AstraZeneca

**Amended Clinical Study Protocol**

| | |
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| Drug Substance | esomeprazole sodium |
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# 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

**Sponsor:** AstraZeneca AB, 151 85 Södertälje, Sweden

**AstraZeneca Research and Development site representative** [redacted]



**The following Amendment(s) and Administrative Changes are included in this amended protocol:**

| Amendment No. | Date of Amendment | Local Amendment No. | Date of local Amendment |
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| Administrative change No. | Date of Administrative Change | Local Administrative change No. | Date of local Administrative Change |
|---|---|---|---|
| 1 | [redacted] | | |

# PROTOCOL SYNOPSIS

## 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

**Clinical Study Team Physician**

[redacted]

**Study centre(s) and number of patients planned**

Patients will be enrolled in the study at 3 centres located in Australia, Germany, and the United Kingdom. The study will include a minimum of 90 (to achieve 76 evaluable patients) neonatal patients, including premature and up to 1 month corrected age with symptoms of GERD (gestational age ≥ 28 to 44 weeks, calculated from last menstrual period or by ultrasound) admitted to a Neonatal Intensive Care Unit (NICU), special care nursery or equivalent hospital ward.

| **Study period** | | **Phase of development** |
|---|---|---|
| Estimated date of first patient enrolled | [redacted] | Phase II/III |
| Estimated date of last patient completed | [redacted] | |

**Primary:**

The primary objective of this study is 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.

**Secondary:**

The secondary objectives of this study are:

- to assess the difference between esomeprazole and placebo in the treatment of symptomatic reflux episodes of GERD.
- 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.

- to assess 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, via pH/impedance monitoring.

- to assess the safety and tolerability of esomeprazole compared to placebo.

**Study design**

This study is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of esomeprazole for the treatment of gastroesophageal reflux disease (GERD) in neonatal patients.

**Target patient population**

Male and female neonatal patients, including premature and up to 1 month corrected age, with symptoms of GERD (gestational age ≥ 28 to 44 weeks, calculated from last menstrual period or by ultrasound) admitted to a Neonatal Intensive Care Unit (NICU), special care nursery or equivalent hospital ward.

**Investigational product, dosage and mode of administration**

This study will use an esomeprazole concentrate of 2.5 mg/mL (as esomeprazole sodium 2.7 mg/mL). The esomeprazole concentrate and placebo will be prepared by dilution of the concentrate with sodium bicarbonate solution prior to use. The dosage of the oral solution of esomeprazole is 0.5 mg/kg/day, which will be administered by nippling or oral gavage.

**Comparator, dosage and mode of administration**

This study will use a placebo concentrate for oral solution which will be administered by nippling or oral gavage.

**Duration of treatment**

Patients will be treated once daily with esomeprazole or placebo for 14 days.

**Outcome variables**

– **Efficacy**

  – **Primary outcome variable:**

– The primary variable is 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.

  – **Secondary outcome variables:**

– The secondary variables are:

- change from baseline in the number of symptomatic reflux episodes of GERD as observed during video recording together with reflux detected from pH/impedance monitoring, and GERD-related sign(s) detected from cardiorespiratory monitoring together with reflux detected from pH/impedance monitoring.

- the number of GERD-related signs of oxygen desaturation, apnea and bradycardia via clinical assessment charts at baseline and at the end of the study.

- the volume and frequency of vomiting episodes (including regurgitation) via clinical assessment charts at baseline and at the end of the study.

- the volume, frequency, and duration of feeding via clinical assessment charts at baseline and at the end of the study.

- the duration of sleep, waking hours, peaceful quietness and crying, as well as gagging, back arching, irritability/crying/fussing, vomiting, oxygen desaturation, apnea and bradycardia via video, pH/impedance and cardiorespiratory monitoring at baseline and at the end of the study.

- the number of GERD-related signs and symptoms associated with weakly acidic reflux episodes via video, pH/impedance and cardiorespiratory monitoring at baseline and at the end of the study.

- symptom severity recorded on the Physician's Global Assessment.

– **Safety**

  – **Secondary outcome variables:**

    Safety outcome variables include adverse events and change from baseline in clinical laboratory evaluations and vital signs.

– **Patient reported outcomes (PROs)**

  - Not applicable

– **Health economics**

  - Not applicable

– **Pharmacokinetic**

  - Not applicable

– **Pharmacodynamic**

– The pharmacodynamic endpoints are:

- number of all types of reflux episodes (acid or non-acid) from intraluminal impedance data (at baseline and after treatment period) including acidic GER episodes (pH<4), weakly acidic GER episodes (pH 4-6.9 inclusive), non acidic GER episodes (pH>7), liquid GER episodes, mixed gas/liquid GER episodes, mean bolus clearance time and mean acid clearance time.

- number of acidic reflux episodes from esophageal pH probe (at baseline and at the end of the study) including number of acidic reflux episodes (pH<4), number of acidic reflux episodes lasting longer greater than 5 minutes, % time pH<4 and % time pH 4 – 6.9 (inclusive).

– **Genetics**

  - Not applicable

**Statistical methods**

There will be two analysis sets for the efficacy evaluation: the intent-to-treat (ITT) and the per-protocol (PP). The ITT set will include all randomized patients who take at least one dose of study medication and have valid efficacy measurements both at baseline and at the end of study. The PP set includes all patients in the ITT set and those who do not have any major protocol violations. The ITT set will be considered the primary analysis set. The safety population will consist of all randomized patients taking at least one dose of study medication.

The primary variable, change from baseline in number of signs and symptoms as observed in the video and detected from cardiorespiratory monitoring, will be analyzed using an analysis of covariance model (ANCOVA), taking the number of episodes at baseline as the covariate.

The number of symptomatic reflux episodes of GERD as observed from the video, together with reflux detected from pH/impedance, and GERD-related signs detected from cardiorespiratory monitoring associated with a reflux from pH/impedance monitoring, will be analyzed and presented in the same way as the primary variable.

Comparisons in percent time of peaceful quietness, sleep, and crying between treatment groups in change from baseline will be made using ANCOVA taking baseline % time as the covariate, so are the comparisons of other GERD-related signs and symptoms.

The Physician's Global Assessment will be analyzed using a CMH test to compare the difference between esomeprazole and placebo, stratifying on baseline severity.

Descriptive statistics will be provided for pharmacodynamic variables.

Descriptive statistics will be provided for the evaluation of the safety profile (eg, AEs, lab parameters, vital signs).

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

| Abbreviation or special term | Explanation |
|---|---|
| Acidic Reflux Episode | Retrograde bolus movement of gastric acid into the esophagus as defined by a pH/impedance measurement with a pH drop < 4 |
| AE | Adverse event (see definition in Section 4.7.1.1) |
| ANCOVA | Analysis of covariance |
| Assessment | An observation made on a variable involving a subjective judgement |
| AUC | Area under the curve |
| AZDD | AstraZeneca Drug Dictionary |
| BP | Blood Pressure |
| °C | Degrees Celsius |
| CRF | Case Report Form |
| CSA | Clinical Study Agreement |
| DCF | Data Clarification Form |
| eCRF | Electronic Case Report Form |
| ECG | Electrocardiogram |
| Ethics Committee | Synonymous to Institutional Review Board and Independent Ethics Committee |
| EU | European Union |
| GER | Gastroesophageal Reflux |
| GERD | Gastroesophageal Reflux Disease |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| ICH | International Conference on Harmonisation |
| I-GERQ | Infant Gastroesophageal Reflux Questionnaire |
| International Co-ordinating investigator | If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and/or activities internationally. |
| IRB | Institutional Review Board |
| ITT | Intent-to-treat |
| kg | Kilogram |

| Abbreviation or special term | Explanation |
|---|---|
| Measurement | An observation made on a variable using a measurement device. |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Medical History | Any clinical observation obtained or reported by a patient or caretaker regarding past, present or newly developed signs or symptoms. This applies to both baseline and/or follow up collection of clinical information. |
| mg | Milligram |
| mL | Milliliter |
| NCR | No Carbon Required |
| Neonatal patients | Infants who are born full term or premature (up to one month corrected age) |
| NICU | Neonatal Intensive Care Unit |
| OAE | Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 4.7.1.1). |
| Outcome variable | A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective. |
| Parameter | A quantity (usually unknown) that characterizes the distribution of a variable in a population of patients. |
| PK | Pharmacokinetic |
| PP | Per-protocol |
| PPI | Proton Pump Inhibitor |
| Principal Investigator | A person responsible for the conduct of a clinical study at the investigational study site. Every investigational study site has a principal investigator. |
| PRO | Patient Reported Outcome |
| SAE | Serious Adverse Event (see definition in Section 4.7.1.1). |
| SAP | Statistical Analysis Plan |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| TPV | Third Party Vendor |
| Vomiting | Includes regurgitation |
| WBDC | Web Based Data Capture |

# 1. INTRODUCTION

## 1.1 Background

Gastroesophageal reflux (GER), the retrograde passage of gastric contents into the esophagus, is presumed to be caused primarily by transient relaxation of the lower esophageal sphincter and is a common occurrence in healthy infants and children (Vandenplas and Sacre-Smits 1987, Nelson et al 1997, Nelson et al 2000). GER is considered to be subclinical or silent if the extent of the reflux is limited to the esophagus, or it can be manifested as regurgitation or vomiting of the gastric contents. This presentation is common in infants and occurs frequently in the first year of life. Regurgitation of at least one episode per day occurs in 50% of infants aged 0 to 3 months and in 67% of infants by 4 to 6 months. In most infants the incidence of regurgitation is significantly reduced or resolves completely by 10 to 12 months (Nelson et al 1997). Uncomplicated GER in infants does not typically require medical therapy and may be addressed with lifestyle changes such as positioning therapy or changes in diet (Rudolph et al 2001).

Simple physiologic reflux evolves into the pathologic condition of gastroesophageal reflux disease (GERD) when the reflux produces an adverse symptomatology. The acidic nature of the refluxate, and the associated pepsin activation, is considered to be the principal irritant causing the mucosal inflammation and the resulting symptomatology and potential long-term sequelae of GERD. Common esophageal manifestations of neonatal GERD include irritability, hematemesis, neck arching, weight loss or poor weight gain, dysphagia, and feeding refusal. Some infants may also experience extraesophageal symptoms and conditions such as coughing, wheezing, apnea, and bradycardia. Some neonatal signs and symptoms of GERD, such as apnea and bradycardia, are of particular concern because of associated life-threatening risks of morbidity and mortality.

The primary goals of treatment of infantile GERD include symptom relief, mucosal healing, promotion of normal weight gain and growth, and prevention of long-term complications. A variety of treatment modalities are available for the clinical management of infantile GERD, including lifestyle changes (positioning therapy, diet changes), medical management with pharmacological agents, and surgical intervention (fundoplication) in cases of failed medical management.

## 1.2 Rationale

Gastric acid secretion is controlled by a negative feedback mechanism under normal physiologic conditions. The proton-transporting enzyme involved in the production of hydrochloric acid in the stomach is known as gastric parietal cell $H^+/K^+$-ATPase, or "proton pump." Compounds that inhibit this enzyme are known as Proton Pump Inhibitors, or PPIs. PPIs bind covalently to the proton pump on the apical surface of the gastric parietal cells, irreversibly inhibiting the inward transport of $H^+$ ions by gastric parietal cell $H^+/K^+$-ATPase.

Esomeprazole, the *S*-isomer of omeprazole, has the capacity to selectively inhibit this enzyme thereby inhibiting gastric acid production.

Esomeprazole has been approved for the treatment of gastroesophageal reflux disease (GERD) and in combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* (*H. pylori*). Approval was first obtained on 10 March 2000 in Sweden and subsequently in the rest of the European Economic Area (EEA), the United States (US), Canada, Australia, and most countries in South America, Africa, and Asia, except in Japan (no application made). More recently, esomeprazole has been approved in the US for risk reduction of nonsteroidal anti-inflammatory drugs (NSAID)- associated gastric ulcer and in the European Union (EU) for the treatment and prevention of ulcers associated with the use of NSAIDs. All approvals are in an adult patient population (patients 18 years of age or older). In addition, esomeprazole has been approved for pediatric use in patients 12 – 17 years of age for the short term treatment of GERD in the US. Since its launch, total worldwide exposure for esomeprazole magnesium has been estimated to be approximately 330 million patient treatment courses (as of 10 March 2006).

Clinical pharmacologic and PK studies in healthy volunteers and patients with GERD indicate that a higher exposure (AUC) and, consequently, a more pronounced gastric acid inhibitory effect was obtained with esomeprazole than with omeprazole (Scott 2002, Andersson 2000, Tran 2002, Gibbons 2003). The metabolism of esomeprazole has also shown less variability compared to omeprazole. Consequently, esomeprazole demonstrates better and more stable acid control in adults than omeprazole (Scott 2002). It is expected that such advantages of esomeprazole over omeprazole in adults could be applied to pediatric patients as well.

Although PPIs have been established as effective pharmacological agents for decreasing the acid released in the stomach and, therefore, the acidic quality of the refluxate in older children and adults with GERD, the efficacy of such therapy remains poorly studied in infants. The purpose of this study is to provide information needed to evaluate the safety and efficacy of esomeprazole in neonatal patients with GERD. In addition, the data collected will more specifically define signs and symptoms of GERD in the preterm and term infant population.

# 2. STUDY OBJECTIVES

## 2.1 Primary objective

The primary objective of this study is 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.

