥10-<20 kg approx 4.83 (2.60-10.9) µM*h

The proposed dose in the art 46 is ca 0.5-0.8 mg/kg in children 1-11 months of age and maximum 1 mg/kg in children 0-1 month.

Based on the mean AUC at 0.99 mg/kg, the exposure in the 1-11 months group would be around 3 µM*h. In the 0-1 month group, the mean exposure would be 5 µM*h or higher depending on the degree of nonlinearity in this age group and also on the weight of the child. However, the protein binding appears lower (free fraction doubled) at a mean basis in this age group. AUC based on total concentration is a function of Clint and fu for esomeprazole as it is a low extraction drug and a lower protein binding may therefore mask a reduced Clint. The unbound concentration, which is the relevant parameter, is dependent on Clint and is therefore unknown in this age group.

From a mean value perspective, the chosen doses appear reasonable based on the PK/PD relationship in the 1-11 year-old children. However, it is expected that oral clearance of drugs, even if normalised by bodyweight, will change (probably increase) during the first year of life. The relationship with age was presented in study NEC-001. A higher AUC normalised for the dose 1 mg/kg was found in children below 12 months than in 12-24 months. This should indicate that children 1-11 months should have a lower dose than the older children. The discrepancy between this and the data in the table could be that the data in children 12-24 months here are specifically shown while in the table the data is grouped on 1-5 and 6-11 year-old children.

Copied from study NEC-001-description above



The applicant should discuss the discrepancy in data and whether based on liver maturation it may be expected that oral clearance /kg bodyweight is similar in the 1-11 months age group. In addition, the applicant should discuss whether the protein binding may be increased also in the younger children within the 1-11 months age range. The applicant should also propose a suitable way to present the available data in children 1-11 months which includes the variability in the group and the age dependency within the group.

The exposures of the metabolites are mainly of interest from a safety perspective (bridge to preclinical data). Although not always well estimated, the metabolite exposure does not appear markedly different in the 1<12 month age ranges than in children 1-11 years. The sulphone metabolite exposure appeared increased in 0-1 month old children although it should be remembered that population PK analysis was used in the 0-1 month old children in contrast to the conventional analysis of rich data available in the other age groups. The applicant should present data on metabolite exposure in adults at multiple dose conditions and compare these with the data in children.

A rough relationship between time with pH over 4 and individual AUC estimates was shown in NEC-001 (children 2-22 months old). In NEC-002 this relationship was weaker, probably due to a substantial time above pH 4 already as baseline. The relationship between % change from baseline in time with pH over 4 and AUC was clearer but the approximate maximum effect was moderate (+ca 50%). The applicant should compare the available data on the AUC vs. time in adults and other age groups with the relationship observed in NEC-001.

In earlier application it has been discussed that CYP2C19 is not present in sufficient amount to be a major metabolising enzyme in children 0-3 months. The applicant should present available data supporting this and discuss whether CYP3A4/7 is the main enzyme likely to be involved in esomeprazole metabolism in these young patients. This may be important from an interaction perspective.

2.2 Clinical phase III studies

Study D9614C00096

Title: A phase III, multicenter, randomized, double-blind, placebo-controlled, parallel group, treatment-withdrawal study to evaluate the efficacy and safety of esomeprazole for the treatment of Gastroesophageal Reflux Disease (GERD) in infants aged 1 to 11 months, inclusive.

➤ Description

This was a multicenter study conducted in the US (16 centres), France (4 centres), Germany (9 centres) and Poland (4 centres). Infants 1 to 11 months old with suspected, symptomatic or endoscopically proven GERD were included in the study.

➤ Methods

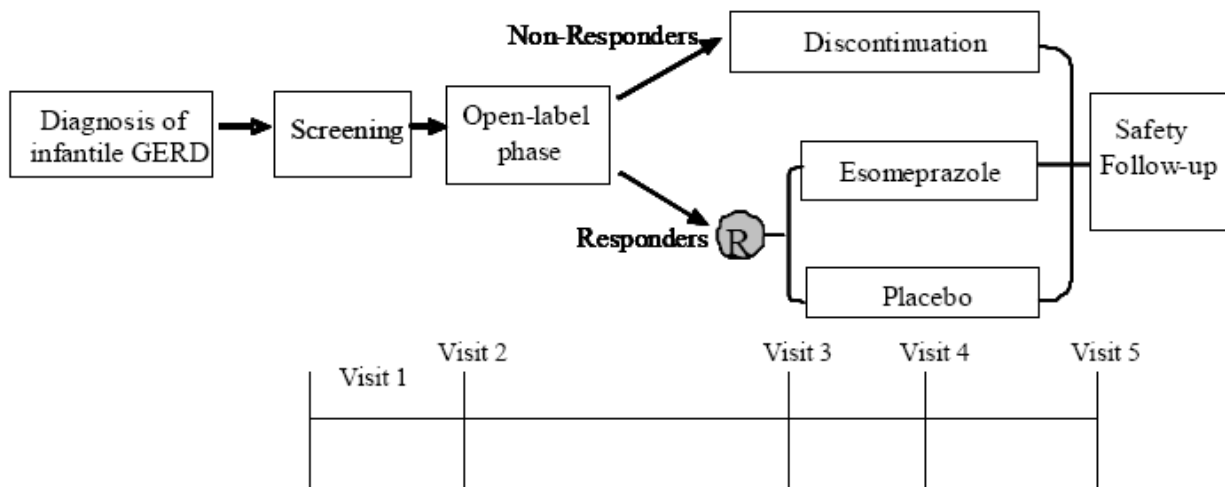
• Objective

The primary objective of the study was to evaluate the efficacy of once daily esomeprazole for reducing oesophageal and supra-oesophageal signs and symptoms of infantile GERD. The secondary objective was to evaluate the safety and tolerability of the treatment.

• Study design

The study was randomized, double-blind, placebo-controlled, parallel group and included a treatment-withdrawal phase. The study was initiated with a 10-day screening period (Visits 1 and 2), a 2-week, open-label treatment phase (ended by Visit 3), a 4-week double-blind, treatment-withdrawal phase (Visits 4 and 5) and a 2-week follow-up period (safety), see Figure 6.

Figure 6. Study flow chart



All infants and toddlers received active treatment in the open-label phase of the study. Only responders according to pre-defined criteria entered the double-blind treatment period. Two weeks after study completion or discontinuation, the caregiver of each patient was contacted by telephone for an assessment of AEs, SAEs and concomitant medication.

• Study population /Sample size

Ninety-eight patients were enrolled into the study and of these patients, 80 were randomized into the double-blind phase.

The infants and toddlers included had a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. The patients were to have failed standard anti-reflux measures (thickened feeds, elimination diet, positioning etc).

- **Treatments**

Patients were treated with the study drug with doses depending on their weight:

<u>body weight</u>	<u>daily dose</u>
3-5 kg	2.5 mg
>5 -7.5 kg	5 mg
>7.5 -12 kg	10 mg

The infants and toddlers were randomized in a 1:1 ratio to receive active and placebo treatment, respectively.

- **Outcomes/endpoints**

A summary of the efficacy variables of the study is shown in Table 12.

Table 12. Efficacy objective and variables

Objective	Variable(s)
To evaluate the efficacy of once daily esomeprazole for reducing the esophageal and supraesophageal signs and symptoms of infantile gastroesophageal reflux disease (GERD).	Primary <ul style="list-style-type: none"> • time from randomization to discontinuation due to symptom worsening in the randomized treatment-withdrawal phase
	Secondary <ul style="list-style-type: none"> • time from randomization to discontinuation due to any reason in the randomized treatment-withdrawal phase • the proportion of treatment responders randomized into the double-blind phase who were classified as treatment successes at the end of the 4-week, double-blind phase of the study. Patients were classified as treatment successes if they maintain their improvement in their symptoms throughout the double-blind phase, without reaching a threshold for discontinuation or discontinuing from the study for any reason • daily patient symptom assessments as reported by the parent/guardian • Physician’s Global Assessment

Patient reported outcome variables as the Paediatric GERD Caregiver Impact Questionnaire (PGCIQ) with a descriptive evaluation of the economic burden of paediatric GERD were also included in the efficacy evaluation (analyzed in a separate report).

The endpoints concerning safety are shown in Table 13.

Table 13. Safety objective and variables

Objective	Summary variables for analysis
To evaluate the safety and tolerability of once daily esomeprazole in infants aged 1 to 11 months, inclusive, with GERD	<ul style="list-style-type: none">- adverse events- clinical laboratory evaluation- physical examination- vital signs

The laboratory safety variables included haematology, serum chemistry and urinalysis.

• **Statistical Methods**

-All formal statistical analyses were performed at the 2-sided $\alpha=0.05$ level with no adjustment for multiplicity. The ITT population was the primary analysis population and a per protocol analysis was not performed in respect of the withdrawal design of the study.

-The primary endpoint was analysed with Cox proportional hazards model with adjustment for treatment. Differences between treatments were expressed as the hazard ratio with the corresponding 2-sided 95 % confidence interval (CI) and p-value.

-Cochran-Mantel-Haenzel tests (stratified by randomization assessment) were used to assess treatment differences in the Physician's Global Assessment.

-Presence and severity of symptoms were summarized descriptively for the different phases of the study.

-It was estimated that 38 patients per group were required, in order to provide at least 90 % power to detect a difference at a 2-sided alpha level of 0.05 using Fisher's exact test. The calculation included an assumption of success rate of 80 % of actively treated and of 40 % of placebo-treated patients.

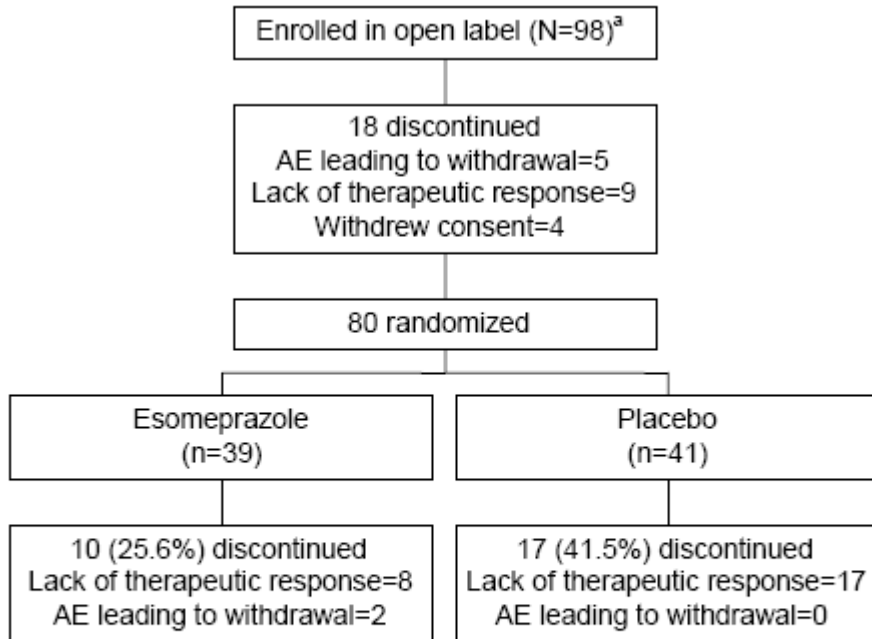
➤ **Results**

• **Recruitment/ Number analysed**

A total of 103 patients were screened of which 5 were not enrolled into the open-label phase. The reasons for not continuing were voluntary discontinuation and non-compliance with the protocol.

The numbers of patients available for analyses are shown in Figure 7.

Figure 7. Patient disposition flow chart



^a Five patients failed to be eligible and were not enrolled in the open-label phase. Reasons for screen failure included voluntary discontinuation by the parent/guardian (4 patients), and non-compliance with the protocol (1 patient).

- **Baseline data**

The demographic and important baseline characteristics of the patients are showed in Table 14.

Table 14. Demographic and baseline characteristics (ITT population)

Characteristic	Category			
	Open-label ^a	All randomized	Double-blind randomized treatment	
			Esomeprazole	Placebo
	(n=98)	(n=80)	(n=39)	(n=41)
Demographics				
Sex [n (%)]				
Male	63 (64.3)	57 (71.3)	30 (76.9)	27 (65.9)
Female	35 (35.7)	23 (28.8)	9 (23.1)	14 (34.1)
Age (months)				
Mean (SD)	4.8 (2.9)	4.9 (2.9)	4.9 (2.6)	4.9 (3.2)
Median	4	4	4	3
Range	1 to 11	1 to 11	1 to 11	1 to 11
Age in months [n (%)]				
1	6 (6.1)	4 (5.0)	1 (2.6)	3 (7.3)
2	17 (17.3)	16 (20.0)	8 (20.5)	8 (19.5)
3	18 (18.4)	13 (16.3)	3 (7.7)	10 (24.4)
4	15 (15.3)	12 (15.0)	10 (25.6)	2 (4.9)
5	10 (10.2)	8 (10.0)	4 (10.3)	4 (9.8)
6	7 (7.1)	5 (6.3)	3 (7.7)	2 (4.9)
7	7 (7.1)	6 (7.5)	4 (10.3)	2 (4.9)
8	2 (2.0)	2 (2.5)	1 (2.6)	1 (2.4)
9	4 (4.1)	4 (5.0)	2 (5.1)	2 (4.9)
10	6 (6.1)	5 (6.3)	1 (2.6)	4 (9.8)
11	6 (6.1)	5 (6.3)	2 (5.1)	3 (7.3)
Race [n (%)]				
Caucasian	86 (87.8)	72 (90.0)	35 (89.7)	37 (90.2)
Black	4 (4.1)	2 (2.5)	2 (5.1)	0
Asian	3 (3.1)	2 (2.5)	1 (2.6)	1 (2.4)
Other	5 (5.1)	4 (5.0)	1 (2.6)	3 (7.3)
Baseline characteristics				
Weight (kg)				
Mean (SD)	6.6 (1.5)	6.8 (1.5)	6.9 (1.6)	6.7 (1.4)
Median	7	7	7	7
Range	3 to 11	4 to 11	4 to 11	4 to 10
Weight group (kg)				
3 to 5 kg	11 (11.2)	8 (10.0)	3 (7.7)	5 (12.2)
>5 kg to 7.5 kg	61 (62.2)	48 (60.0)	26 (66.7)	22 (53.7)

>7.5 kg	26 (26.5)	24 (30.0)	10 (25.6)	14 (34.1)
Height (cm)				
Mean (SD)	64.2 (5.8)	64.6 (5.7)	64.6 (5.4)	64.5 (6.0)
Median	64	64	64	64
Range	49 to 75	49 to 75	57 to 75	49 to 74
BMI (kg/m ²)				
Mean (SD)	16.0 (1.9)	16.2 (1.9)	16.4 (1.9)	16.0 (1.9)
Median	16	16	16	16
Range	11 to 22	11 to 22	12 to 22	11 to 20
Head circumference (cm)				
n	97	79	39	40
Mean (SD)	42.1 (2.7)	42.4 (2.6)	42.5 (2.6)	42.2 (2.7)
Median	42	42	42	42
Range	35 to 49	37 to 49	39 to 48	37 to 49
Dose/body weight (mg/kg) ^b				
Mean	0.88	0.89	0.86	0.92
Range	0.50 to 1.33	0.50 to 1.33	0.51 to 1.28	0.50 to 1.33

^a All patients received open-label esomeprazole during the open-label phase.

^b Dose in mg/kg at the start of the open-label treatment period (Visit 2) when all patients were to receive open-label esomeprazole.

ITT Intent to treat; SD Standard deviation.

Data derived from [Table 11.1.2.1 Section 11](#).

There were more boys than girls included in both phases of the study and the majority of the infants and toddlers were Caucasians. There were no major differences in baseline demographic variables between the randomized groups. According to the MAH, babies that entered the study had on average a lower weight for age and weight for length compared to an age-matched population (US CDC growth charts, 2000).

The baseline diagnoses of the included child population are shown in Table 15.

Table 15. Baseline diagnosis of GERD

Disease history	N (%) of patients in each category			
	Open-label ^a	All randomized	Double-blind randomized treatment	
			Esomeprazole	Placebo
	(n=98)	(n=80)	(n=39)	(n=41)
Diagnostic tool				
n	66 (67.3)	56 (70.0)	26 (66.7)	30 (73.2)
X-ray	30 (30.6)	26 (32.5)	11 (28.2)	15 (36.6)
Endoscope	20 (20.4)	14 (17.5)	8 (20.5)	6 (14.6)
pH probe	17 (17.3)	16 (20.0)	9 (23.1)	7 (17.1)
Other	24 (24.5)	21 (26.3)	9 (23.1)	12 (29.3)
Verified GERD ^b				
n	50 (51.0)	44 (55.0)	21 (53.8)	23 (56.1)
X-ray	18 (18.4)	16 (20.0)	7 (17.9)	9 (22.0)
Endoscope	15 (15.3)	11 (13.8)	7 (17.9)	4 (9.8)
PH probe	12 (12.2)	12 (15.0)	5 (12.8)	7 (17.1)
Other	16 (16.3)	16 (20.0)	7 (17.9)	9 (22.0)
Erosive disease [n (%)]				
LA Grade A ^c	4 (4.1)	4 (5.0)	3 (7.7)	1 (2.4)
LA Grade B ^c	2 (2.0)	2 (2.5)	1 (2.6)	1 (2.4)
LA Grade C ^c	0	0	0	0
LA Grade D ^c	0	0	0	0
Non-erosive disease findings				
Barrett's esophagus	1 (1.0)	0	0	0
Stricture	0	0	0	0
Hiatus hernia	3 (3.1)	3 (3.7)	2 (5.1)	1 (2.4)
Malignancy	0	0	0	0
Other abnormal	5 (5.1)	1 (1.3)	0	1 (2.4)

^a All patients received open-label esomeprazole during the open-label phase.

^b Non-verified GERD was based on clinical diagnosis of symptomatic presentation alone. Verified GERD was based on a diagnostic procedure such as X-ray, endoscope, or PH probe.

^c Erosive disease LA score classification: Grade A is 1 (or more) mucosal break no longer than 5 mm that does not extend between the tops of 2 mucosal folds; Grade B is 1 (or more) mucosal break more than 5 mm that does not extend between the tops of 2 mucosal folds; Grade C is 1 (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but which involves less than 75% of the circumference; D is 1 (or more) mucosal break that involves at least 75% of the circumference.

Data derived from [Tables 11.1.3.2 and 11.1.3.3](#), Section 11.

Twenty patients (20.4 %) had an endoscopic examination at baseline and of these patients 6 were found to have erosive disease.

• **Efficacy results**

Eighteen of the patients in the open-phase part of the study discontinued from the study, 9 because of lack of result and 5 due to AEs.

The percentage of patients that discontinued due to symptom worsening (Primary efficacy variable) is shown in Table 16.