## 2.2 Secondary objectives

The secondary objectives of this study are:

- to assess the difference between esomeprazole and placebo in the treatment of symptomatic reflux episodes of GERD.

- 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

- to assess 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, via pH/impedance monitoring

- to assess the safety and tolerability of esomeprazole compared to placebo

# 3. STUDY PLAN AND PROCEDURES

## 3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This will be a multicentre, randomized double-blind, placebo-controlled study to evaluate the efficacy and safety of 0.5 mg/kg esomeprazole administered once daily for the treatment of symptomatic GERD in neonatal patients. Patient's size and medical condition must allow for performance of all study related procedures and administration of investigational product as judged by the investigator.

At the point of study entry, the patient will be an inpatient in the Neonatal Intensive Care Unit (NICU), special care nursery, or equivalent hospital ward and will be expected to remain an inpatient for the treatment period of the study. If the patient is discharged prior to completion of the treatment phase, patients may be given the option of having at home visits for study drug administration at the discretion of the investigators. These patients will need to be readmitted to the hospital for final study day procedures.

Patients will be enrolled at 3 centres located in Australia, Germany and the United Kingdom. Approximately 30 patients are expected to be randomized at each investigational site.

Figure 1 presents the study flow chart. Table 1 presents a study summary of scheduled assessments and procedures.

The signs and symptoms and other variables to be assessed may be divided into 3 groups, gastrointestinal, neurobehavioral and cardiorespiratory, and they are:

**Gastrointestinal**

- volume and frequency of vomiting (including regurgitation)

- small volume (teaspoonful to a tablespoonful or 5 - 15 mL of feed)

- medium volume (1 to 2 tablespoonful or 15 - 30 mL of feed)

- large volume (more than 2 tablespoonful or > 30 mL of feed)
- volume, frequency, and duration (time to complete feeds) of feeding

**Neuro-Behavioral**

- duration of sleep
- duration of waking hours
- peaceful quietness (defined as awake and quiet)
- duration of crying episodes
- gagging
- back arching
- irritability/crying/fussing

**Cardiorespiratory**

- oxygen desaturation episodes as defined by a fall in $O_2$ saturation to < 85%
- apnea episodes defined as a pause in respiratory effort equal to or for >20 seconds
- bradycardia episodes or a decrease in heart rate <100 beats per minute

### 3.1.1 Study Days –3 to 0 (Baseline)

Prior to any assessments or procedures, each patient's parent/guardian will be required to provide written informed consent. At this visit, the physician/designee will obtain and evaluate the patient's medical history, including prior and concomitant medications for study inclusion.

A physical examination (including measurement of weight, length and head circumference), vital signs (blood pressure, heart rate, temperature, and respiration rate), laboratory assessments and review of all inclusion/exclusion criteria will be done prior to study entry.

Clinical assessment charts, which are based upon a modified version of the Orenstein's Infant Gastroesophageal Reflux Questionnaire (I-GERQ), will be completed by the study personnel. The clinical assessment charts will not be completed on the day pH/impedance monitoring is conducted. Baseline clinical assessment charts will be recorded for a 24 hour period on the day before pH/impedance monitoring. The data will be summarized and recorded in the electronic case report form (eCRFs).

This study day will also include esophageal pH monitoring, intraluminal impedance monitoring, cardiorespiratory monitoring, and video monitoring for 8 hours. (See Section

3.1.6). A combined pH/impedance probe (microelectrodes) will be positioned in the esophagus by the study nurse or qualified study personnel (ie, medical or nursing staff). The placement of the probe will be scheduled so that it coincides with feeding time (ie, will occur just prior to feeding). Every attempt should be made to schedule this monitoring at the same time of day for baseline and final study day and to include at least 2 feeding times (See Section 4.6.1.1). The patient will continue to be monitored for reflux only using intraluminal impedance and pH recording for a total of 18 - 24 hours.

Patients must have a normal electrocardiogram (ECG) at baseline (historical documentation is acceptable) without clinically significant findings as deemed by the investigator.

A Physician Global Assessment of the patient's GERD-related symptoms over the last 24 hours will also be completed (see Section 4.6.6).

Adverse events (AEs) and serious adverse events (SAEs) will be documented during the course of the study once informed consent is obtained. The investigator or designee will assess these events on each study day.

### 3.1.2 Study Day 1 (Randomization and first day of study medication)

Day 1 of study participation is the randomization day and the first day of study drug administration. Patients who meet all inclusion and do not violate any exclusion criteria will be randomized to either treatment with esomeprazole 0.5mg/kg or placebo. Dosing will be based on the patient's daily bodyweight, per NICU standards. The investigational product will be administered approximately 30 minutes prior to a morning feeding on each study day as described in Section 3.4.

Vital signs will be collected and weight and length will be measured. Recording of the clinical assessment charts will be resumed once the pH/impedance monitoring has concluded.

Adverse events (AEs), concomitant medications, and serious adverse events (SAEs) will be documented. The investigator or designee will assess these events on each study day.

### 3.1.3 Study Days 2-13 (or the day prior to the final study day)

The investigational product will be administered approximately 30 minutes prior to a morning feeding on each study day as described in Section 3.4. Dosing will be based on the patient's daily bodyweight, per NICU standards.

Vital signs will be collected and weight and length will be measured.

Clinical assessment charts will be recorded on a continuous basis. The end of study clinical assessment chart will be recorded during a 24 hour period on the day prior to the final study day when the pH/impedance monitoring will be performed. This data will be summarized and recorded in the eCRF.

Adverse events (AEs), concomitant medications, and serious adverse events (SAEs) will be documented. The investigator or designee will assess these events on each study day.

### 3.1.4 Study Day 14 or Final Study Day

Final study day is planned to be Day 14; however, patients who complete at least 10 days of treatment will have all final study day procedures performed. Patients who discontinue early, prior to Day 10, will need to complete all final study procedures except video/pH/impedance monitoring.

The final dose of study drug will be administered. based on the patient's body weight, per NICU standards.

A physical examination (including measurement of weight, length and head circumference), vital signs (blood pressure, heart rate, temperature, and respiration rate) and laboratory assessments will be performed.

This study day will include esophageal pH monitoring, intraluminal impedance monitoring, cardiorespiratory monitoring, and video monitoring for 8 hours. Every attempt should be made to schedule this monitoring at the same time of day as the baseline monitoring, to include at least 2 feeding times and to begin approximately 2 hours before dosing and end 6 hours after dosing). The patient will continue to be monitored for reflux only for a total of 18 – 24 hours.

A Physician Global Assessment of the patient's GERD-related symptoms over the last 24 hours will also be completed (see Section 4.6.6).

Assessment of AEs, concomitant medications, and SAEs will be completed.

### 3.1.5 Safety Follow–up

Following administration of the final dose of study drug, all patients (discontinued or completed) will have a safety follow-up evaluation performed as in-patient or office visit. The safety follow up visit will occur 14 days (+/- 2days) after final dose.

This visit will include evaluation vital signs, and physical exam.

Adverse events (AEs), concomitant medications, and serious adverse events (SAEs) will be documented. All ongoing AEs must be followed until resolution or until the investigator decides and documents that no further follow-up is necessary. AstraZeneca may request additional information about such AEs.

### 3.1.6 pH/intraluminal impedance/video monitoring

Placement of the pH/impedance probe will be scheduled so that it coincides just prior to feeding time if possible. If necessary, a separate feeding tube may be placed beside the pH/impedance probe, through which the investigational product may be given to the patient. (See Section 3.4.2)

Esophageal pH/intraluminal impedance will be measured and recorded for a total of 18 - 24 hours using the Sandhill Scientific Insight System. A portion of this (8 hours) will be integrated with the Respironics Alice 5 Diagnostic Sleep System, and will include measurement of cardiorespiratory data such as respiration rate, heart rate, ECG and oxygen levels, as well as video, sound and movement monitoring. A synchronizing device, developed for this study, will be used to integrate the data. Video will be recorded for 8 hours (approximately) and approximately 6 hours should be considered evaluable, which is defined as having a clear image, the camera pointed at the child, and the face and upper body are visible. The 8 hours of video should ideally include at least 2 feedings and include dosing on the final study day (2 hours before and 6 hours after dosing). Every attempt should be made to collect baseline and final study day evaluations during the same time of day.

This 8 hours of data will be downloaded onto a computer and then stored on 2 duplicate sets of 2 DVDs (or equivalent media), each labelled with patient identifier information. One set of DVDs will be kept at the study site and the other will be sent to the AstraZeneca contract research organization (CRO) data management representative.

The study nurse or qualified site personnel (ie, medical or nursing staff) will prepare surveillance notes while the monitoring is occurring. Comments from the surveillance notes will be marked on the integrated system during the review process for both the baseline and final study day visits.

The site will review the video to ensure that approximately 6 hours are considered evaluable before randomization of the patient. Patients without approximately 6 hours of evaluable video at baseline will be discontinued.

Qualified site personnel will also review the 8 hours of pH/impedance data recorded during the video monitoring and mark events in the system where applicable.

A qualified reader, (either a central reader or site specific as applicable) per standard guidelines, will review the 8 hours of all the integrated data (cardiorespiratory monitoring, pH, impedance and video) and document any correlations between the events and the presence of reflux. The start and stop time of events will be determined so that durations can be calculated. The reader who will be reviewing the integrated data, as well as all site personnel, will be blinded to the investigational product assigned to the patient.

The 18 – 24 hour pH/impedance data will be used to calculate the reflux index in those patients that complete this procedure. However, as long as patients have completed the 8 hours of video monitoring, they will be considered evaluable regardless of whether they complete the remaining pH/impedance monitoring.

The following assessments of all types of reflux episodes (acid or non-acid) will be made at baseline and after treatment using standard reports from the pH/intraluminal impedance monitoring:

- acidic GER episodes (pH<4)

- weakly acidic GER episodes (pH 4 – 6.9)
- non acidic GER episodes (pH≥7)
- liquid GER episodes
- mixed gas/liquid GER episodes
- mean bolus clearance time
- mean acid clearance time

The following assessments of acidic reflux episodes will be made at baseline and after treatment using the standard reports from the esophageal pH probe based on the entire time of pH monitoring:

- number of acidic reflux episodes (pH<4)
- number of acidic reflux episodes greater than 5 minutes
- % time pH < 4
- % time pH 4 – 6.9

**Figure 1 Study flow chart**

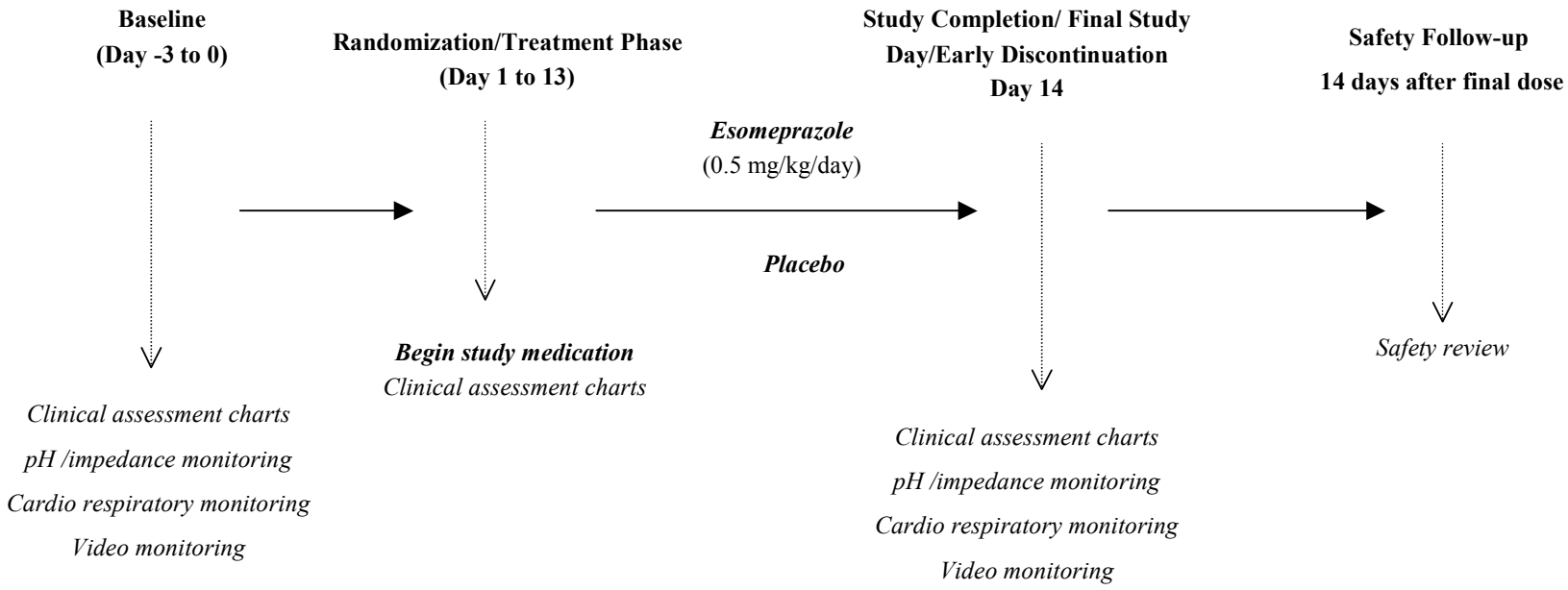

**Table 1 Study summary of assessments and procedures**

| **Assessment/Procedure** | **Baseline** Day -3 to Day 0 | **Randomization /Treatment** Day 1-13 | **Study Completion/ Early Discontin-uation** Day 14 [k] | **Safety Follow-up** 14 days (+/-2 days) after final dose [m] |
|---|---|---|---|---|
| Informed consent | X | | | |
| Clinical assessment chart | X [e] | X [e] | | |
| Medical history | X | | | |
| pH monitoring and impedance | X [f] | | X [l] | |
| Cardiorespiratory monitoring | X | | X | |
| Video monitoring | X [f] | | X [l] | |
| Inclusion and exclusion criteria | X | | | |
| Vital signs [a] | X | X | X | X |
| Physical examination [b] | X | X [i] | X | X |
| ECG | X [g] | | | |
| Laboratory evaluation | X [h] | | X | |
| Prior and concomitant medications | X | X | X | X |
| Dosing administration | | X | X | |
| Randomization | | X [j] | | |
| Physician Global Assessment | X | | X | |
| Adverse event assessment [c] | X | X | X | X |
| Serious adverse event assessment [d] | X | X | X | X |