Table 16. Analysis of time to discontinuation due to symptom worsening (ITT population)

Treatment	N % of patients with event ^a		Comparison between groups		
			Hazard ratio	95% CI	p-value ^b
Esomeprazole (n=39)	15	38.5	0.69	0.35 to 1.35	0.2751
Placebo (n=41)	20	48.8			

^a Patients classified as discontinuing due to symptom worsening.

^b Analysis via Cox Proportional Hazards model adjusting for treatment.

Data derived from [Table 11.2.2.1](#), Section 11.

The result indicated a lower risk for esomeprazole treated patient, however, the difference was not statistically significant. The major differences between the groups were observed during the first 2-weeks of the double-blind phase, see Table 17.

Table 17. Cumulative percentage of patients discontinuing due to worsening symptoms (ITT population)

Variable	Esomeprazole (n=39)	Placebo (n=41)
Total discontinued (n [%])	15 (38.5)	20 (48.8)
Censored or event free (n [%])	24 (61.5)	21 (51.2)
Cumulative % patients who discontinued ^a		
Week 0	0	0
Week 1	2.6	14.6
Week 2	20.5	29.3
Week 3	23.1	31.7
Week 4	39.4	49.3

^a Estimated using the Kaplan-Meier method.

Data derived from [Table 11.2.2.3](#), Section 11.

For the other efficacy endpoint variables, numerical (in favour of esomeprazole) but not statistically significant, differences were observed.

- **Safety results**

Of the 98 included infants and toddlers entering the open-label phase of the study, all were given esomeprazole according to the protocol. For a summary of the exposure, see Table 18.

Table 18. Overview of exposure (SA population)

Study period/Extent of exposure (days) ^a	N (%) of patients in each category		
	Open-label ^b (n=98)	Double-blind randomized treatment	
		Esomeprazole (n=39)	Placebo (n=41)
Open-label^c			
n	98	39	41
Mean (SD)	14.3 (2.6)	14.3 (1.7)	14.9 (1.7)
Median	14	14	14
Range	4 to 21	11 to 19	12 to 19
Double-blind			
n		39	41
Mean (SD)		24.6 (8.0)	21.7 (9.5)
Median		27	27
Range		5 to 42	2 to 30

^a Exposure was calculated by the difference between the last dose date and first dose date plus 1 day.

^b All patients received open-label esomeprazole during the open-label phase.

^c During this period, all patients were given open-label esomeprazole.

Data derived from [Table 11.3.9](#), Section 11.

The median number of days exposed to the study drug both in the open phase and during the double-blind period for both groups was 14 days.

A summary of AEs in open label and double-blind phases of the study are shown in Table 19 and Table 20.

Table 19 Adverse events in any category of patients in the open-label phase (SA population)

Category of adverse event ^a	N (%) of patients in each category	
	Open-label ^b (n=98)	Discontinued in the open-label phase ^c (n=18)
Any adverse event (n [%])	47 (48.0)	11 (61.1)
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	4 (4.1) ^d	2 (11.1)
Discontinuations of study treatment due to adverse events	5 (5.1)	5 (27.8)
Treatment-related adverse events	4 (4.1)	2 (11.1)
Total number of adverse events (n)		
Any adverse event ^d	68	17
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	4	2
Discontinuations of study treatment due to adverse events	6	6
Treatment-related adverse events	4	2

^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

^b All patients received open-label esomeprazole during the open-label phase.

^c A subgroup of all patients who were enrolled in the open-label phase, but not subsequently randomized into the double-blind phase.

^d One additional patient (E2002005) had an SAE of gastroenteritis that started before entering the open-label phase; this patient was subsequently randomized to the double-blind phase.

^e Events counted by preferred term, ie, for subjects with multiple events falling under the same preferred term. Only 1 occurrence of the event was counted. The number of events could exceed the number of subjects.

Data derived from Table 11.3.1.1, Section 11.

Table 20. Adverse events in any category of patients in the double-blind phase (SA population)

Category of adverse event ^a	Double-blind randomized treatment	
	Esomeprazole (n=39)	Placebo (n=41)
Any adverse event (n [%])	23 (59.0)	27 (65.9)
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	3 (7.7)	0
Discontinuations of study treatment due to adverse events	2 (5.1)	0
Treatment-related adverse events	1 (2.6)	1 (2.4)
Total number of adverse events (n)		
Any adverse event ^b	79	56
Serious adverse events leading to death	0	0
Serious adverse events not leading to death	5	0
Discontinuations of study treatment due to adverse events	3	0
Treatment-related adverse events	1	1

^a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

^b Events counted by preferred term, ie, for subjects with multiple events falling under the same preferred term. Only 1 occurrence of the event was counted. The number of events could exceed the number of subjects.

Data derived from Table 11.3.1.2, Section 11.

Seven patients had SAEs during the study, none was considered to be related to the study drug. Seven patients discontinued due to an adverse event, 5 patients in the open-label phase and 2 who received double-blind treatment. None of the events were considered to be related to the study drug.

Four patients had treatment-related AEs (abdominal pain, regurgitation, tachypnea, and increase in ALT) all of which developed during the open-label phase.

There were no clinically relevant findings or trends regarding haematology, clinical chemistry, urinalysis, vital signs or physical examination observed with esomeprazole.

No new safety signals were identified in the study.

Assessor's comments: The result of the present study provides no convincing evidence to support that esomeprazole is more effective than placebo in reducing the signs and symptoms of GERD in the age-group 1-11 months. The population studied was heterogeneous. A minority had endoscopically confirmed erosive disease while others had a diagnosis based on the symptomatic presentation only. The chosen efficacy primary endpoint was a crude surrogate variable that might not correctly have mirrored efficacy. Thus, the target population was not sufficiently characterized and endpoints might have been to crude to measure efficacy. No firm conclusions can be drawn on the efficacy of esomeprazole in the present population.

Furthermore, intraluminal oesophageal pH measurements were also performed for a minority only. Even though abnormal pH seems not to be closely correlated to severity of symptoms in infants it could have been of value for evaluating the quantity, frequency and duration of acid reflux episodes.

Oesophagitis is rare in this young population and treatment should only involve patients with proven GERD. Although the pathophysiology is considered to be the same as in adults, extrapolation from adult

is not straightforward. Compared to older children and adults the clinical presentation in this young age-group is different and in the majority of infants symptoms do resolve without pharmacological interventions. In comparison with adults and older children the major difference is the ongoing maturation in the young infants and the possible transient nature of the disease.

There might be paediatric patients that would benefit from treatment with esomeprazole. However, such a subpopulation has not been identified in the present study and benefit in this age group has not been proven.

No new safety signals were identified in the study.

Study D9614C00004

Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of esomeprazole once daily for the treatment of Gastroesophageal Reflux Disease (GERD) in neonatal patients, including premature and up to 1 month corrected age.

➤ Description

This multicentre study was conducted at 3 centres, one in Australia, one in Germany and one in the United States. Term neonatal patients, and premature up to 1 month corrected age, were included in the study.

➤ Methods

• Objective(s)

The primary objective of the study was to compare the efficacy of esomeprazole with that of placebo in the treatment of signs and symptoms of GERD (observed by video and cardiorespiratory monitoring) in neonatal patients. Secondary objectives were to assess the differences between esomeprazole and placebo in:

- treatment of symptomatic reflux episodes of GERD;
- treatment of other GERD-related signs and symptoms (via video, pH/impedance, cardiorespiratory monitoring);
- reducing the number of all reflux episodes and acidic episodes (pH<4);
- safety and tolerability.

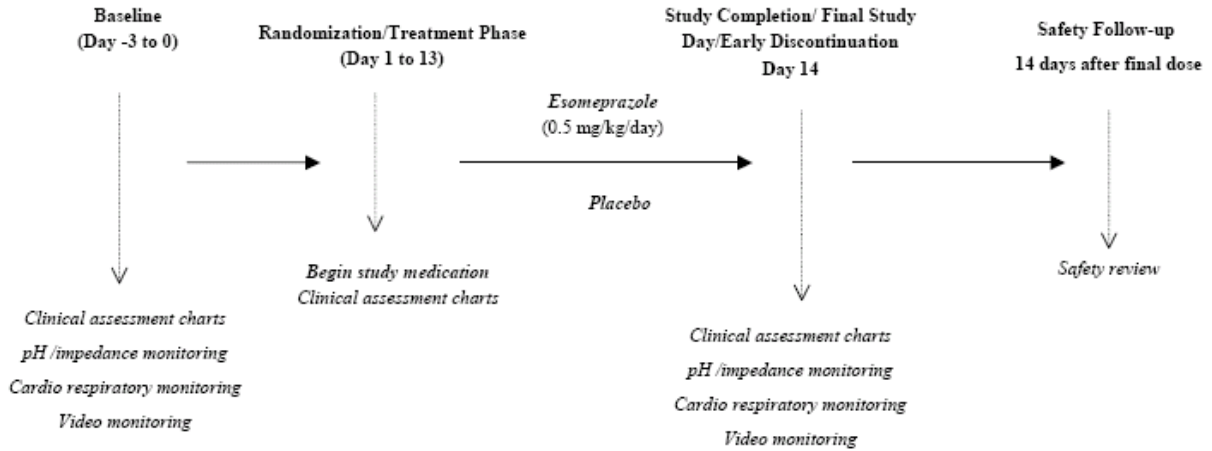
• Study design

The study was randomized, double-blind and placebo-controlled. At the start of the study all patients were inpatients in a neonatal intensive care unit, and were expected to be so during the treatment period. In case of an earlier discharge, an option was to have a home visit for drug administration and readmission to the hospital for the final study day procedures.

At baseline all patients had a physical examination, vital signs, laboratory assessments, ECG and clinical assessment charts were recorded. Combined pH and impedance monitoring was recorded for a minimum of 18 hours. The patients were filmed with a video camera for 8 hours and cardiorespiratory monitoring was performed simultaneously. After randomization and treatment for 14 days the procedures performed at baseline were repeated. After 14 days an in-patient or office visit was scheduled for a safety follow-up evaluation.

The design of the study is shown in Figure 8.

Figure 8. Study flow chart



- **Study population /Sample size**

It was planned that 90 patients should be enrolled into the study but due to difficulties in recruiting only 52 were included.

Full term patients or patients with a gestational age or post-conceptual age ≥ 28 to 44 weeks with GERD, as observed by 8-hour video and cardiorespiratory monitoring, were included.

- **Treatments**

Esomeprazole was administered by nasogastric or orogastric tube or by nipple at 0.5 mg/kg/day, 30 minutes before feeding. There were no differences in appearance between the active and the placebo product.

- **Outcomes/endpoints**

A summary of efficacy objectives and variables is shown in Table 21.

Table 21. Efficacy and pharmacodynamic objectives and corresponding variables

Objective	Variable(s) ^a
<p>Primary: To assess the difference between esomeprazole and placebo in the treatment of signs and symptoms of GERD as observed by 8-hour video and cardiorespiratory monitoring in neonatal patients</p>	<p>Primary: Change from baseline in the number of occurrences of symptoms of GERD, as observed from video recording, and GERD-related signs detected from cardiorespiratory monitoring</p>
<p>Secondary: To assess the difference between esomeprazole and placebo in the treatment of symptomatic reflux episodes of GERD</p>	<p>Secondary: Change from baseline in the number of occurrences of symptoms of GERD (impedance-detected events with pH <4.0), including only signs and symptoms of GERD temporally associated with reflux episodes (+/-2 min, +2 minutes, or +5 minutes after reflux start)</p>
<p>Secondary: To assess the difference between esomeprazole and placebo in the treatment of weakly acidic, non-acid, and any reflux episodes of GERD</p>	<p>Change from baseline in the number of occurrences of symptoms of GERD), including only signs and symptoms of GERD temporally associated with weakly acidic (pH 4.0-6.9 inclusive), non-acidic (pH >7.0), and any (acidic, weakly acidic, or non-acidic) reflux episodes (+/-2 min, +2 minutes, or +5 minutes after reflux start)</p>
<p>Secondary: To assess the difference between esomeprazole and placebo in the treatment of other GERD-related signs and symptoms via video, pH/impedance, and cardiorespiratory monitoring</p>	<p>Secondary: Change from baseline in the:</p> <ul style="list-style-type: none"> • number of GERD-related events observed during the video monitoring period by event type and the number of events that coincide with an acid reflux • durations of sleep, waking hours, peaceful quietness, and crying observed during the video monitoring period • number of GERD-related signs as recorded in the clinical assessment charts • Physician Global Assessment (PGA) score of GERD-related symptoms
<p>Secondary: To assess via pH/impedance monitoring the efficacy of esomeprazole compared to placebo in reducing the number of: (a) all types of reflux episodes (acid or non-acid) and (b) acidic reflux episodes, defined as pH <4.0</p>	<p>Secondary: change from baseline from pH/impedance data: number of acidic reflux episodes, weakly acidic reflux episodes, non-acidic reflux episodes, liquid reflux episodes, and mixed gas/liquid reflux episodes; and mean bolus and mean acid clearance time change from baseline from pH data: number of acidic reflux episodes (ie, pH <4.0), number of acidic episodes lasting longer than 5 minutes, % time pH <4.0, % time pH 4.0-6.9 (inclusive)</p>

^a The variables in this table reflect changes to the original protocol that are described in the SAP (Appendix 12.1.9) and further detailed in Section 5.8.1.

Symptoms of GERD were; gagging, back arching, irritability/crying/fussing and vomiting.

Signs of GERD detected from the cardiorespiratory monitoring were;

- oxygen desaturation (defined as a fall in oxygen saturation < 85 %)
- bradycardia (decrease in heart rate < 100 beats/minute for ≥ 5 seconds)
- apnea (defined as a pause in respiratory effort for ≥ 20 seconds).

The safety variables included are shown in Table 22.

Table 22. Safety variables

Objective	Summary variables for analysis
Secondary: To assess the safety and tolerability of esomeprazole compared to placebo	<ul style="list-style-type: none">• Adverse events• Clinical laboratory evaluation• Physical examination• Vital signs

• **Statistical Methods**

The ITT population was the primary population for all efficacy analysis. All statistical tests and confidence intervals were 2-sided. A *p*-value of ≤ 0.05 was considered statistically significant.

The change from baseline of GERD symptoms and secondary pharmacodynamic variables were analysed using ANCOVA. Only descriptive data were summarised from the clinical assessment charts and safety assessment. The Physician global assessments were checked for differences between the groups with Cochran-Mantel-Haenszel test.

All endpoints were further analysed in the subgroup of patients with a percentage time of reflux <4.0 at baseline of ≥ 11 %.

The safety population consisted of all patients that had received at least one dose of study medication.

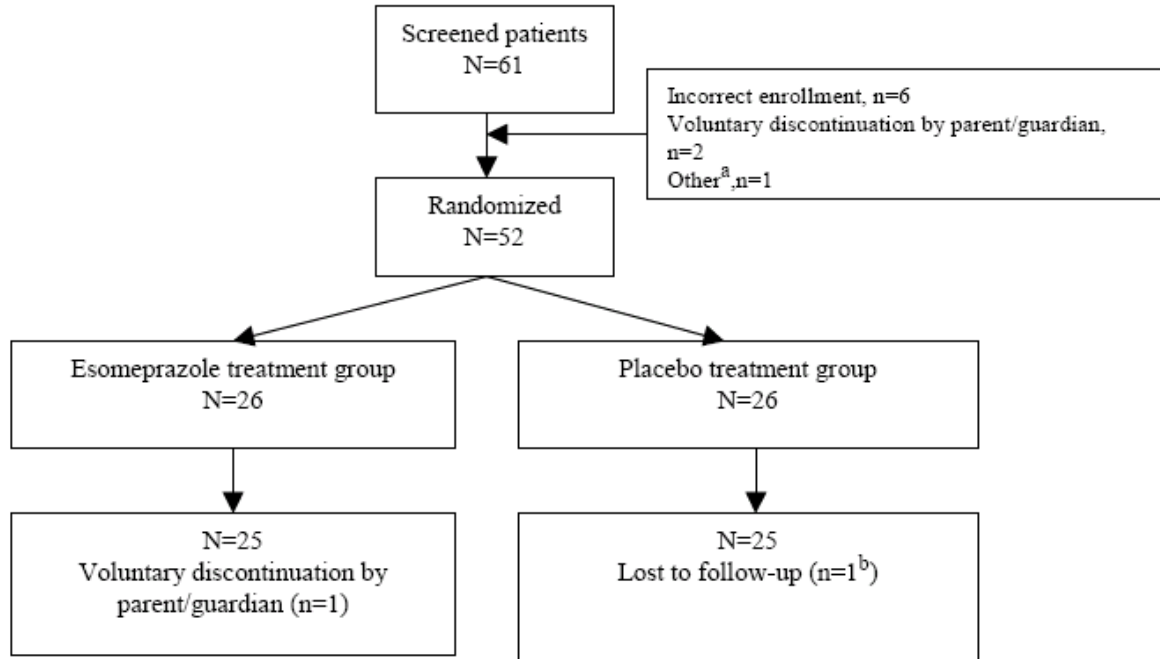
➤ **Results**

• **Recruitment/ Number analysed**

It was planned that 90 patients needed to be randomized in order to achieve 76 evaluable patients. Thirty-eight patients per treatment arm were required to provide at least 80 % power at the 2-sided alpha level of 0.05 to detect a difference in symptomatic episodes from baseline.

The numbers of patients available for analysis is shown in Table 23.

Table 23. Patient disposition flow chart



^a Study drug for this patient defrosted in transit and was unusable.

^b Patient E1002003 received all 14 doses of study medication and was discharged from the study. The patient was subsequently lost to follow-up between the study completion visit and the safety follow-up visit.

All 52 patients were available for the safety analysis and for the ITT population, one patient in the active group did not have valid measurements and therefore only 51 were included in the analysis.

- **Baseline data**

Demographic and key baseline characteristics are presented in Table 24.

Table 24. Demographic and baseline characteristics

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

ITT Intent-to-treat; SD standard deviation; BMI body mass index

Note: For all patients: mean (SD) dose of study medication=0.5 (0) mg/kg; median dose=0.5 mg/kg; range=0.5 to 0.6 mg/kg.

Data derived from [Table 11.1.2. 1](#) in Section 11.

There were more girls than boys included in the study and the majority of patients were Caucasians. The weight and length of patients in both groups was similar to that of a general US population. The mean age was 47 days, and due to incorrect listing at one of the centres the gestational age range at birth was 24 to 40 weeks.

- **Efficacy results**

Primary endpoint:

There were no statistically significant differences between esomeprazole and placebo for the primary endpoint, change from baseline in number of occurrences of symptoms of GERD, Tables 25 and 26.