[a] Including temperature, blood pressure (BP), heart rate and respiration rate.
[b] Including weight, length and head circumference.
[c] Adverse events will be recorded from the day when the parents sign the informed consent. All ongoing AEs must be followed until resolution or until the investigator decides and documents that no further follow-up is necessary. AstraZeneca may request additional information about such AEs.
[d] Serious adverse events will be recorded from the day when the parents sign the informed consent.
[e] Baseline and final study day clinical assessment charts will be recorded during the 24 hour period before pH/impedance monitoring.
[f] pH/impedance/video monitoring begins once clinical assessment charts and other baseline procedures have been completed.
[g] Patients must have a normal ECG at baseline (historical documentation is acceptable) without clinically significant findings as deemed by the investigator.
[h] Stool hemoccult performed at baseline only.
[i] Weight and length only.
[j] Randomization occurs on Day 1.
[k] Minimum of 10 days of treatment.
[l] Patients who discontinue early, prior to Day 10, will need to complete all final study procedures except video/pH/impedance monitoring.
[m] A post-study follow-up (in patient or office) safety assessment will occur 2 weeks following administration of the last dose of study drug for each patient.

## 3.2 Rationale and risk/benefit assessment

### 3.2.1 Rationale for study design, doses and control groups

This prospective study will employ a randomized, double-blind, placebo controlled design to evaluate the efficacy and safety of esomeprazole for the treatment of GERD in neonatal patients. The primary goal of the pharmacologic treatment of GERD is to reduce the exposure of the esophageal and supraesophageal mucosa to gastric acid by its effect on acid suppression. Currently available therapies for GERD include antacids, histamine-2 receptor antagonists ($H_2$RAs), or proton pump inhibitors (PPIs), and prokinetic agents. Although antacids and the prokinetic agent, cisapride, have been shown to have modest efficacy in infants or children (Cucchiara et al 1984, 1987, Cohen et al 1999), their safety profiles do not support their use as primary therapies in infants (Rudolph et al 2001). In contrast, $H_2$RAs have been considered front-line therapy (Cucchiara et al 2000) and various studies have demonstrated their efficacy in a pediatric population (Rudolph et al 2001).

The dosing of esomeprazole, 0.5 mg/kg, will be based on daily body weight. The rationale of exposure-response relationship was used to extrapolate the esomeprazole dose from adults to children. The esomeprazole exposure (AUC) and the response (efficacy and safety) for pediatric patients was estimated via a comprehensive PK and population PK modeling analysis of the omeprazole PK data in adult and pediatric patients and esomeprazole PK data in adults (Appendix C). The dose of 0.5 mg/kg/day is expected to provide a reasonable chance of efficacy while yielding potential exposures within the safety margin.

At the present time, there is limited safety data for doses of 0.5 mg/kg/day for the very young neonates (less than 5 days). However, data from a recently concluded study (AstraZeneca Clinical Study Report for Study SH-NEC-0001) in infants up to 24 months of age indicate no trends of clinical relevance regarding safety variables in relation to doses of esomeprazole 0.25 mg/kg or 1.0 mg/kg. In addition, preliminary population kinetics data from another study using the same dose of esomeprazole and same target population as Study SH-NEC-0001 do not indicate any safety concerns. For the reasons outlined above, our maximum proposed dose for neonatal studies dealing with pre-term and term neonates with GERD related symptoms will be 0.5 mg/kg/day.

PPIs have shown a remarkable tolerability profile in both adults and children. In an AstraZeneca omeprazole pediatric study (AstraZeneca Clinical Study Report No. 250, 2001), some children ages 0 months to 24 months inclusive had AUC exposures up to 3 times the mean exposure seen in adults administered the maximum labelled omeprazole dose (40 mg), and no drug-related side effects were reported. Additionally, examination of literature for the safety of the 2 PPIs with labelling for use in both pediatric patients and adults, omeprazole and lansoprazole, have not found any significant differences in safety between pediatric patients and adults at a similar exposure (AUC) (Scott 2002, Andersson 2000, Tran 2002, Gibbons 2003).

The use of a placebo group in the present study will provide the means to effectively analyze the efficacy and safety of esomeprazole therapy in an infantile GERD population. The

justification for allowing patients into the placebo arm is consistent with standards of medical practice which primarily include non-pharmacological treatments (ie, positioning and thickened feeds) for variable periods of time. It is at the discretion of the investigator to decide when pharmacological treatment is needed. Therefore, these patients will still receive non-pharmacological standard of care while on placebo.

Measurement of esophageal pH is a widely used method for establishing the diagnosis of GERD, in children as well as in adults. The method can also be used for evaluating the therapeutic effect of drugs, such as esomeprazole, in the treatment of GERD. Whereas esophageal pH only reflects acid related reflux, intraluminal impedance can be used to evaluate the total reflux pattern irrespective of pH. Thus, pH measurement in combination with intraluminal impedance measurement provides a more complete measure of the therapeutic response to a drug.

Orenstein's Infant Gastroesophageal Reflux Questionnaire (I-GERQ) is a questionnaire that has been validated in some populations of infants (Orenstein et al 1996). The clinical assessment charts used in this study are based upon this validated questionnaire. The actual questionnaire will not be used in this study.

The study personnel will administer the investigational product thus ensuring treatment compliance.

### 3.2.2 Risk/benefit and ethical assessment

See Section 3.2.1 for rationale for a placebo-controlled study design.

## 3.3 Selection of study population

### 3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrollment but were never enrolled eg, patient screening log. This information is necessary to establish that the patient population was selected without bias.

### 3.3.2 Inclusion criteria

For inclusion in the study, patients must fulfil all of the following criteria:

1. Patients' parent/guardian must provide written informed consent prior to the execution of any study-related procedures.

2. Patients must be full term or have gestational age ≥ 28 to 44 weeks (calculated from last menstruations or ultrasound).

3. Patients must be an inpatient in the Neonatal Intensive Care Unit (NICU), special care nursery, or equivalent hospital ward at the point of study entry and will be expected to remain an inpatient for the treatment period of the study. If the patient is discharged prior to completion of the treatment phase, patients may be given the option of having at home visits for study drug administration at the discretion of the

investigator. These patients will need to be readmitted to the hospital for final study day procedures.

4. Patients must have the following observed clinical findings: any two (either individually or in any combination) of (1) apnea +/- bradycardia +/- oxygen desaturations, (2) vomiting/gagging, (3) irritability/pain at least every second feed or at least twice every eight hours, and present for at least 5 days or increasing in frequency or severity over 3 days. At least 2 of the occurrences of the above should be reproducible during the 8 hour video.

5. Patient's size and medical condition must allow for performance of all study related procedures and administration of investigational product as judged by the investigator.

6. Patients must be on a stable mode of feeding or with minimal variations in feeding as judged by the investigator for at least 2 days prior to randomization.

### 3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Patients who exhibit total resolution of all signs and symptoms of GERD during the initial 8 hour video assessment.

2. Use of any pharmacological antireflux therapy (other than study drug) within 72 hours prior to any pH/impedance monitoring. Antacids may be used if it is required during the study as "rescue therapy", but are not allowed to be taken ± 1 hour to administration of the investigational product and also not 4 hours before and throughout the pH-impedance monitoring at baseline and the final study day.

3. Patients with a history or a current need for resectional or reconstructive surgery of the gastrointestinal tract (esophagus, stomach, duodenum or jejunum).

4. Patients with any condition that may require surgery during the course of the study.

5. Patients who must remain on any of the following concomitant medications during the course of the study: bismuth-containing products, barbiturates, anti-convulsants, warfarin, narcotics, antineoplastic agents, $H_2$ receptor antagonists, sucralfate, anti-emetics, pro-motility drugs (eg, cisapride, metoclopramide, macrolide antibiotics such as erythromycin). Use of topical erythromycin is permissible. However, occasional use of restricted medications, when medically indicated after enrollment, is permissible at the discretion of the investigator. If any restricted medication is used, the name of the medication and the reason for taking it should be recorded on the eCRF.

6. Patients with the following diseases/conditions: active gastrointestinal bleed, allergic gastroenteropathies, eosinophilic gastroenteritis, bleeding disorders, active

seizure disorder, on-going treatment for seizure disorder, acute pancreatitis or meningitis.

7. Patients with acute respiratory distress within 72 hours prior to enrollment or the likelihood of acute or worsening respiratory distress during the course of the study.

8. Patients who are febrile per NICU standards on the day of randomization.

9. Patients with any acute or chronic illness that, in the opinion of the investigator, would place the patient at risk because of their participation in the study ***or*** potentially confound the study data by including the patient. Conditions that should be considered for exclusion (however, exclusion is neither required nor limited to): acute pneumonia, acute respiratory syncytial virus, recent trauma, known or suspected abuse or neglect, severe malabsorption, fever of unknown origin, or any unstable or severe renal, hepatic, cardiac, pulmonary, metabolic, or congenital problems that could put the child at risk by participating in the study. Severe fetal alcohol syndrome and newborn drug withdrawal syndrome should be considered for exclusion. The decision to exclude a patient from study participation in these cases will be made by the investigator and/or AstraZeneca physician based on the severity of the condition and potential risk to the patient.

10. Patients with abnormal screening laboratory values will be excluded only if the investigator and/or sponsor determine the abnormalities to be unexplained or clinically significant in a way that would put the patient at risk from study participation.

11. Known or suspected hypersensitivity to any esomeprazole formulation or substituted benzimidazoles.

12. Patients who have used any other investigational compound prior to the screening visit. Patients who have used investigational devices or products that are not systemically absorbed prior to the screening visit should be discussed with the sponsor on a case-by-case basis prior to study enrollment.

13. Patients who have any condition that, in the judgment of the investigator, would make performance of any of the study procedures unsafe, or which would make it unlikely that the patient would complete the study and all study procedures to final study day.

14. Need for switch of feeding route during study or change in the type of feeding must be carefully decided on a case-by-case basis.

15. Previous enrollment or randomization of treatment in the present study.

### 3.3.4 Restrictions

For drugs not allowed during the study, refer to exclusion criteria no. 4. Food thickeners can be used in the 72-hour period up to four hours prior to the pH/impedance monitoring. Antacids may be used if required during the study as "rescue therapy", but are not allowed to be taken ± 1 hour to administration of the investigational product and also not 4 hours before and throughout the pH-impedance monitoring at baseline and the final study day. Occasional use of restricted medications, when medically indicated after enrollment, is permissible at the discretion of the investigator. If any restricted medication is used, the name of the medication and the reason for taking it should be recorded on the eCRF.

Due to the medical, procedural and other logistical limitations inherent to this patient population (neonates and premature babies), every effort will be made to follow the protocol's designated procedures and variable measurements. However, at the investigator's discretion and with the sponsor's approval, some of these may need to be waived or adjusted based on patient size and medical condition without constituting a protocol deviation. Other standard of care procedures that a patient may require during the study will be documented at the time of performance.

### 3.3.5 Discontinuation of patients from treatment or assessment

#### 3.3.5.1 Criteria for discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are:

- Voluntary discontinuation by the patient's parent or guardian who are at any time free to discontinue their participation in the study, without prejudice to further treatment.
- Safety reasons as judged by the investigator and/or AstraZeneca
- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
- Incorrect enrollment or randomization of the patient.
- Development of exclusion criteria.
- Patient lost to follow-up

#### 3.3.5.2 Procedures for discontinuation

If a patient discontinues participation or is withdrawn, the Clinical Monitor for the site must be contacted. The reason for, and date of, discontinuation for all patients from the study will be documented in source documents and the eCRF.

Parent or guardians who discontinue their child/ward should always be asked about the reason(s) for their discontinuation and about the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Final visit procedures should be conducted. Adverse events should be followed up and any clinical assessment charts should be completed for the patient. All patients will be followed with a safety evaluation 14 days (+/- 2 days) after the final dose of study drug (Section 3.1.4).

#### 3.3.5.3 Procedures for handling incorrect enrolled patients

Patients not meeting the inclusion/exclusion criteria for a study should, under no circumstances, be enrolled into the study - there can be no exceptions to this rule. Where patients not meeting the study criteria are enrolled in error, incorrectly randomized, or where patients subsequently fail to meet the criteria for the study post enrollment, the patient should be discontinued and procedures from Section 3.3.5.2 should be followed.