Table 25. Summary of the normalized number of GERD events observed from video and cardiorespiratory monitoring (ITT)

Treatment	Visit	Number of events			Change from baseline		
		Mean (SD)	Median	Range	Mean (SD)	Median	Range
Esomeprazole (n=25)	Baseline	184.66 (78.53)	159.88	101.84 to 412.90			
	Final	156.65 (75.11)	137.01	95.21 to 465.74	-28.01 (77.70)	-21.48	-209.32 to 240.02
Placebo (n=26)	Baseline	183.10 (77.46)	155.15	84.33 to 395.37			
	Final	158.31 (75.89)	139.41	70.43 to 425.90	-24.79 (44.25)	-16.24	-105.85 to 53.07

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

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

GERD gastroesophageal reflux disease; ITT intent-to-treat; SD standard deviation

Data derived from Table 11.2.1. 2 in Section 11.

Table 26. Analysis of the change from baseline in the total number of GERD events

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

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

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

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

GERD gastroesophageal reflux disease; ITT intent-to-treat; ANCOVA analysis of covariance

Data derived from Table 11.2.1. 9, Section 11.

Secondary endpoints:

There were statistically significant differences in change from baseline in the total number of GERD events associated with acidic reflux (pH<4.0) for all 3 temporal associations (ie. +/- 2 minutes, + 2 minutes, + 5 minutes after reflux start). These differences were not observed between treatment groups in signs and symptoms associated with weakly acidic reflux (pH 4.0 to 6.9) nor non-acidic reflux (pH≥7.0).

A statistically significant decrease from baseline was also observed for neurobehavioral symptoms class associated with acid reflux (back arching and irritability /crying/ fussing events).

The total number of gastrointestinal, neurobehavioral or cardiorespiratory events did not change over the course of the study and there were no differences between the groups.

No statistically significant differences between groups were observed in individual symptom types (sleeping, crying, peaceful quietness) or in the Physician global assessment of GERD symptoms.

The subgroup analysis of patients with a reflux index at baseline > 11% showed a statistically significant decreased total numbers of oxygen desaturation events and for events associated with acid reflux.

The number of acidic reflux events did not differ between the groups (P= 0.0737) but the number of acidic reflux events longer than 5 minutes and the % of time the pH was < 4.0 was statistically significant in favour of the active treatment in comparison with placebo.

- **Safety results**

Of the 52 patients included in the study, half of them received esomeprazole and the half placebo. For a summary of exposure, see Table 27.

Table 27. Overview of exposure to study medication (SA population)

Extent of exposure^a (days)	Esomeprazole (n=26)	Placebo (n=26)
Mean (SD)	12.5 (2.5)	12.7 (1.6)
Median	14	14
Range	4 ^b to 16 ^c	9 to 14

^a Exposure was calculated by the difference between the last dose date and first dose date plus 1 day.

^b Patient E1002007 was voluntarily discontinued by parent/guardian after receiving 4 doses of study medication.

^c Dosing for Patient E1003002 was delayed due to surgery although the patient received all 14 doses (ie, 14 doses in 16 days).

Data derived from [Table 11.3.9. 1](#) in Section 11.

The number of days exposed were similar in the two groups.

A total of 6 esomeprazole (23 %) treated patients experienced 10 AEs. The corresponding figures for the placebo treated group were 9 (34.5 %) patients with 14 AEs. No SAEs occurred in the active group while 3 patients experienced 4 SAEs in the placebo group.

The most commonly reported AE were gastrointestinal disorders (9.6 %), infection/infestations (7.7 %) and investigations (5.8 %).

Adverse events listed by preferred term are shown in Table 28.

Table 28. Number (%) of patients with AEs, sorted by decreasing order of frequency (SA)

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

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

Data derived from [Table 11.3.3. 1](#) in Section 11.

One AE (placebo group) was considered to be treatment related (anaemia neonatal of mild severity). There were no deaths occurring during the study period.

At the pre-study visit and on the final day, blood and urine samples were taken for determination of haematology, clinical chemistry and urinalysis. No clinically important trends or group differences were identified although isolated changes were observed. None was regarded as clinically relevant and all were representative of the neonatal population.

There were no clinically significant trends within or between the groups of vital signs and of the physical examination assessed at baseline, day 1 and final study day.

No new safety signals were identified in this population of babies.

Assessor's comments: The result of the present study in preterm and neonatal patients is not convincing to support that esomeprazole is more effective than placebo in the treatment of signs and symptoms of GERD in paediatric patients 0-1 month old. There were no statistically significant differences between the treatment groups for the primary endpoint, change from baseline in number of occurrences of symptoms of GERD.

There was a statistically significant difference between the groups concerning the secondary efficacy variable, change from baseline in the total number of GERD events associated with acid reflux. However, the number of acidic reflux events was numerically lower in the active group (borderline significant). Thus, evaluating this secondary endpoint, in total number of GERD events associated with reflux cannot provide support for a clinically relevant effect as the primary endpoint failed.

The studied population had symptoms at baseline historically considered to be related to GERD. However the diagnosis of GERD was not verified at inclusion. Oesophageal pH and intraluminal impedance were used to identify all types of reflux episodes but not for verifying the diagnosis at baseline. However, there seems to be a poor correlation between oesophageal pH and symptoms and the clinical value of increasing the pH in this young age group is questioned. Symptoms were not strongly correlated to acidic events and occurred also in relation to events that were non-acidic.

Consequently, treatment with esomeprazole decreased the numbers of acidic reflux episodes in immature patients but had no clinical benefit for the patient in improving symptoms.

There were no new safety signals identified in the study.

3. Discussion on clinical aspects

Clinical efficacy

No firm conclusions can be drawn from the submitted studies in support of the present application on the efficacy of esomeprazole in the treatment of GERD in preterm, neonates, infants and toddlers.

The results from the Phase II studies were inconclusive due to the study designs, i.e. the limited scientific value in the absence of a control group (NEC 2) and mainly due to the lack of symptom improvement (NEC 1).

The results from the two Phase III studies provided no convincing evidence to support that esomeprazole was more effective than placebo in reducing the signs and symptoms of GERD in the age-groups 1-11 months and 0-1 month-olds. The populations studied were heterogeneous with diagnoses of GERD based mainly on symptomatic presentations. Thus, the target populations were not sufficiently characterized and the endpoints used might have been too crude to measure efficacy. The challenge of identifying subjects with typical symptoms of GERD and also of differentiating between physiological gastroesophageal reflux (GER), that resolves without intervention, from GERD in individuals < 1 year is acknowledged.

There seems to be a poor correlation between oesophageal pH and symptoms in the youngest age group since symptoms were not strongly correlated to acidic events. Furthermore, the majority of the preterm infants and neonates (NEC 2) had intragastric pH > 4 during a greater part of the time at baseline.

To conclude, the efficacy of esomeprazole in the treatment of preterm, neonates, infants and toddlers with symptoms of GERD is yet to be proven.

Safety

There were no new safety signals identified in 0-11 month-olds treated for up to 6 weeks with esomeprazole. This information could be of use for the prescribing physician and it is therefore proposed that sections 4.2 and 5.1 are amended with these observations on safety in a following type II variation.

V. **RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION 1ST ROUND**

➤ **Overall conclusion**

The pharmacokinetic information indicate that the doses proposed will give similar mean esomeprazole exposure in children 1-11 months as in the older age groups with approved dose recommendations. However, it is not completely clear whether the comparative data is multiple-dose data, as should be the case for a comparison to be possible. The PK/PD relationship observed in this age range indicate that maximum effect on time with pH>4 is obtained at AUC approximately over 2-3 $\mu\text{M}\cdot\text{h}$ while the mean exposure obtained with the proposed dose is ca 3 $\mu\text{M}\cdot\text{h}$. However, there are some discrepancies in the comparative data on exposures and the applicant should address this.

I children 0-1 month, a population analysis of sparse samples is available. Data on protein binding is available from 5 patients indicating that the free fraction is doubled. Thus, the unbound concentration should have been used and the study is inconclusive. The PK/PD data indicate that there is a relationship between exposure and pH but also that the baseline pH is quite high in the population.

The pharmacokinetic data in children 1-11 months could be included in section 5.2 and the applicant should propose an adequate text.

Although the pathophysiology is considered to be the same as in adults, extrapolation from adult is not straightforward. Compared to older children and adults the clinical presentation in this young age-group is different and in the majority of infants, symptoms do resolve without pharmacological interventions. In comparison with adults and older children the major difference is the ongoing maturation in the young infants and the possible transient nature of the disease.

Oesophagitis is rare in this young population and treatment should only involve patients with proven GERD.

There might be a subgroup of paediatric patients that would benefit from treatment with esomeprazole. However, such a subpopulation has not been identified in the present studies. With the data at hand no added benefit as compared to placebo in this population had been shown.

The beneficial effect of esomeprazole in the treatment of preterm, neonates, infants and toddlers with symptoms of GERD is yet to be proven.

Submitted data is not sufficient for the suggested changes in the SmPC Sections 4.1 and 4.2.

The benefit risk balance for esomeprazole when used in older children, adolescents and adults is not affected by the present result, and remains positive.

➤ **Recommendation**

Submitted data is not sufficient for the suggested changes in the SmPC Sections 4.1 and 4.2.

The MAH should provide supplementary information and propose an adequate 5.2 text as part of this worksharing procedure (see section VI "Request for Supplementary Information") The MAH is invited to comment on the Rapporteurs SPC proposals.

The SmPC amendments (introduced through a future variation procedure) proposed by the Rapporteur are shown below:

Section 4.2.

Paediatric patients

The experience of treatment with esomeprazole in infants < 1year is limited and is therefore not recommended. See section 5.1.

Section 5.1.

Paediatric patients

In two placebo-controlled studies including a total of 105 infants treated for 2 weeks and 29 treated for an additional 4 weeks from a mixed population. There were no differences between esomeprazole and placebo for the chosen endpoints, time to discontinuation due to symptom worsening and change from baseline in number of occurrences of symptoms of GERD.

The safety profile appeared to be similar to that seen in adults.

The MAH should provide supplementary information and propose an adequate 5.2 text as part of this worksharing procedure (see section VI “Request for Supplementary Information”) The MAH is invited to comment on the Rapporteurs SPC proposals.

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions:

1. The applicant should discuss the discrepancy in the data on esomeprazole mean exposure in different age groups. NEC-001 indicate that an increased exposure is expected in children below 1 year while the tabulated comparative data indicate that the mean exposure should be similar.
2. A reduced protein binding was observed in children 0-1 months of age. The applicant should discuss whether it is expected that children in the lower part of the 1-11 month range also will have a reduced protein binding.
3. The applicant has proposed in earlier applications that CYP2C19 is not available until 3 months of age. This indicates that CYP3A then would be the major enzyme and therefore has implications for the interaction text. The applicant should comment.
4. The applicant should propose an adequate text in section 5.2 reflecting the data available in children 1-11 months of age.

VII. RESPONSE ASSESSMENT

Question #1

The applicant should discuss the discrepancy in the data on esomeprazole mean exposure in different age groups. NEC-001 indicate that an increased exposure is expected in children below 1 year while the tabulated comparative data indicate that the mean exposure should be similar.

Response from the MAH

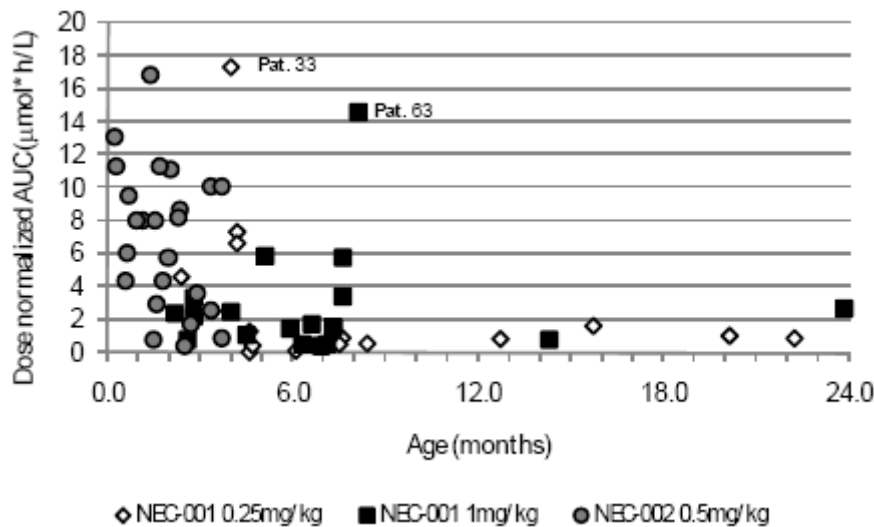
AstraZeneca recognises that the “Esomeprazole exposure – Comparison across age groups” table (PAR Table 17; Critical Expert Overview of Paediatric data dated 15 December 2009 Table 2) is unclear. To clarify:

- All data presented in Table 17 are multiple-dose data.
- The exposure data for study NEC-002 presented under the column heading “<1 month” are based on all patients with evaluable PK data (n=24). By <1 month of age is meant <1 month post-term, where term is 38 gestational weeks.

- The exposure data from patients ≤ 12 months old in study NEC-001 are presented under the column heading “1 to 11 months”, thus the data from the patients >12 months of age (n=6) are not included in Table 17. The data from the patients >12 months of age are presented in the NEC-001 study report.

As can be seen in Table 17, the children in the youngest age group, <1 month of age, had a higher exposure compared to those 1 to 11 months of age than would be expected based on dose alone. Thus, the geometric mean AUC_{τ} and CSS_{max} after the administration of 0.5 mg/kg esomeprazole in the infants <1 month of age was 2.45 $\mu\text{mol}\cdot\text{h}/\text{L}$ and 0.74 $\mu\text{mol}/\text{L}$, respectively, which is only slightly lower than corresponding values observed in infants 1 to 11 months of age after the administration of 1.0 mg/kg (3.51 $\mu\text{mol}\cdot\text{h}/\text{L}$ and 0.87 $\mu\text{mol}/\text{L}$, respectively), indicating a somewhat lower metabolic rate in the youngest children. The exposure in the youngest children also had a higher geometric mean AUC compared to those 1 to 5 years of age receiving 5 mg esomeprazole (0.26 mg/kg) (2.45 $\mu\text{mol}\cdot\text{h}/\text{L}$ versus 0.74 $\mu\text{mol}\cdot\text{h}/\text{L}$) than would be expected based on dose alone. This is in agreement with what has previously been reported in the literature of higher metabolic rate in paediatric subjects aged 6 months to 2 years and to some extent also in children aged 2 to 12 years than in other paediatric subjects (Ginsberg et al 2002). This is also reflected in Figure 1. On the other hand, the youngest children had lower exposure compared the those 1 to 5 years of age receiving 10 mg esomeprazole (0.71 mg/kg) and also those 6 to 17 years of age (Table 17) than would be expected based on dose alone. This result is not in agreement with the finding by Ginsberg et al that the half life of drugs is generally 3 to 9 times longer in neonates than in adults. There is no obvious explanation to this discrepancy; however, it is consistent with the findings in a study in which paediatric patients 0 to 17 years old received intravenous administration of esomeprazole (Study D9615C000211). Thus, plasma clearance normalized by body weight was found to be 0.17 L/h/kg in the age group 0 to 1 month compared to approximately 0.25 L/h/kg in the age groups 1 to 11 months and 1 to 5 years, and approximately 0.12 L/h/kg in the age groups 6 to 11 years and 12 to 17 years.

Figure 1 Dose normalized AUC_{τ} for esomeprazole versus age following repeated (7/8 days) oral administration of esomeprazole in children aged 0 to 2 years.



Patient 33 (1 mg/kg) had considerably higher plasma concentrations of esomeprazole and metabolites compared to the other patients in this dose group, possibly indicating dosing error. Patient 63 received the doses in evening on days 1 to 6 but in the morning on day 7 (PK day), thus less than 24 hours between doses.

1 Note: this study was recently submitted to MPA and Concerned Member States in connection with a type II variation for Nexium for intravenous use: new paediatric indication (GERD) in children and

adolescents 1-18 years of age (MRP no: SE/H/0211/003/II/079) and the study report is also attached to this response for ease of reference.

RMS Assessment

The AUCs in figure 1 is normalised to dose/kg bodyweight. If understood correctly from the primary evaluation.

The doses proposed by the applicant are as follows:

Children 1-11 months

<i>Weight 3 to 5 kg:</i>	<i>2.5 mg once daily for up to 6 weeks</i>	<i>(i.e. 0.8-0.5 mg/kg)</i>
<i>Weight >5 kg to 7.5 kg:</i>	<i>5 mg once daily for up to 6 weeks</i>	<i>(i.e. 0.67-<1 mg/kg)</i>
<i>Weight >7.5 kg:</i>	<i>10 mg once daily for up to 6 weeks</i>	<i>(i.e. <1.33 mg/kg)</i>

Children 0- to 1-month-old

<i>Weight \geq 2.5 kg:</i>	<i>2.5 mg once daily for up to 4 weeks</i>	<i>(i.e. \leq1 mg/kg)</i>
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The approved dose in children 1-2 years old is 10 mg once daily in patients weighing \geq 10 <20 kg ie 0.5-1 mg/kg. Thus, based on the figure, it seems children 8 months and younger will have an increased exposure. Little data is present here between 8 and 12 months.

Question #2

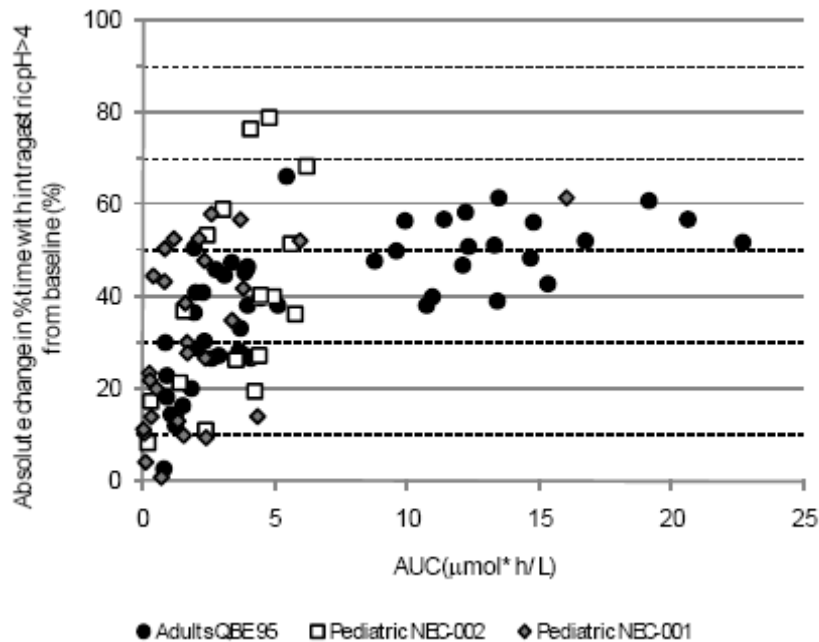
A reduced protein binding was observed in children 0-1 months of age. The applicant should discuss whether it is expected that children in the lower part of the 1-11 month range also will have a reduced protein binding.