## 3.4 Treatments

### 3.4.1 Identity of investigational product and comparators

A solution of esomeprazole sodium or placebo, which will be diluted with a sodium bicarbonate solution at the time of administration, will be used as investigational products in this study. The investigational products are described in Table 2.

Solution for oral use containing esomeprazole concentrate or placebo must be thawed, diluted and otherwise handled according to handling instructions that will be sent together with the investigational products.

The esomeprazole concentrate or placebo should be thawed at room temperature (15-25°C), protected from light. The thawing and diluting should be finished within 60 minutes. The study personnel will fill in the date and time that the concentration was thawed on the esomeprazole/placebo vial's label when the concentrate is removed from the freezer.

The sodium bicarbonate solution should be thawed at room temperature (15-25°C). The thawing will take approximately 60 minutes. After thawing the solution should be used for dilution within 8 hours. The study personnel will fill in the date and time that the sodium bicarbonate solution was thawed on the vial's label when the solution is removed from the freezer.

The diluted solution can be handled at room temperature (15-25°C), protected from light, and should be used within 60 minutes. The study personnel will fill in the date and time of dilution on the vial's label. For safety reasons, the reconstituted solution and remaining esomeprazole/placebo concentrate must be discarded immediately after use.

**Table 2 Identity of Investigational Product**

| Investigational Product | Dosage form and strength | Container | Manufacturer | Formulation Number [a] |
|---|---|---|---|---|
| Esomeprazole | Concentrate for oral solution 2.5 mg/mL | Vials of 10 mL containing 2 mL | AstraZeneca R&D Mölndal Sweden | H 1713-01-02 |
| Placebo | Concentrate for oral solution | Vials of 10 mL containing 2 mL | AstraZeneca R&D Mölndal Sweden | H 1723-01-01 |
| Sodium bicarbonate | Oral solution 23.3 mg/mL | Vials of 20 mL containing 9 mL | AstraZeneca R&D Mölndal Sweden | H 1714-01-02 |

[a] The batch number will be recorded in the Study Master File and identified in the Clinical Pharmacology Study Report.

### 3.4.2 Doses and treatment regimens

The intention is to administer esomeprazole at 0.5 mg/kg/day. This dose will be given based on the patient's daily body weight, per NICU protocols.

The investigational product will be given once daily 30 minutes prior to a morning feeding during the treatment period. Study personnel will perform drug administration, by oral gavage (using a nasogastric or orogastric tube), or by nippling.

The esomeprazole concentrate and placebo solutions will be prepared by dilution of the concentrate with sodium bicarbonate solution prior to use. Dilution will be made into sodium bicarbonate vials. Each dose (0.5 mg/kg/day) will be administered in a volume of 2 mL/kg of liquid ( = 0.5 mmol sodium bicarbonate and 0.5 mg esomeprazole/placebo of diluted solution per kg). This will be followed by administration of 5-10 mL of sterile water or formula.

### 3.4.3 Labelling

The packaging and labelling of study drug will be performed at Investigational Products, AstraZeneca R&D Mölndal, Sweden. Labelling will be in the local language for each country in accordance with Good Manufacturing Practice (GMP) and local regulatory requirements.

The vials containing esomeprazole or placebo will be labelled with at least the following information: sponsor´s name and phone number, name of product, strength, dosage form, number of dosage units, study code and order reference, randomization code, period of use, eg, expiry date, and storage condition.

The vials containing sodium bicarbonate solution will be labelled with at least the following information: sponsor´s name and phone number, name of product, strength, dosage form, number of dosage units, study code and order reference, period of use, eg, expiry date, storage condition, and dosage. The investigator's name and randomization code will be filled in on the label at the study site.

The esomeprazole/placebo concentrate will be packaged per patient in kits. The label on each of these vials and the outer box will contain pre-printed patient numbers according to the randomization list.

The sodium bicarbonate will be packaged in bulk. The label on the sodium bicarbonate vials will be a two-part label. One part will be permanently affixed to the vial and the other part will be a peel-off portion for insertion into the source documents. At the time of the dilution, the randomization code from the esomeprazole/placebo concentrate should be filled in on the label and on the tear-off part by study personnel.

All labels will be translated into local languages and each marketing company (MC) will be able to modify the text to meet local regulatory requirements.

### 3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions (freezer, below -15°C). A description of the appropriate storage and shipment conditions are specified on the investigational product bottle label.

### 3.4.5 Accountability

Study drug will not be distributed to the medical institution until the contract is concluded between the medical institution and AstraZeneca. The study drug provided to the medical institution must only be used as directed by the study protocol. The Investigational Product Storage Manager is responsible for managing the study drug from receipt by the institution until the destruction of the study drug. All unused study drug should be destroyed at the local study site according to local standard operating procedures. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describe the specific requirements.

## 3.5 Method of assigning patients to treatment groups

A preliminary identifying number (enrollment number) will be allocated to all patients at baseline, so that patients can be identified without making assumptions about their subsequent eligibility for the main study. Patients who do not meet the eligibility requirements for the treatment period will be considered screen failures and will keep their assigned identifying numbers.

Patient eligibility will be established before treatment randomization. Patients will be randomized strictly sequentially, as patients are eligible for randomization. If a patient discontinues from the study, the patient number will not be reused, and the patient will not be allowed to re-enter the study. If a number or a treatment is allocated incorrectly, no attempt should be made to remedy the error once study medication has been dispensed. The patient will continue with the allocated randomization code and corresponding clinical supplies. AstraZeneca or its designee should be notified as soon as the error is discovered.

## 3.6 Blinding and procedures for unblinding the study

### 3.6.1 Methods for ensuring blinding

Patients who meet all study entry criteria and who provide written informed consent will be randomized in a blinded fashion into the treatment phase. Double-blind technique will be used in the treatment phase of the study. There will be no differences in the appearance between the vials of esomeprazole and placebo concentrate.

### 3.6.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available to the investigator(s) or pharmacists at the study centre

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomization. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

## 3.7 Pre-study, concomitant and post-study treatment(s)

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the investigator(s) and reported to the Sponsor. The administration of all medication (including investigational products) must be recorded in the appropriate sections of the case report form (eCRF). No excluded medications (see Section 3.3.3) may be administered. The need for administration of any excluded medication may require withdrawal of the patient from the study or may render the patient's data un-evaluable.

## 3.8 Treatment compliance

On all study days, study personnel will administer the investigational product.

# 4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

## 4.1 Primary variable

The primary variable is 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.

- For other efficacy variables, see Table 3.

## 4.2 Screening and demographic measurements

Each patient will undergo a baseline assessment prior to study Day 1 (first day of study drug treatment). This will consist of:

- demographic data (date of birth, sex and race)
- medical history and documentation of normal ECG
- physical examination and vital signs - see Table 5
- laboratory screening (haematology, biochemistry and urinalysis)
- cardiorespiratory monitoring
- esophageal pH-monitoring
- intraluminal impedance monitoring
- video monitoring

Data listed above are to be recorded in the eCRF at the pre-entry visit.

## 4.3 Patient-Reported Outcomes (PROs)

Not applicable

## 4.4 Health Economic measurements and variables

Not applicable

## 4.5 Pharmacokinetic measurements and variables

Not applicable

## 4.6 Efficacy and pharmacodynamic measurement and variables

The study objectives and endpoints are summarized in Table 3.

**Table 3 Study objectives and endpoints**

| Objective | Endpoint | Summary statistic for analysis | Analysis method |
|---|---|---|---|
| **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 | **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 | **Primary:** mean change from baseline in symptomatic episodes by treatment group | **Primary:** ANCOVA, taking baseline number of episodes as a covariate, will be used for the treatment comparison |

**Table 3 Study objectives and endpoints**

| Objective | Endpoint | Summary statistic for analysis | Analysis method |
|---|---|---|---|
| **Secondary:** To assess the difference between esomeprazole and placebo in the treatment of symptomatic reflux episodes of GERD | **Secondary:** number of GERD-related signs (oxygen desaturation, apnea, bradycardia) at baseline and at end of study via clinical assessment charts | **Secondary:** (a) mean percentage of patients with each GERD-related sign (ie, #patients with event divided by #randomized in a treatment group), and separately for patients having at least one of the 3 signs, at baseline and end of study by treatment group<br>(b) mean percentage of apnea resolution rate (ie, #patients having apnea at baseline and having no apnea at the end of study divided by #patients having apnea at baseline) by treatment group (only considering patients having apnea at baseline) | **Secondary:** Descriptive statistics will be provided for the endpoints of interest |
| | **Secondary:** volume and frequency of vomiting episodes at baseline and at end of study via clinical assessment charts | **Secondary:** (a) mean percentage of patients with small/medium/large vomiting volume at baseline and at end of study by treatment group<br>(b) mean change from baseline in number of vomiting episodes by treatment group | |
| | **Secondary:** volume, frequency and duration of feeding at baseline and end of study via clinical assessment charts | **Secondary:** (a) mean volume per feeding and mean frequency of feeding by treatment group<br>(b) mean total feeding volume over 24 hours per kilogram by treatment group<br>(c) mean feeding duration by treatment group | **Secondary:** Cochran-Mantel-Haenszel (CMH) test stratifying on baseline severity will be used for treatment comparison |
| | **Secondary:** symptom severity recorded on the Physician's Global Assessment | **Secondary:** mean percentage of patients with no symptom (severity = none) at the end of study by baseline severity and by treatment group | |

**Table 3 Study objectives and endpoints**

| Objective | Endpoint | Summary statistic for analysis | Analysis method |
|---|---|---|---|
| **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 | **Secondary:**<br>(1) Durations of sleep, waking hours, peaceful quietness, and crying, at baseline and after treatment period<br><br>(2) Number of gagging, back arching, irritability/crying/ fussing, vomiting, apnea, bradycardia, and oxygen desaturation, at baseline and after treatment period<br><br>**Secondary**: change from baseline in the number of symptomatic reflux episodes of GERD, as observed during video recording together with a reflux detected from pH/impedance monitoring, and GERD-related sign(s) detected from cardiorespiratory monitoring together with a reflux detected from pH/impedance monitoring, at baseline and after treatment period | **Secondary:**<br>(1) Mean change from baseline in percentage of peaceful quietness time by treatment group;<br>mean change from baseline in percentage of sleep time by treatment group;<br>mean change from baseline in percentage of crying time by treatment group<br>(2) For each sign and symptom separately, or combined as appropriate, mean percentage of patients with sign or symptom, at baseline and after treatment, by treatment group<br>For each sign and symptom separately, or combined as appropriate, mean change in number of events from baseline by treatment group<br><br>**Secondary**: mean change from baseline in symptomatic reflux episodes associated with a reflux detected from pH/impedance by treatment group | **Secondary:**<br>(1) Differences in mean change from baseline in %time will be compared between treatment groups, using ANCOVA taking baseline %time as the covariate.<br>(2) Difference between treatment groups in %patients having no sign or symptom will be compared using a chi-square test.<br>Change from baseline in # events will be compared between treatment groups using ANCOVA, taking baseline # events as the covariate.<br><br>**Secondary:**<br>ANCOVA, taking baseline number of episodes as a covariate, will be used for the treatment comparison |
| | **Secondary**: number of GERD-related signs and symptoms associated with weakly acidic reflux episodes at baseline and at the end of study | **Secondary:** mean change from baseline in number of GERD-related symptoms by treatment group | **Secondary:**<br>Descriptive statistics will be provided for the endpoints of interest |

**Table 3 Study objectives and endpoints**

| Objective | Endpoint | Summary statistic for analysis | Analysis method |
|---|---|---|---|
| **Secondary:** to assess the efficacy of esomeprazole, compared to placebo, in reducing the number of<br>(a) all types of reflux episodes (acid or non-acid)<br>(b) acidic reflux episodes, defined as pH < 4,<br>via pH/impedance monitoring | **Secondary:**<br>(a) from impedance data:<br>separately for baseline and after treatment period:<br>Numbers of acidic episodes, weakly acidic episodes, non-acidic episodes, liquid GER episodes, mixed gas/liquid GER episodes, mean bolus clearance time, mean acid clearance time<br><br>(b) from pH data<br>separately for baseline and after treatment period:<br>number of acidic reflux episodes (ie, pH<4),<br>number of episodes lasting longer than 5 minutes,<br>%time pH<4,<br>%time pH 4-6.9 (inclusive) | **Secondary:**<br>(a) mean change from baseline in mean number of episodes and clearance time by treatment group<br><br>(b) mean change from baseline in numbers of acidic reflux, in episodes lasting longer than 5 minutes, in %time pH <4, in %time pH 4-6.9 (inclusive), by treatment group | **Secondary:**<br>Descriptive statistics will be provided for the endpoints of interest. |
| **Secondary:** To assess the safety and tolerability of esomeprazole compared to placebo | **Secondary:** Adverse events, and change from baseline in clinical laboratory parameters and vital signs | **Secondary:** mean percentage of patients with AEs, changes from baseline in lab parameters and vital signs by treatment group | **Secondary:**<br>Descriptive statistics |

### 4.6.1 Esophageal pH and intraluminal impedance monitoring

Combined esophageal pH and intraluminal impedance monitoring assessments will be performed for 18 – 24 hours twice during the study. The first one will be carried out at the baseline visit. The second pH-monitoring assessment will be made on the final study day.

The 18 – 24 hour pH/impedance data will be used to calculate the reflux index in those patients that complete this procedure. However, as long as patients have completed the 8 hours of video monitoring, they will be considered evaluable regardless of whether they complete the remaining pH/impedance monitoring.