Response from the MAH

AstraZeneca wants to clarify that due to limited plasma volume in study NEC-002 the plasma samples from 5 patients were pooled, and thus separate data on protein binding is not available for the 5 patients individually. There are no data available regarding Esomeprazole protein binding in children 1 to 11 months of age. However, there is an ongoing study regarding protein binding in children aged 0 to 17 years using surplus plasma from [Study D9615C00021](#), which study evaluated the PK of esomeprazole and its main metabolites following intravenous administration of esomeprazole. AstraZeneca would therefore like to await the results from the protein binding study before answering this question. We currently expect the report with the study results to be completed by September 2010 and will provide it upon request.

In respect of related comments in the body of the PAR, it has previously been shown that the effect of esomeprazole on gastric acid secretion, measured as the reduction of pentagastrin stimulated acid output and time with intragastric pH>4, is mainly dependent on AUC ([Junghard et al 2002](#)). Similar results were seen in studies NEC-001 and NEC-002. As indicated in [Figure 2](#), the effect on intragastric pH, measured as change in time with intragastric pH>4 from baseline, for a given AUC seems to be slightly more pronounced in children compared to that in adults. Lower capacities to produce gastric acid in children might possibly have contributed to this finding. The capacity to produce gastric acid has been reported to gradually increase from time of birth to reach similar levels as adults by 6 months of life ([Boyle 2003](#)). In addition to frequent feeding, a lower capacity to produce gastric acid could have contributed to the long time with intragastric pH>4 that was already observed in the children at baseline. Furthermore, as only a slight difference in the PK/PD relationship is seen between the children in study NEC-002 and adults ([Figure 2](#)), the lower protein binding observed in the youngest children seems not to be of any importance for the effect of esomeprazole. Therefore, it is the opinion of AstraZeneca that study NEC-002 is conclusive and provides important information regarding the PK and PD of esomeprazole in children 0 to 1 month of age.

Figure 2 The relationship between exposure (AUC^a) of esomeprazole at steady state and the effect on intragastric pH measured as change in time with intragastric pH>4 from baseline, in children aged 0 to 2 years and adults.



^a AUC_τ for NEC-002

The adult data are derived from study SH-QBE-0095 in which healthy male subjects of all CYP2C19 genotypes (homozygous and heterozygous extensive metabolisers and poor metabolisers) received repeated oral administration of 10 mg, 20 mg and 40 mg esomeprazole.

RMS Assessment

Presently, there is only pooled data on the protein binding of esomeprazole in children 0-1 months of age. It is welcomed that the applicant investigates this in the ongoing study. The question posed was not responded to, ie whether it may be assumed that the protein binding also is lower in the youngest children in the 1-11 months interval. In the absence of these data, the PK results may not be fully evaluated. It is possible that Clint, which affects the unbound drug concentration, is overestimated. It is appreciated that the applicant will investigate this further. In absence of these data it is difficult to assess the observed PK/PD relationship as total concentrations are used and as there may be patient groups within the 0-2 years range, which will have a lower protein binding.

Question #3

The applicant has proposed in earlier applications that CYP2C19 is not available until 3 months of age. This indicates that CYP3A then would be the major enzyme and therefore has implications for the interaction text. The applicant should comment.

Response of the MAH

Data included with earlier applications suggests that CYP2C19 is not present in sufficient amounts to be a major esomeprazole metabolizing enzyme in children aged 0 to 3 months ([Expert Report: Clinical documentation on Losec for Pediatric use](#)). This is also evident from [Study D9615C00021](#) data (Appendix 12.2.6, Listing 12.2.6.1 – Listing of Pharmacokinetic Parameters of Esomeprazole). Instead, CYP3A4/7 seems to be the most important enzyme for the metabolism of esomeprazole in these young children. However:

1. The affinity of esomeprazole to different enzymes in general, and to CYP3A4/7 in particular, is not believed to be different in children than in adults and therefore, as in adults, there should not be any potential for esomeprazole in children to interact with compounds metabolized by CYP3A4/7 even if it is the major metabolising enzyme at this young age, and
2. Clarithromycin (a CYP3A inhibitor) does not have a significantly different impact on the metabolism rate of esomeprazole in poor metabolisers compared to populations that mostly consist of extensive metabolisers, a comparison analogous to young children as CYP3A is the major metabolising enzyme in both young children and poor metabolisers. In adults, clarithromycin resulted in an approximate doubling of esomeprazole exposure in both poor metabolisers (SHQBE-0086 with esomeprazole 40 mg qd, 114% increase) and in populations that mostly consisted of extensive metabolisers (SH-QBE-0034 with esomeprazole 40 mg qd, 70% increase; SH-QBE-0040 with esomeprazole 20 mg bid, 127% increase).

Therefore, even though CYP3A4/7 seems to be the most important enzyme for the metabolism of esomeprazole in these young children it is not likely to have any implications for the interaction potential and hence no impact on the interactions text.

RMS Assessment

It is agreed that different effects of omeprazole on CYP enzymes are no expected in absence of CYP2C19 unless a higher Esomeprazole exposure is reached.

The magnitude of the chlaritromycin effect in CYP2C19 PMs may be extrapolated to the new born children and is surprising as CYP3A is supposed to be the main metabolising enzyme. Possible the effect of a potent inhibitor such as ketoconazole, could be different between the groups. However, no changes of section 4.5 are needed at present.

Question #4

The applicant should propose an adequate text in section 5.2 reflecting the data available in children 1-11 months of age.

Response of the MAH

In response to the above question, and to the related comments in the Conclusion and Recommendation sections of the PAR, AstraZeneca responds as follows regarding SmPC sections 4.1, 4.2, 5.1 and 5.2:

Section 5.2:

AstraZeneca proposes the following text, which also includes text regarding infants <1 month of age since we also have study data available for this age group Following repeated dose administration of 1.0 mg/kg esomeprazole in 1 to 11 month old infants, the exposure (AUC) was slightly higher than that observed after 0.5 mg/kg esomeprazole in <1 month old infants, but similar to that observed after 10 mg in 1 to 11 year-olds, and 20 mg in 12 to 18 year-olds as well as adults.

Section 5.1:

With regards to the text proposed by the Rapporteur for section 5.1, AstraZeneca would like to propose a new text that reflects both the study in those aged 1 to 11 months (D9614C00096) and the one conducted in <1 month old infants (D9614C00004), since the two studies differ in respect to age groups treated, treatment duration and doses used. In a placebo-controlled study (98 patients aged 1-11 months) to evaluate efficacy and safety in patients with GERD, esomeprazole 1 mg/kg once daily was given for 2 weeks (open-label phase) and 80 patients were included for an additional 4 weeks (doubleblind, treatment-withdrawal phase). There was no significant difference between esomeprazole and placebo for the primary endpoint time to discontinuation due to symptom worsening, or the secondary endpoints.

In a placebo-controlled study (52 patients aged <1 month) to evaluate efficacy and safety in patients with symptoms of GERD, esomeprazole 0.5 mg/kg once daily was given for a minimum of 10 days. There was no significant difference between esomeprazole and placebo in the primary endpoint, change from baseline of number of occurrences of symptoms of GERD. There was a significant reduction in one of the secondary endpoints, change from baseline in total number of GERD events associated with acid reflux. Following repeated dose administration of 0.5 mg/kg and 1.0 mg/kg esomeprazole in <1 month old and 1 to 11 month old infants, respectively, the effect on intragastric pH, expressed as change in percentage of time with intragastric pH>4 from baseline, is similar to that observed after esomeprazole 20 mg in adults. In addition, 0.5 mg/kg and 1.0 mg/kg esomeprazole in <1 month old and 1 to 11 month old infants, respectively, results in a significant reduction in esophageal acid exposure. The safety profile for esomeprazole was similar to that seen in adults.

Sections 4.1 and 4.2:

AstraZeneca has considered the recommendation that the submitted data is not sufficient for the suggested changes to sections 4.1 and 4.2 and accepts the text proposed by the Rapporteur for section 4.2 as follows:

Paediatric patients

The experience of treatment with esomeprazole in infants <1 year is limited and is therefore not recommended. See section 5.1.

RMS Assessment

Section 5.2:

Due to the lack of data on protein binding in the 1-11 month age group and due to the lower protein binding in children <1 month, the data is considered not sufficiently reliable for inclusion in the SPC. The information may be misleading if included in the SPC. Furthermore, we do not agree with the conclusion that the exposure in 1-11 month-old children and 1-11 year-old children is similar.

Section 4.2:

A slight rewording is proposed:

*“The experience of treatment with esomeprazole in infants <1 year is limited and **treatment** is therefore not recommended. See section 5.1*

RMS Assessment

Section 5.1

Taking together the Applicants proposal for inclusion of data in section 5.1 and also to limit the amount of information, this section should be rephrased as follows:

deletions by the rapporteur in ~~strike through~~ additions by the rapporteur in **bold italics**

In a placebo-controlled study (98 patients aged 1-11 months) ~~to evaluate~~ efficacy and safety in patients with **signs and symptoms of GERD were evaluated**. ~~e~~esomeprazole 1 mg/kg once daily was given for 2 weeks (open-label phase) and 80 patients were included for an additional 4 weeks (doubleblind, treatment-withdrawal phase). There was no significant difference between esomeprazole and placebo for the primary endpoint time to discontinuation due to symptom worsening. ~~or the secondary endpoints.~~

Comment:

*(Study D9614C00096, 1 to 11 month-olds): The population group was heterogeneous and the majority had a diagnosis based on symptomatic presentation only. **Signs and symptoms** should therefore be included. Results of secondary endpoints seem superfluous.*

In a placebo-controlled study (52 patients aged <1 month) ~~to evaluate~~ efficacy and safety in patients with symptoms of GERD **were evaluated**. ~~e~~esomeprazole 0.5 mg/kg once daily was given for a minimum of 10 days. There was no significant difference between esomeprazole and placebo in the primary endpoint,

change from baseline of number of occurrences of symptoms of GERD. ~~There was a significant reduction in one of the secondary endpoints, change from baseline in total number of GERD events associated with acid reflux.~~

Comment:

(Study D9614C00004, premature to 1 month): Results of the primary endpoint and not secondary endpoints are recommended to be presented in the SPC.

~~Following repeated dose administration of 0.5 mg/kg and 1.0 mg/kg esomeprazole in <1 month old and 1 to 11 month old infants, respectively, the effect on intragastric pH, expressed as change in percentage of time with intragastric pH>4 from baseline, is similar to that observed after esomeprazole 20 mg in adults. In addition, **Results from the two studies further showed that** 0.5 mg/kg and 1.0 mg/kg esomeprazole in <1 month old and 1 to 11 month old infants, respectively, **results in a significant reduction in esophageal acid exposure. reduced the mean percentage of time with intra-oesophageal pH<4.**~~

Comment:

Regarding intragastric-pH: no comparison with adult patients has been provided and the section should be deleted.

The safety profile for esomeprazole was **appeared to be** similar to that seen in adults.

Comment:

Since no direct comparison between the study population and adults has been provided and the section should be amended.

Additional comments by the MAH:

The MAH has provided additional information and clarifications regarding three comments in the PAR

1. *The population PK model development is very briefly described and it is difficult to judge how well the model describes the data and whether model development has been adequate and a more complete description would have been appreciated. Possibly Appendix 12.2.5 (not submitted) to the study report contains that information. [Appendix 12.2.5](#) to NEC-002 is now included as an attachment to this response document.*

The applicant should present data on metabolite exposure in adults at multiple dose conditions and compare these with the data in children.

The exposure of the 5-hydroxy and sulphone metabolites in children 0 to 11 months of age are summarized together with corresponding data in children 1 to 11 years of age and adults in [Table 1](#). The exposure to the 5-hydroxy and sulphone metabolites in children 0 to 11 months of age are well within the range of corresponding values observed for 5 mg to 20 mg esomeprazole in children 1 to 11 years of age and for 20 mg and 40 mg in adults. As the Rapporteur commented, the estimation of the exposure to the sulphone metabolite in the children 1 to 11 months (and probably also 1 to 11 years) of age is uncertain and probably underestimated due to the short sampling period (up to 6 hours post dose).

Table 1 Geometric mean (range) AUC_t (µmol•h/L) for the 5-hydroxy and sulphone metabolites of esomeprazole following repeated oral administration in children 0 to 11 years of age and adults

Age group	0 to 1 month ^a	1 to 11 months		1 to 5 years		6 to 11 years		Adults	
Dose	0.5 mg/kg (n=23)	0.25 mg/kg (n=12)	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=11)	40 mg (n=12)
5-hydroxy	0.44 (0.33-0.64)	0.11 ^b (0.02-0.35)	0.33 ^c (0.12-1.55)	NA	NA	NA	NA	0.12 (0.06-0.26)	0.52 (0.22-1.63)
Sulphone	4.87 (0.58-19.46)	0.19 (0.01-2.28)	1.01 (0.16-8.65)	0.44 (0.18-1.61)	4.87 (2.27-8.19)	3.19 (1.25-6.26)	7.19 (5.39-13.30)	3.76 (1.38-9.38)	13.49 (5.61-23.27)

^a AUC_t is presented for this age group

^b n=6

^c n=12

Data for children 1 to 11 years of age are derived from study D9614C00099 (included in MAA Nexium Sachets 10 mg submission - MRP no SE/H/0211/004)

Data for adults are derived from Study SH-QBE-0088

3. There seems to be a poor correlation between oesophageal pH and symptoms in the youngest age group since symptoms were not strongly correlated to acidic events. Furthermore, the majority of the preterm infants and neonates (NEC 2) had intragastric pH >4 during a greater part of the time at baseline.

It is correct to note that intragastric acidity was “>4 during a greater part of the time at baseline”, most probably because of repeated feedings with breast milk or formula (pH approximately 7.0 or above). This was, however, not reflected in the extent of acid exposure in the oesophagus. Contrary to what is typically seen in adults, despite moderate intragastric acidity there were extended periods of oesophageal acidity at baseline and thus oesophageal exposure to activated pepsin. Baseline percentages of time with intra-oesophageal pH<4 ranged between 11.6% and 19.5% in our studies in infants and neonates (Table 2). Such extensive periods of time with pH<4 would, in adults, be of significant clinical concern.

Table 2 Estimated means for percentage of time with intra-oesophageal pH<4 at baseline and following treatment with esomeprazole

Study	NEC-001	NEC-002	D9614C00004	
Treatment	1.0 mg/kg	0.5 mg/kg	0.5 mg/kg	Placebo
Baseline	12.5 ^b	15.7	19.50	14.44
Following treatment ^a	5.54	7.1	8.78	16.68

^a Treatment duration was one week for NEC-001 and NEC-002 and 24 hours for D9614C00004

^b Baseline for one of the NEC-001 treatment groups (0.25 mg/kg) was 11.6%

Table 2 also illustrates the pronounced reduction in intra-oesophageal acidity observed following treatment with esomeprazole. Recent PPI studies in infantile GERD, including AstraZeneca esomeprazole Studies NEC-001, NEC-002, 004 and 096, suggests that symptoms historically considered to be related to GERD in the youngest age groups are often nonspecific and not related to acid-reflux disease.

However, Study 004 has demonstrated that for neonates with suspected GERD responsive to treatment with acid suppression, esomeprazole provides a profound acid-suppressive effect versus placebo. In addition, Study 004 demonstrated a significant impact on neurobehavioural symptoms (back arching and irritability/crying/fussing) that are associated with acid reflux as diagnosed by pH/impedance measurements, thereby underscoring the need to redefine the target population that could potentially benefit from treatment with esomeprazole (and presumably other PPIs).

These new data, while suggesting that many symptoms of GERD in infants are non-specific and on their own should not guide treatment, do not indicate a different disease process from adult GERD. Rather, they emphasize the importance of more clearly defining the type of infant who may benefit from acid

suppression based on diagnostic confirmation. This will allow targeted treatment of the disease, which ultimately has a similar pathophysiology and potential long-term complications as in adults.

The FDA is currently considering the difficulties associated with studying PPIs in paediatric patients <1 year of age. At the 21 June 2010 Paediatric Advisory Committee meeting the FDA advised that one of the days at the upcoming Meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC) in early November 2010 will focus on the design of clinical trials in such patients, including for example disease definitions, relevant endpoints and the possibility of extrapolation from data in adults.

VIII. RAPPORTEUR'S OVERALL CONCLUSION

Some pharmacokinetic information indicate that the doses proposed will give similar mean esomeprazole exposure (based on total concentrations) in children 1-11 months as in the older age groups with approved dose recommendations. However, the data on exposure over age as compared to children 12-24 months old indicate that children under 12 months will receive a higher esomeprazole exposure. Thus, the available data are contradictory. Pooled data on protein binding is available from 5 patients in the 0-1 month age group and indicate that the free fraction is doubled. There is no data on the protein binding in patients in the 1-11 months age group and it is not known whether patients in the lower range of this interval also have a reduced protein binding. As a reduced protein binding will lead to an overestimation of CL_{int}, which determined the pharmacologically active, unbound, exposure, it is possible that the unbound exposure is higher than the presented figures.

The PK data is considered too uncertain to include in section 5.2 of the SPC.

The PK/PD relationship observed in the 1-11 months age range indicate that maximum effect on time with pH>4 is obtained at AUC approximately over 2-3 $\mu\text{M}\cdot\text{h}$ while the mean exposure obtained with the proposed dose in one of the data sets is ca 3 $\mu\text{M}\cdot\text{h}$.

The PK/PD data indicate that there is a relationship between exposure and pH but also that the baseline pH is quite high in the population. The relationship is based on total concentrations and there may be subgroups in the population that have an increased unbound drug exposure.

Although the pathophysiology is considered to be the same as in adults, extrapolation from adult is not straightforward. Compared to older children and adults the clinical presentation in this young age-group is different and in the majority of infants, symptoms do resolve without pharmacological interventions. In comparison with adults and older children the major difference is the ongoing maturation in the young infants and the possible transient nature of the disease.

Oesophagitis is rare in this young population and treatment should only involve patients with proven GERD.

There might be a subgroup of paediatric patients that would benefit from treatment with esomeprazole. However, such a subpopulation has not been identified in the present studies. With the data at hand no added benefit as compared to placebo in this population had been shown.

The beneficial effect of esomeprazole in the treatment of preterm, neonates, infants and toddlers with symptoms of GERD is yet to be proven.

Submitted data is not sufficient for the suggested changes in the SmPC Sections 4.1, 4.2 and 5.2.

The benefit risk balance for esomeprazole when used in older children, adolescents and adults is not affected by the present result, and remains positive.