#### 4.6.1.1 Method of assessment

Esophageal pH as well as intraluminal impedance will be measured per protocol ([redacted]). Placement of the probe will be scheduled close to and prior to feeding time. The probe will be positioned with the esophageal sensor above the LES per available standards of care (Strobel et al 1979, Omari TI et al 1999). The insertion of the probe will be done by qualified study personnel. Placement of the probe should be confirmed by X-ray, and the tip of the probe should be placed between T6 and T8.

The intraluminal impedance measurements allow detection of esophageal reflux based on changes in resistance (ohms) to alternating electrical current flow (<6μA at a frequency of 1 kHz ) between a series of ring sensors on the probe, when liquid and/or gas bolus moves between them. The signals from the data loggers are converted into ohms (Ω) by the same computer software used for the pH data. The pH and intraluminal impedance data will be downloaded onto a computer by the study personnel for subsequent analysis.

#### 4.6.1.2 Calculation or derivation of outcome variables

The following pharmacodynamic variables will be calculated for each patient and recording period:

**Esophageal pH monitoring:**

- number of acidic reflux episodes (pH<4)
- number of acidic reflux episodes greater than 5 minutes
- % time pH < 4
- % time pH 4 – 6.9 (inclusive)

**Intraluminal impedance monitoring:**

- number of acidic GER episodes (pH<4)
- number of weakly acidic GER episodes (pH 4 – 6.9)
- number of non acidic GER episodes (pH≥7)
- number of liquid GER episodes
- number of mixed gas/liquid GER episodes
- mean bolus clearance time
- mean acid clearance time

### 4.6.2 Video monitoring

The patient will be filmed with a video camera for approximately 8 hours (2 hours before and 6 hours after dosing) during the pH/impedance monitoring period. The video recordings should be scheduled at the same time of day for Baseline and final study day to include at least 2 feeding times.

#### 4.6.2.1 Method of Assessment

A qualified reader will review per standard guidelines the video and determine the presence or absence of symptomatic episodes in the images in conjunction with pH/impedance monitoring and other measurements.

#### 4.6.2.2 Calculation or derivation of outcome variables

The qualified reader will determine if each event recorded in the integrated video/pH/impedance data (those which were marked either through the surveillance notes of the site staff or the review of the pH/impedance data) is related to reflux and if they are, whether the event is acidic, weakly acidic or non acidic from the pH data and nature of the event (liquid or mixed liquid/gas reflux) from the impedance data. Events to be evaluated include the neuro-behavioral variables:

**Neuro-Behavioral**

- duration of sleep
- duration of waking hours
- peaceful quietness (defined as awake and quiet)
- duration of crying episodes
- gagging
- back arching
- irritability/crying/fussing

### 4.6.3 Cardiorespiratory monitoring

Cardiorespiratory monitoring will be performed for 8 hours at baseline and final study day (See Section 3.1.6). Other standard of care monitoring during the study will be carried out at the discretion of the principal investigator (See Section 3.3.4) and appropriate findings will be documented on the clinical assessment charts.

#### 4.6.3.1 Method of Assessment

Assessments will be made using standard monitoring equipment and will be noted on the clinical assessment charts or as part of the video/pH/impedance evaluation.

#### 4.6.3.2 Calculation or derivation of outcome variables

The following variables will be calculated for each patient and recording period:

- number of oxygen desaturation episodes as defined by a fall in $O_2$ saturation to < 85%
- number of apnea episodes defined as a pause in respiratory effort equal to or for >20 seconds
- number of bradycardia episodes or a decrease in heart rate <100 beats per minute

### 4.6.4 Clinical assessment charts

Clinical assessment charts, which are based upon a modified version of the Orenstein's (IGERQ) questionnaire, will be completed by the study personnel. Clinical assessment charts will be completed on all study days except on days of pH/impedance monitoring (baseline and final study day). For all subjects randomized in the study, only the symptoms recorded before baseline pH/impedance monitoring and the day before the end of study will be entered into the eCRF. However, all clinical assessment charts from enrolled/randomized patients will be monitored for safety reasons and stored as source data.

#### 4.6.4.1 Method of Assessment

The charts record feeding times and possible 'reflux-related' events. The chart records the daily frequency and timing of cardiorespiratory symptoms including apnea, gastrointestinal symptoms of vomiting, and neuro-behavioral symptoms of irritability/crying/fussing, back arching, and gagging in relation to feeding times and changes in the symptoms over time. Volumes of vomits and feeding will be estimated. These events are recorded as they occur by the study personnel.

#### 4.6.4.2 Calculation or derivation of outcome variables

Volume and frequency of vomiting (including regurgitation) will be collected. Volume will be categorized as:

- small volume (teaspoonful to a tablespoonful or 5 - 15 mL of feed)
- medium volume (1 to 2 tablespoonful or 15 - 30 mL of feed)
- large volume (more than 2 tablespoonful or > 30 mL of feed)

Volume, frequency, and duration (time to complete feeds) of feeding

### 4.6.5 Weight and Length

The patient's weight (naked), in kg, will be recorded on each study day and length (cm) will be recorded on each study day. The differences between the baseline visit and final visit will be used to determine the overall change in weight and length.

### 4.6.6 Physician Global Assessment

Investigators will be asked to complete the Physician Global Assessment of patient symptomatology at baseline and on the final study day.

#### 4.6.6.1 Methods of assessment

Investigators will complete the Physician's Global Assessment by responding to the following and the Investigator will record their answers in the eCRF:

Please provide your overall clinical impression of the patient's GERD-related symptoms over the past 24 hours and the severity scale will be defined as follows:

| Severity | Score | Description |
|---|---|---|
| **None** | 0 | No symptoms |
| **Mild** | 1 | Symptoms present but not interfering with daily activities |
| **Moderate** | 2 | Symptoms present and somewhat interfering daily activities |
| **Severe** | 3 | Symptoms present and greatly interfering or preventing daily activities |

Daily activities include feeding, sleeping, and as otherwise noted in the protocol.

#### 4.6.6.2 Calculation or derivation of outcome variables

Patients with severity of "None" from the Physician Global Assessment will be considered as having no GERD-related symptoms. Percentage of patients with no symptoms will be calculated, for baseline and end of study separately, by adding up patients with no symptoms divided by total number of patients with assessment data for a treatment group.

## 4.7 Safety measurements and variables

The methods for collecting safety data are described below.

### 4.7.1 Adverse events

#### 4.7.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

**Adverse event**

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg,., tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

**Serious adverse event**

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?” For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B to the Clinical Study Protocol.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as “yes”.

**Other Significant Adverse Events (OAE)**

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious),

dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

#### 4.7.1.2 Recording of adverse events

Adverse Events spontaneously reported by the study personnel throughout the study, in response to an open question: "Has the child had any health problems during the study days/since the previous assessment", or revealed by observation will be recorded in the eCRF.

Information about AEs will be collected after informed consent is obtained by the parent/guardian at the pre-entry visit until the completion of the 14-day follow-up office visit after the last dose of study drug. SAEs will be reported during the entire study period.

Abnormalities in laboratory values need not be recorded as AEs, unless the abnormal values constitute an SAE, lead to discontinuation of administration of investigational product, or the investigator considers it to be of such clinical importance as to merit recording the event as an AE.

The time/date when the AE started and stopped, maximum intensity, action taken with regard to investigational product, causality, outcome and whether it constitutes an SAE or not will be recorded in the eCRF for each AE.

The intensity as judged by the study personnel will be rated according to the following scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.8.1.1. An AE of severe intensity need not necessarily be considered serious. For example, colicky pains which persist for several hours may be considered severe, but not a SAE. On the other hand, a few voluminous diarrheas, which initially result in only a limited degree of disability, might eventually be considered an SAE due to the vulnerability to volume losses in these infants.

All ongoing AEs must be followed until resolution or until the investigator decides and documents that no further follow-up is necessary. AstraZeneca may request additional information about such AEs.

Adverse events will be classified by AstraZeneca according to the terminology of MedDRA.

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, Procedures in case of overdose, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

#### 4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If follow-up indicates a change in the SAE from serious to fatal or life-threatening, this information needs to be available in the WBDC system within 1 calendar day.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that become serious but which is not fatal or life threatening a report should be received within 5 days.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day 1 for all fatal and life-threatening cases and by day 5 for all other SAEs.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca (see section 8.1).

### 4.7.2 Laboratory safety measurements and variables

#### 4.7.2.1 Methods of assessment

Blood and urine samples for determination of biochemistry, haematology and urinalysis variables (Table 3) will be taken at the pre-entry visit and on the final study day according to the normal routine at the study site. The date of collection will be recorded on the appropriate eCRF. The total volume of blood taken for the laboratory draws for the study will not exceed 3 mL. (Table 5) If venous blood is not available, heel prick samples are acceptable.

The blood and urine samples will be analysed at the local laboratory using routine analyses. The local laboratory will provide the AstraZeneca monitor with up-to-date reference ranges for the different laboratory variables. Values of concern should be followed up at the discretion of the investigator.

The investigator or sub-investigator must review all lab values prior to the randomization of a patient and throughout the study. The investigator or sub-investigator must assess the clinical significance of all out of range values. Follow up on out of range values will be at the discretion of the investigator except for patients who discontinue from the study due to the out of range laboratory value or if the lab abnormalities are clinically significant.

All lab data must be entered into the eCRF on an ongoing basis according to data entry instructions.

Additionally, a stool hemoccult will be performed at baseline only. The hemoccult analysis will be completed at the site by the investigator or study nurse.

**Table 4 Laboratory Safety Variables**

| Routine Biochemistry* | Haematology | Urinalysis |
|---|---|---|
| Alanine Aminotransferase (ALT) | Total white cell count | Blood |
| Aspartate Transaminase (AST) | Differential white cell count | Ketones |
| Alkaline Phosphatase (ALP) | Haemoglobin/Hematocrit | Hemoglobin |
| Albumin | Mean Corpuscle Volume (MCV) | Nitrites |
| Bicarbonate | Red blood cell count (RBC) | pH |
| Bilirubin, Total | Platelet count | Protein |
| Bilirubin, Fractionated | | Specific gravity |
| Calcium | | Microscopic evaluation |
| Creatinine | | |
| Glucose | | |
| LDH | | |
| Potassium | | |
| Sodium | | |
| Urea Nitrogen (BUN) | | |
| Gamma GT | | |
| Total protein | | |

* Blood serum samples will be analysed.

#### 4.7.2.2 Derivation or calculation of outcome variables

All patients with laboratory values will be included in the laboratory summary. The lab values will be used for the calculation of mean baseline value, mean final value and mean change from baseline.

### 4.7.3 Vital signs and physical examination

The patient will have physical examinations performed at the baseline visit and the final study day to assess the following items: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, lungs, abdomen, and neurological. All physical examinations will be performed by a physician or medically qualified personnel (eg, nurse practitioner or physician's assistant).

Vital signs will be assessed at baseline visit, Day 1 and final study day. The following assessments will be recorded: weight, length, head circumference, blood pressure, heart rate, temperature, and respiration rate (See Table 5). The patient's weight (naked), in kg, and length will be recorded daily.

**Table 5 Vital signs and physical parameters**

| Investigation | Method |
|---|---|
| Weight (naked) | Per weight scales |
| Height/length | Per stadiometer or tape measure |
| Head circumference | Per tape measure |
| Temperature | Tympanic (preferred) or rectal |
| Blood Pressure | Systolic and diastolic, per NICU protocols |
| Heart rate | 15 seconds by wrist |
| Breathing rate | 15 seconds by observation |

Patients must have a normal ECG at baseline (historical documentation is allowed) without clinically significant findings as deemed by the investigator.

#### 4.7.3.1 Methods of assessment

Any clinically relevant change from the finding at baseline, as determined by the investigaor will be considered an adverse event and recorded on the appropriate eCRF page.

#### 4.7.3.2 Derivation or calculation of outcome variables

Mean change from baseline for vital signs will be summarized by treatment.

## 4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study is as follows:

**Table 6 Volume of blood to be drawn from each patient**

| Assessment | | Sample volume (mL) | No. of samples | Total volume (mL) |
|---|---|---|---|---|
| Safety | Clinical chemistry and hematology | 1.5 | 2 | 3 |
| **Total** | | | | **3** |

### 4.8.1 Analysis of biological samples

#### 4.8.1.1 Clinical chemistry samples

The analyte stability limits defined by the local laboratory will be applied to all analyses performed on behalf of AstraZeneca. The local laboratory will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the local laboratory may be amended in accordance with its Standard Operating Procedures. The local laboratory will inform AstraZeneca of the stability limits relevant to this study before the first parent/guardian gives informed consent for his/her child to take part in the study.

# 5. DATA MANAGEMENT

Data will be entered in the Web Based Data Capture (WBDC) system at the investigational site. The WBDC system will be authorized and approved by AstraZeneca and set up and maintained by the CRO. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions within agreed timelines. The eCRF Instructions will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, edited and Source Data Verification (SDV) has been performed, the Principal Investigator will be notified to sign a hard copy of the eCRF signature page and send it to the CRO for imaging. An electronic copy of the eCRF will be provided to the investigational site after the study database has been locked and will be archived at the investigational site.

Data checks will be run and data validation performed continuously by the CRO. The investigator should answer any queries raised by AstraZeneca or CRO during the entire duration of the study including the clean-file process.

Adverse events and Medical/Surgical history will be classified according to the terminology of the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the CRO and reviewed and approved at AstraZeneca R&D Wilmington.

It is the responsibility of the Investigator to complete Serious Adverse Event Form when applicable. It is the AstraZeneca monitor's responsibility to ensure that any Serious Adverse Event Form is fully completed.

Data will be cleaned on a regular basis by the CRO. All decisions on the evaluability of the data from each patient must have been made and documented before the randomization codes are broken and the study is unblinded.

A minimum of data will be collected for screen failure subjects. The Data Management Plan will be written by the CRO and approved by AstraZeneca. This document will provide information on data flow, timelines and all data management activities planned for the study, including responsibilities for the personnel involved in the processes and validation procedures.

# 6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 6.1 Statistical evaluation – general aspects

A comprehensive Statistical Analysis Plan (SAP) describing the determination of the analysis populations, handling of missing data, and the calculations of the derived variables, will be prepared by Biostatistics and reviewed/approved by the study team before the unblinding of the data.

## 6.2 Description of outcome variables in relation to objectives and hypotheses

The primary objective of this study is to evaluate if there is a difference between esomeprazole and placebo in the treatment of signs and symptoms of GERD as observed in an 8-hour video recording along with cardiorespiratory monitoring. Video, pH/impedance, and cardiorespiratory monitoring will occur at baseline (before treatment) and the final study day. Symptoms or symptomatic reflux episodes of GERD will be determined by a qualified reader, in a blinded fashion, by review of the video recording, the pH/impedance monitoring, and the cardiorespiratory monitoring. Other variables can be found in Table 3.

## 6.3 Description of analysis sets

There will be two analysis sets for the efficacy evaluation: the intent-to-treat (ITT) and the per-protocol (PP). The ITT set will include all randomized patients who take at least one dose of study medication and have valid efficacy measurements both at baseline and at the end of study. The ITT set will be considered the primary analysis set. The PP set includes all patients in the ITT set and those who do not have any major protocol violations. A detailed description of the PP population will be included in the SAP. The safety population will consist of all randomized patients taking at least one dose of study medication.

## 6.4 Method of statistical analysis

The primary variable, change from baseline in number of signs and symptoms as observed in the video and detected from cardiorespiratory monitoring, will be analyzed using an analysis of covariance model (ANCOVA), taking the number of episodes at baseline as the covariate. The number of signs and symptoms at baseline, at the end of the study, change from baseline, and % change from baseline will be presented for the treatment comparison.

The secondary variables, including the number of symptomatic reflux episodes of GERD as observed from the video, together with reflux detected from pH/impedance, and GERD-related signs detected from cardiorespiratory monitoring associated with a reflux from pH/impedance monitoring, will be analyzed and presented in the same way as the primary variable.

Percent time of peaceful quietness, sleep, and crying will be summarized from video monitoring data for each patient separately, at baseline and at the end of the study. For each parameter (ie, % time of peaceful quietness, sleep, and crying) change from baseline in % time will be calculated. The comparisons between treatment groups in change from baseline will be made using ANCOVA taking baseline % time as the covariate. For each parameter, the % time at baseline, at the end of study, and change from baseline will be presented for evaluating the treatment difference.

Other GERD-related signs and symptoms (eg, gagging, back arching, irritability/crying/ fussing, vomiting, apnea, bradycardia, oxygen desaturation) will also be assessed at baseline and at the end of the study via video and cardiorespiratory monitoring along with measurements from pH/impedance monitoring. The number of these events will be summed up for each patient at each time point for each sign and symptom individually or combined as appropriate. Change from baseline in number of events will be compared between treatment groups using ANCOVA, taking the baseline number of events as the covariate. Patients will also be categorized as 'having' or 'not having' the sign or symptom, individually or combined as appropriate. Difference between treatment groups in percentage of patients having no event will be compared using a chi-square test. Percentage of patients having no event at baseline as well as at the end of study will be tabulated for each treatment group separately.

The Physician's Global Assessment will be collected at baseline and at the end of the study. A CMH test stratifying on baseline severity will be used to compare the difference between esomeprazole and placebo in the percentage patients having no symptoms. A summary table of the percentage of patients having no symptoms at the end of the study will be presented by baseline severity for each treatment group separately.

Descriptive statistics will be provided on change from baseline in number of signs and symptoms, the primary efficacy endpoint, for various sub-groups if appropriate (eg, site, age group, days on study medication). Descriptive statistics will be provided on other efficacy endpoints of interest (eg, percentage of cardiorespiratory events, percentage of apnea resolution rates, percentage on vomiting categories, pharmacodynamic parameters).

Descriptive statistics will be provided for the evaluation of the safety profile (eg, AEs, lab parameters, vital signs).

## 6.5 Determination of sample size

No relevant historical data on symptomatic episodes in this patient population was available for the sample size calculation. It was assumed that the standard deviation is about 1.5 times greater than the difference between treatment groups in number of symptomatic episodes.

Under the assumption, it would need 38 patients per group to provide at least 80% power at alpha of 0.05 to detect a difference between esomeprazole and placebo in change of symptomatic episodes from baseline.

## 6.6 Interim analyses

No interim analysis is planned for this study. The safety subteam (See Section 6.7), however, may choose to request any analysis it feels necessary, including unblinding the data, to protect the safety of the patients in the study.

## 6.7 Data monitoring board

There will not be a data monitoring board; however a Data and Safety Monitoring Plan will be available for this study. The Clinical Study Physician will monitor the SAEs on a continuous basis. A Drug Safety Physician will review all serious unexpected reports that are assessed by the investigator to be causally related to study drug within 15 days from AstraZeneca notification of the event. In addition, a safety subteam, consisting of the AstraZeneca Drug Safety Physician(s), Drug Safety Scientist, Clinical Study Physician, Study Delivery and other Clinical Study Team members will meet on a regular basis to review blinded study data regarding SAEs, non-serious AEs, discontinuation criteria, clinically significant laboratory data and vital signs. The safety subteam may request additional evaluations at their discretion from the site.

The safety subteam will also review any safety issues that arise from other Nexium pediatric studies. Ad hoc safety meetings will be held anytime a potential safety issue is identified. Any potential safety signals identified which might impact upon the benefit-risk of the product or protocol or lead to a change in the way the product is administered within future clinical trials or the post-marketing setting will be communicated in a timely manner to investigators and regulatory authorities.

Study therapy identity will only be unblinded during the safety data review if considered imperative. Unblinding may take place where knowledge of patient's study treatment is crucial to the definition, or progression, of a critical safety issue that may contribute to a decision regarding the continuation, or otherwise, of the study.

# 7. STUDY MANAGEMENT

## 7.1 Monitoring

Before first patient into the study, a representative of AstraZeneca will visit the investigational study site to:

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of

AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the investigator

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study site, including visits to:

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed
- perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the centre needs information and advice.

The monitor(s) will verify data from the eCRFs against source data to ensure accuracy and completeness of documentation.

## 7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority; or an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

## 7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

Before the first subject is entered into the study, the investigational staff will be trained to use the WBDC system by AstraZeneca personnel or delegates.

## 7.4 Changes to the protocol

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to or approved by each Ethics Committee, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her centre. The distribution of these documents to the regulatory authority will be handled according to local practice.

## 7.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol shall prevail.

## 7.6 Study timetable and end of study

Before a patient's enrollment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- Written approval of the study by the Ethics Committee.
- Written approval of the study, if applicable, by the regulatory authority.

The end of study is defined as date of database lock, which is the time point after which no patient will be exposed to study related activities.

# 8. ETHICS

## 8.1 Ethics review

AstraZeneca will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enrol any patient into the study.

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

## 8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

## 8.3 Informed consent

The principal investigator(s) at each centre will ensure that the patient's parent/guardian is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The parent/guardian must also be notified that they are free to discontinue his/her child from the study at any time. The patient's parent/guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The parent/guardian's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator(s) must store the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient's parent/guardian.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

## 8.4 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by *randomization code / study code / initials*.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

# 9. PROCEDURES IN CASE OF EMERGENCY OR OVERDOSE OR PREGNANCY

## 9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician or the Drug Safety Physician at the AstraZeneca Research and Development site shown below.

| Role in the study | Name | Address & telephone number |
|---|---|---|
| Study Delivery Team Leader | [redacted] | [redacted] |
| Study Delivery Team Physician | [redacted] | [redacted] |
| 24-hour emergency cover at central R&D site. | Information Centre at AstraZeneca | [redacted] |

## 9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

## 9.3 Procedures in case of overdose

For the purpose of this study, an overdose will be any dose in excess of that specified in the protocol. Adverse events reported after treatment with esomeprazole in children are *very* few and all reports deal with experiences in children > 1 year of age (between 3 and 17 years old). The most common adverse events reported are rash, vomiting, diarrhoea and neurological symptoms such as dizziness. In case of an overdose the drug is considered to have a low acute

toxicity. There is no specific inhibitor of esomeprazole and the treatment must be symptomatic. If an overdose were to occur, the site should immediately notify AstraZeneca.

- Use of study medication in doses in excess of that specified in the protocol should not be recorded in the eCRF as an AE of 'Overdose' unless there are associated symptoms or signs.

- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRFs.

- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. In addition, the overdose should be reported on the separate AstraZeneca "Clinical Study Overdose Report Form."

- An overdose without associated symptoms should not be recorded as an AE in the eCRFs. The overdose should be reported on the separate AstraZeneca "Clinical Study Overdose Report Form".

## 9.4 Procedures in case of pregnancy

Not applicable.

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**Clinical Study Protocol: Appendix B**

| | |
|---|---|
| Drug Substance | esomeprazole sodium |
| Study Code | D9614C00004 |
| Appendix Edition Number | 1 |
| Appendix Date | [redacted] |

# Appendix B
# Additional Safety Information

# FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

## Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

## Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

## Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

*Examples of such events are:*

- *Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment*
- *Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine*
- *Intensive treatment in an emergency room or at home for allergic bronchospasm*
- *Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation*
- *Development of drug dependency or drug abuse.>>*

# A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

| Clinical Study Protocol Appendix C | |
|---|---|
| Drug Substance | esomeprazole sodium |
| Study Code | D9614C00004 |
| Appendix Edition Number | 1 |
| Appendix Date | [redacted] |

# Appendix C
# Dose determination for esomeprazole pediatric studies

# Dose Determination for Esomeprazole Pediatric Studies

[redacted]

Submitted by: AstraZeneca LP, 1800 Concord Pike, Wilmington, DE 19850

Table of contents

## Abstract

The esomeprazole doses selected for the pediatric GERD studies were based on the methodologies described in this document. These doses will provide a reasonable chance of efficacy with a supportable safety margin. The doses selected for each age group are outlined below:

| AZ Protocol # | Age Group | Design | Dose(s) |
|---|---|---|---|
| D9614C00095 | Premies 0 up to 1 month, corrected age | A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Treatment-Withdrawal Study to Evaluate the Pharmacokinetics, Efficacy, and Safety of Esomeprazole for the Treatment of Gastroesophageal Reflux (GER)-Associated Apnea in Neonatal Patients, Premature up to 1 Month Corrected Age<br><br>Open-label phase =5 to 7 days<br><br>Randomized withdrawal phase =up to 1 week | 0.25-0.5 mg/kg<br><br>Open-label phase: 0.5 mg/kg<br><br>Randomized withdrawal phase: 0.5 mg/kg, 0.25 mg/kg or placebo |
| D9614C00096 | Infants 1 month up to 11 months, inclusive | A 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<br><br>Open-label phase =5 to 7 days<br><br>Randomized withdrawal phase =up to 1 week | 1.5, 2.5, 3, 5 and 10 mg<br><br>Stratified by weight:<br><br>3 kg≤Weight<5 kg: open-label phase: 3 mg, randomized withdrawal phase: 3 mg, 1.5 mg or placebo<br><br>5 kg≤Weight<7.5 kg: open-label phase: 5 mg, randomized withdrawal phase: 5 mg, 2.5 mg or placebo<br><br>7.5 kg≤Weight<12 kg: open-label phase: 10 mg, randomized withdrawal phase: 10 mg, 5 mg or placebo |

| AZ Protocol # | Age Group | Design | Dose(s) |
|---|---|---|---|
| D9614C00097 | Children 1 year up to 11 years, inclusive | A Multicenter, Parallel-Group Study to Evaluate the Safety and Clinical Outcome of Once Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Pediatric Patients Ages 1-11 Years, Inclusive<br><br>Duration =8 weeks | 5, 10 and 20 mg<br><br>Stratified by weight:<br><br>8 kg≤Weight<12 kg: 5 or 10 mg<br>12 kg≤Weight<60 kg: 10 or 20 mg |

Since esomeprazole is the S-isomer of omeprazole, the pharmacokinetic (PK), pharmacodynamic (PD), efficacy and safety data from omeprazole, as well as esomeprazole, were used to guide the dosing selection. First, omeprazole PK data were used to develop a model to predict the effects of age and weight on omeprazole clearance. Then omeprazole and esomeprazole data, from both pediatric and adult patients, relating exposure (AUC) to efficacy and safety, were examined. From these analyses, the desired exposures for esomeprazole in pediatric subjects were determined. Next, a PK model for esomeprazole in adults was developed and modified using the age and weight parameters previously derived from omeprazole PK data. Finally, this model was used to predict the doses of esomeprazole required to achieve the desired AUCs for each of the above pediatric populations.

Therefore, based on the available data using reasonable modeling techniques, these doses should have a suitable safety margin while still providing a high likelihood of efficacy. The following document contains a complete description of the methods used to select the doses.

## 1. INTRODUCTION:

Esomeprazole, the S-isomer of omeprazole, is a selective inhibitor of the proton pump $H^+/K^+$-ATPase in the parietal cell in the gastric oxyntic mucosa. Clinical pharmacology studies in healthy adult volunteers and patients with gastroesophageal reflux disease, indicate that a more pronounced gastric acid inhibitory effect along with higher area under the plasma concentration versus time curve (AUC) were obtained with esomeprazole than with omeprazole for equivalent doses. The metabolism of esomeprazole has also shown less polymorphic variability compared to omeprazole. Consequently, esomeprazole demonstrates better and more stable acid control in adults than omeprazole[1]. It is expected that the advantages of esomeprazole over omeprazole in adults could be applied to pediatric subjects. Previous studies of Pharmacokinetics (PK), Pharmacodynamics (PD), efficacy and safety for the use of omeprazole and other proton pump inhibitors in adults and children[2-7], and for the use of esomeprazole in adults[1, 8-9] have provided data to extrapolate esomeprazole doses from adults to pediatric subjects.

The purpose of this report is to establish appropriate esomeprazole doses for esomeprazole pediatric studies based on the rationale of exposure and response[10].

## 2. DATA ANALYZED:

Four data sets were used in this analysis:

1. Pharmacodynamic (PD) data (percent of time with gastric pH>4 and gastric median pH) in 9 pediatric subjects with age ranging from 4.5 to 27 months following repeated intravenous (iv) infusion of omeprazole from literature[4] and 36 adults from AstraZeneca study SH-QBE-0008 following repeated oral administration of omeprazole
2. Pharmacokinetic (PK) data following repeated iv infusion of omeprazole in 16 pediatric subjects with age ranging from 10 days to 27 months reported by Andersson et al[3] and Faure et al[4] and 16 adults from AstraZeneca study SH-QBE-0061.

3. PK data following repeated oral administration of omeprazole in 66 pediatric subjects with age ranging from 0.5 months to 16 year olds and 36 adults with age ranging from 30 to 58 years old from AstraZeneca studies I-245, I-250, I-678 and SH-QBE-0008
4. PK data following repeated oral administration of esomeprazole in 36 adults with age ranging from 30 to 58 year olds from AstraZeneca study SH-QBE-0008

Detailed descriptions of each of these data sets are shown in Table 1.

## 3. METHODS

### 3.1 BRIDGING ESOMEPRAZOLE SAFETY BETWEEN PEDIATRIC SUBJECTS AND ADULTS

Potential difference in esomeprazole safety between pediatric subjects and adults was evaluated using the observed safety information in pediatric subjects and adults at similar omeprazole exposure (AUC) following administration of omeprazole from AstraZeneca internal database and a literature survey. The observed or reported difference in safety between pediatric subjects and adults (if any) following administration of omeprazole was considered to be applicable to esomeprazole since esomeprazole is the S-isomer of omeprazole.

### 3.2 BRIDGING ESOMEPRAZOLE EFFICACY BETWEEN PEDIATRIC SUBJECTS AND ADULTS

Potential difference in esomeprazole efficacy between pediatric subjects and adults was evaluated by plotting the PD endpoints (percent of time with gastric pH>4 and gastric median pH) against the exposure (AUC) for both adults and pediatric subjects following administration of omeprazole (data set 1). In addition, a literature survey was also conducted to obtain information on other proton pump inhibitors (PPIs). The difference in efficacy between pediatric subjects and adults (if any) following administration of omeprazole and other PPIs

was again considered to be applicable to esomeprazole because all PPIs have a common mechanism of action.

## 3.3 BRIDGING ESOMEPRAZOLE PHARMACOKINETICS BETWEEN PEDIATRIC SUBJECTS AND ADULTS

Body weight and age are two major factors determining the pharmacokinetic differences between adults and pediatric subjects. The most important PK parameter is the clearance (apparent clearance for oral dose administration), which directly relates to the exposure (AUC). Previous omeprazole PK studies in pediatric subjects and adults (data sets 2&3) were used to establish a model of using population mean omeprazole clearance in adults to predict population mean omeprazole clearance in different pediatric age groups with body weight and age. Given that esomeprazole is one of the two isomers of omeprazole, such a model was assumed to be reasonably applicable to esomeprazole when the population mean omeprazole clearance is substituted by the population mean esomeprazole clearance.

### 3.3.1 DESCRIPTIVE ANALYSIS FOR OMEPRAZOLE CLEARANCE

Descriptive statistics for the clearance (apparent clearance for oral doses) were generated using data sets 2&3 to compare the difference in omeprazole clearance among different age groups, and to compare the difference in the clearance between omeprazole and esomeprazole in adults.

### 3.3.2 OMEPRAZOLE PK MODELING ANALYSIS

Population PK modeling analysis was conducted for the repeated oral omeprazole dose group (data set 3) using the following covariate models for body weight and age

$$CL/F = (CL/F)_{std} \times (WT/70)^{0.75} \times (1 - CL_{age} \times e^{-KCLage \times Tage}) \quad (1)$$

$$V/F = (V/F)_{std} \times (WT/70) \times (1 + V_{age} \times e^{-KVage \times Tage}) \quad (2)$$

where CL/F is the apparent clearance, V/F is the apparent volume of distribution, $(CL/F)_{std}$ and $(V/F)_{std}$ are the apparent clearance and the apparent volume of distribution for a person with a standard body weight of 70 kg, respectively, WT is the body weight, $T_{age}$ is time after birth, $CL_{age}$ and $V_{age}$ are parameters estimating the fractional difference from $(CL/F)_{std}$ and $(V/F)_{std}$, respectively, at birth, $KCL_{age}$ and $KV_{age}$ are the rate constants of the age-related changes of CL/F and V/F, respectively. The power function relationships between CL/F and WT and between V/F and WT with exponents of 0.75 and 1, respectively in equations (1) and (2), are called allometric covariate model for body weight[11]. The body weight was customarily normalized by the standard body weight of 70 kg. Equations (1) and (2) reflect the fact that both CL/F and V/F increase as the body weight increases, and that CL/F correlates with the body weight in a nonlinear manner. The exponential function models for age effects on both CL/F and V/F in equations (1) and (2) assumed a first order process and model putative effects of age on drug disposition that the apparent clearance increases as the age increases, but the apparent volume of distribution decreases from birth due to the loss of water[12].

The population PK modeling analysis was focused on data set 3, which has the largest number of subjects; however, there were only one neonate and three infants (0.5-4.2 months) in this data set. The next oldest in the data set was 1.6 years. Consequently, the typical population PK modeling analysis with equations (1) and (2) as covariate models of body weight and age may not have given stable parameter estimates of $CL_{age}$, $V_{age}$, $KCL_{age}$ and $KV_{age}$. Data set 1 has a better distribution of pediatric subjects in the different age groups, but there were no individual omeprazole concentration data available in the study by Faure et al[4]. As a result, the typical population PK modeling analysis could not be done using this data set. However, since CL/F (F=1 for iv infusion PK data) was available (or could be derived) for all studies in data set 1, equation (1) was used to estimate the impact of age on the clearance by using non-linear regression with the allometric covariate model for the body weight. The effect of age on the volume of distribution was not examined, as the volume of distribution was not reported in the literature[4].

### 3.3.3 ESOMEPRAZOLE PK MODELING ANALYSIS

Population PK analysis was also conducted with the PK data following repeated daily oral esomeprazole doses (data set 4) using an allometric covariate model for body weight ($CL/F= (CL/F)_{std} \times(WT/70)^{0.75}$ and $V/F= (V/F)_{std} \times(WT/70)$) to obtain the parameter estimate of population mean apparent clearance of esomeprazole, $(CL/F)_{std}$, for a subject with typical body weight of 70 kg. The age effects on CL/F and V/F were not examined because all subjects in the data set are adults no more than 60 years old.

Population PK software NONMEM (Version 5.1, University of California, San Francisco) was used to implement all the population PK analyses[13].

## 3.4 CRITERIA FOR DOSE SELECTION FOR ESOMEPRAZOLE PEDIATRIC STUDIES

It has been well established that the inhibition of acid secretion by esomeprazole is well correlated with the exposure (AUC )[8,9], which is subsequently determined by the (apparent) clearance (AUC=Dose/(CL/F)). The relationship between the esomeprazole exposure (AUC) and the acid inhibition can be adequately described by a sigmoid $E_{max}$ model [8,9]

$$\text{Acid inhibition}= (E_{max}\times AUC^{\gamma}/( AUC^{\gamma}+AUC^{\gamma}_{50}) \qquad (3)$$

where $E_{max}$ is the maximum acid inhibition (100%), $AUC_{50}$ is a value of AUC achieving 50% acid inhibition and $\gamma$ is the sigmoidicity factor reflecting the steepness of the exposure and response relationship. The reported value of $AUC_{50}$=0.68 umol/L with a sigmoid coefficient $\gamma$=1.43 implies that at three times of the $AUC_{50}$ for this sigmoid $E_{max}$ exposure and response relationship, the acid inhibition will reach more than 80%[8]. Therefore, we believe a dose that results in AUC 3-fold higher than $AUC_{50}$ should be considered to be the minimum effective dose in adults.

The 40 mg esomeprazole oral dose has been widely used in the treatment of acid–related disease in adults with no apparent safety concerns. Study SH-QBE-0008 reported that the upper limit of 95% confidence interval of the esomeprazole exposure (AUC) is 16.17 (umol.hr/L) for the 40 mg esomeprazole oral dose in adults, which approximately correspond to 24 times of the $AUC_{50}$ (0.68 umol.hr/L). Thus, a dose that generates an exposure AUC meeting $AUC/AUC_{50}$ less than 24 was considered to be a safe dose in adults.

Collectively, an esomeprazole dose with an exposure AUC greater than 3 and less than 24 times of the $AUC_{50}$ was found to be a reasonable dose for both efficacy and safety in adults. These limits were scaled to different pediatric subject groups according to the difference (if any) in esomeprazole efficacy and safety between adults and pediatric subjects established in 3.1 and 3.2.

## 3.5 STRATEGY FOR SEARCHING APPROPRIATE ESOMEPRAZOLE DOSES IN PEDIATRIC SUBJECTS

The dose selection for esomeprazole pediatric studies was established by first applying the dose adjustments observed in the omeprazole pediatric studies based on the difference in geometric mean clearance among different age groups in Table 1. A range of doses was then evaluated by the exposure and response criteria. The exposure (AUC) of esomeprazole for the different doses, calculated as Dose/(CL/F), was simulated using the relationship of body weight and age to esomeprazole clearance (established in 3.3) for an assortment of pediatric subjects. The comparison of the simulated esomeprazole exposures, for the various possible doses, allowed us to then select the ones meeting the prescribed limits of efficacy and safety established in 3.4 for different pediatric subject groups.

# 4. RESULTS AND DISCUSSIONS:

## 4.1 BRIDGING ESOMEPRAZOLE SAFETY AND EFFICAY BETWEEN ADULTS AND PEDIATRIC SUBJECTS

Proton pump inhibitors (PPI) have shown a remarkable tolerability profile in both adults and children. In an AstraZeneca omeprazole pediatric study (I-250), some children had AUC exposures up to 3 times the mean exposure seen in adults administered the maximum labeled omeprazole dose (40 mg), and no drug related side effects were reported. Examination of literature for the safety of the two proton pump inhibitors with labeling for use in both pediatric subjects and adults, omeprazole and lansoprazole, have not found any significant differences in safety between pediatric subjects and adults at a similar exposure (AUC)[1,5-7].

The plot of percent of time with gastric pH>4 and gastric median pH vs. AUC following administration of omeprazole in both adults and pediatric subjects is shown in Figure 1. It indicates that children are no less sensitive to acid inhibition than adults at similar omeprazole exposure. This was also observed in the pediatric study for Lansoprazole[6], a proton pump inhibitor with a similar mechanism of action to esomeprazole.

These results indicate that it is likely that the difference in safety and efficacy between pediatric subjects and adults at the same omeprazole exposure (AUC) is negligible. These attributes of omeprazole are also likely true for esomeprazole, the S-isomer of omeprazole. Consequently, the dose adjustment for esomeprazole can be based on the differences in esomeprazole pharmacokinetics between pediatric subjects and adults. In addition, the limits of esomeprazole exposure in adults, 3 and 24 times the $AUC_{50}$ (0.68 umol.hr/L) for lower and upper limits, respectively, can be used for pediatric subjects without adjustment.

## 4.2 BRIDGING ESOMEPRAZOLE PHARMACOKINETICS BETWEEN ADULTS AND PEDIATRIC SUBJECTS

### 4.2.1 OMEPRAZOLE PK MODELING ANALYSIS

Population PK analysis suggests that the concentration time courses following repeated daily oral omeprazole dose (data set 3) are adequately described by a one-compartment disposition model with an allometry covariate model for body weight, and a first order absorption model with an absorption lag time. Age was not identified as a significant covariate for either clearance or volume of distribution according to equations (1) and (2) in this data set. The relationship of body weight to the apparent omeprazole clearance $(CL/F)_{omeprazole}$ is

$$(CL/F)_{omeprazole} = 23.5 \times (WT/70)^{0.75} \quad (4)$$

The number 23.5 (L/hr) is the population mean omeprazole apparent clearance for an adult with a standard body weight of 70 kg. Physiologically, omeprazole clearance should be related to age since the CYP2C19, an enzyme mainly responsible for metabolizing omeprazole, starts to develop at birth and needs some time to reach adult level[5-6]. The lack of such an effect in the population PK analysis may have been due to the fact that there are only four subjects aged 0.5 to 4.2 months in the data set. Data set 1, omeprazole PK data for daily repeated iv infusion, is more adequately represented by younger pediatric subjects. There were 16 children with ages ranging from 10 days to 27 months. Based on the reported clearance, body weight and age for each individual in the data set, nonlinear regression for the relationship between clearance and weight and age using equation (1) revealed that age is a significant covariate for the clearance. The estimated $CL_{age}$ and $KCL_{age}$ are 1 and 10.9 (1/years), respectively. Plugging the age effect on clearance into equation (4) based on equation (1) yields a physiologically plausible relationship of body weight and age to the apparent omeprazole clearance $(CL/F)_{omeprazole}$:

$$(CL/F)_{omeprazole} = 23.5 \times (WT/70)^{0.75} \times (1-e^{-10.9 \times Tage}) \quad (5)$$

where the unit of $T_{age}$ is in year. A unit of $CL_{age}$ in equation (5) implies a negligible clearance for a newborn, and a value of 10.9 (1/year) for the $KCL_{age}$ implies a half-life of 23 days for the maturity of the CYP2C19 isoenzyme mainly responsible for the metabolism of both omeprazole and esomeprazole. These values are consistent with the fact that CYP2C19 activity is not detectable in fetuses and newborns younger than 24 hours old and surges between 8 and 28 days[6]. The half-life of 23 days for the maturity of CYP2C19 after birth infers that the enzyme will almost reach full maturity in three months (more than 5 half-lives).

### 4.2.2 ESOMEPRAZOLE PK MODELING ANALYSIS

Population PK analysis of esomeprazole concentration time profiles of 36 adults following five daily repeated esomeprazole 20 mg oral dose (data set 4) also found that esomeprazole concentration time profiles were adequately described by a one-compartment disposition model with an allometry covariate model for body weight, and a first order absorption model with an absorption lag time. The estimated population mean apparent clearance for esomeprazole is 13. 6 (L/hr). Replacing the population mean apparent clearance for omeprazole in equation (5), 23.5 (L/hr), by the estimated population mean apparent clearance for esomeprazole 13.6 (L/hr) leads to the following relationship of body weight and age to the apparent esomeprazole clearance:

$$CL/F=13.6\times(WT/70)^{0.75}\times(1-e^{-10.9\times Tage}) \qquad (6)$$

This equation was used to simulate the esomeprazole exposure AUC for different body weights and ages in different esomeprazole doses.

## 4.3 ESOMEPRAZOLE DOSE SELECTION FOR DIFFERENT AGE GROUPS

### 4.3.1 NEONATAL PATIENTS, PREMATURE UP TO 1 MONTH CORRECTED AGE

Esomeprazole will be administered using a nasogastric or orogastric tube and an appropriate esomeprazole solution formulation will be prepared for this age group. Dose in mg/kg will be used for this age group. Doses around 0.5 mg/kg at an increase or a decrease in 0.25 mg/kg

were evaluated. Table 2 shows that 0.25-0.5 mg/kg dose is likely to show a reasonable chance of efficacy and an acceptable safety for body weight ranging from 1 to 6.5 kg. At the present time, there is limited safety data for doses of 0.5 mg/kg/day for the very young neonates (less than 5 days). However, as suggested by the results of other studies (AZ data on file,) and literature reports[13-17], there is progressive maturation of the hepatic metabolic enzymes over the first week of life irrespective of gestational age. Therefore, our proposed dose for neonatal studies dealing with pre-term and term neonates with obstructive apnea will be 0.5mg/kg/day during the open label phase. This study population is expected to require at least a 4 day period of investigation prior to enrollment, for other causes of apnea, which may include a full sepsis work up ,EKG, and other various tests indicated per standard medical practice. In addition, both Pneumographic and pH probes studies require an additional day prior to dosing. Therefore, we don't anticipate patients being dosed at an age younger than 5 days.

### 4.3.2 INFANTS 1 UP TO 11 MONTH OLDS

The dosage form for esomeprazole in this age group will be a capsule, which will be dispersed in an appropriate liquid vehicle or alternatively in apple sauce for administration**.** Doses will be manufactured in absolute doses rather than in mg/kg for this age group. Given that 1.5, 2.5, 5 and 10 mg are the doses feasible to manufacture, five doses, 1.5, 2.5, 3, 5 and 10 mg, are evaluated with different ages and possible weights. Table 3 shows that doses of 2.5, 3 and 5 mg can be applicable to this age group, while 1.5 mg may have potential insufficient efficacy for an infant weighing more than 7 kg and 10 mg may have potential safety concern for infants less than 5.5 kg. To maximize the potential of efficacy and minimize the risk, the following doses were selected for infants: 3-5 kg (1.5 and 3 mg capsule → maximal range 0.6- 1 mg/kg/day), 5-7.5 kg ( 2.5 and 5 mg capsule → maximal range 0.67-1 mg/kg/day), and 7.5 – 12 kg ( 5 and 10 mg capsule → maximal range 0.8-1.3 mg/kg/day), respectively.

### 4.3.3 CHILDREN 1 UP TO 11 YEAR OLDS

The dosage form for esomeprazole in this age group will be a capsule, but will be dispersed in applesauce for children unable to take the capsules. Doses of 5, 10 and 20 mg were evaluated for this age group. Table 4 shows that 10 mg dose is efficacious and safe for this age group for all different weights, while the 5 mg may yield insufficient exposure for children weighing more than 35 kg and 20 mg may have unnecessary exposure for the children less than 12 kg. To maximize the potential efficacy while assuring an acceptable safety, 5 and 10 mg were selected for children with body weight more than 8 kg but less than 12 kg, and 10 and 20 mg were used for children weighing more than 12 kg.

### 4.3.4 CHILDREN 12 UP TO 16 YEAR OLDS

There is no necessity to adjust the dose for 12-16 years adolescents judging from the descriptive analysis of the repeated omeprazole dose administration in Table 1.

The principle of establishing the esomeprazole doses for different pediatric groups in this analysis is based on the allometric covariate relationship between the drug disposition and body weight ($CL/F= (CL/F)_{std} \times (WT/70)^{0.75}$ and $V/F= (V/F)_{std} \times (WT/70)$). Allometric covariate model for scaling dose for pediatrics have been used in other therapeutics and has been scientifically documented[11,12,14,15].

All the dose selections are based on the assumption that an exposure (AUC) resulting in an efficacious and safe treatment in adults for esomeprazole can be equally applied to pediatric population. It has been pointed out that the efficacy in pediatric subjects may not be able to be extrapolated from PK/PD data alone[16]. The assumption of a similar safety profile between adults and pediatric subjects also needs to be confirmed. In addition, potential difference in bioavailability among the formulations used in adults and pediatric subjects may result in biased dose determinations for pediatric subjects. Consequently, all those suggested esomeprazole doses above for pediatric studies might be subject to further revision when more

clinical experience for the use of esomeprazole and other proton pump inhibitors in adults and pediatrics becomes available.

## 5. CONCLUSIONS:

From pharmacokinetic and pharmacodynamic point of view, the following doses are proposed for esomeprazole pediatric studies.

- For neonates and premature babies up to 1 month corrected age: 0.25 - 0.5 mg/kg
- For infants of 1-11 months old
  - 3-5 kg: 1.5 or 3 mg (0.6- 1 mg/kg/day)
  - 5 - 7.5 kg: 2.5 or 5mg (0.67-1 mg/kg/day)
  - 7.5 –12 kg: 5 or 10 mg (0.8-1.3 mg/kg/day)
- For children 1 to 11 years old
  - 8-12 kg: 5 or 10 mg
  - >12 kg: 10 or 20 mg
- There is no necessity for dose adjustment for 12-16 years old adolescents, so the adult doses of 20 and 40 mg will be used.

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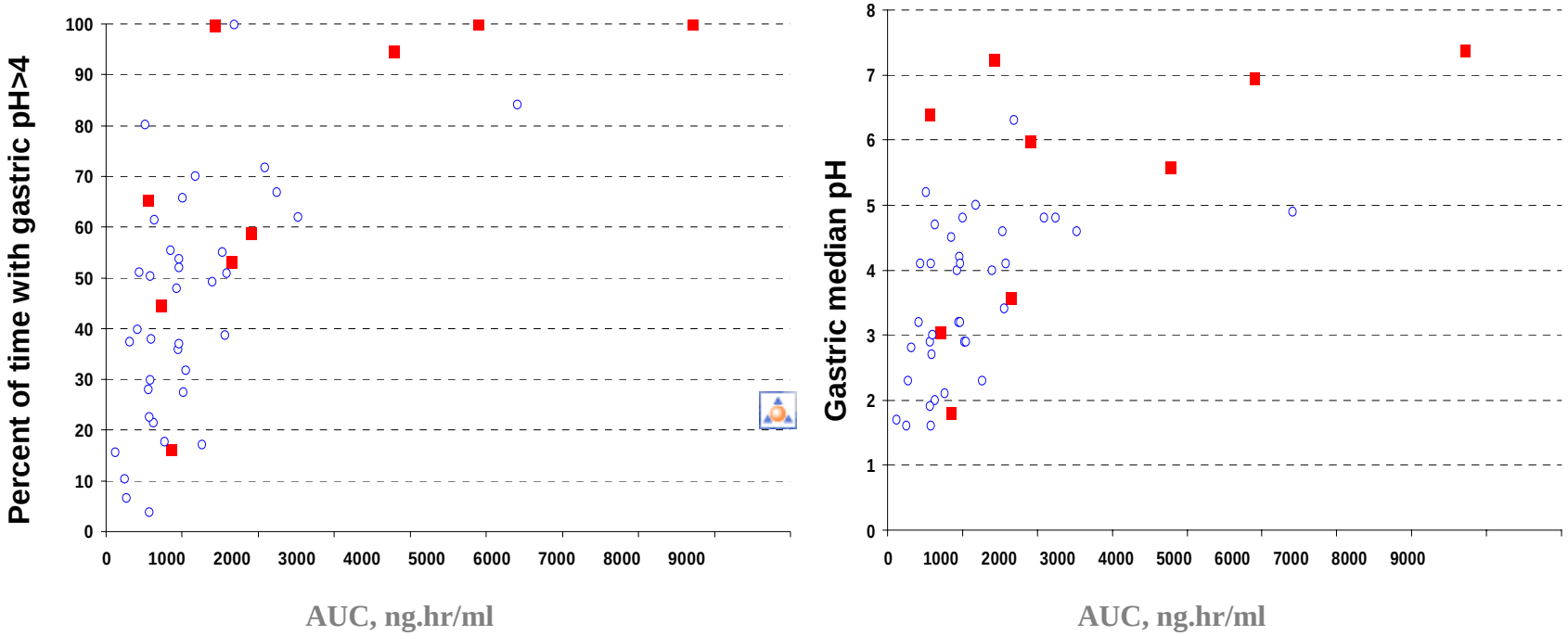


**Figure 1. Difference of exposure (AUC) and PD endpoint (percent of time with gastric pH>4, Gastric median Ph) between adults and children with age ranging from 4.5 to 27 months. Square: Children, Circle:Adults**

Table 1 Description of Data Sets Used in the Analysis

| Data set | Description | Studies | | No. of Subjects | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 0-3 Months | 3-12 months | 1-11 years | 12-16 years | Adults | All |
| 1 | PK/PD studies in repeated iv infusion of Prilosec. PD endpoints: Percent of time with gastric pH>4, Gastric median pH | SH-QBE-0061, Faure, C. et al[4] | N | -- | 3 | 6 | -- | 16 | 25 |
| | | | Dose | 0.4-1.3 mg/kg iv infusion in 60 minutes | | | | 40 mg iv infusion in 30 minutes | -- |
| 2 | PK studies in repeated iv infusion of Prilosec | SH-QBE-0061; Andersson T. et al[3], Faure, C. et al[4] | Geomean clearance (L/hr) | 0.4 | 3.2 | 4.8 | -- | 9.7 | -- |
| | | | N | 3* | 5 | 8 | -- | 16 | 32 |
| | | | Dose | 0.4-1.3 mg/kg iv infusion in 30 or 60 minutes | | | | 40 mg iv infusion in 30 minutes | -- |
| | | | Dose ratio relative to adults | 1/25 | 1/3 | 1/2 | -- | 1 | -- |
| 3 | PK studies in repeated oral dose administration of Prilosec | Prilosec 245, 250, 678 and SH-QBE-0008 | Geomean clearance (L/hr) | 1.3 | 1.2 | 16.6 | 21.6 | 24.6 | -- |
| | | | N | 3 (1)** | 1 | 37 (24) | 25(15) | 36 (36)*** | 102(67) |
| | | | Dose | 1 mg/kg | | 0.7/1.4 mg/kg, 10/20 m | | 20 mg | |
| | | | 0 | 1/18 | 1/20 | 2/3 | 1 | 1 | -- |
| 4 | PK studies in repeated oral dose administration of Nexium | SH-QBE-0008 | Geomean of clearance (L/hr) | -- | -- | -- | -- | 13.7 | -- |
| | | | N | -- | -- | -- | -- | 36 (35)*** | 36 (35) |
| | | | Dose | -- | -- | -- | -- | 20 mg | |

* 3 subjects were 10 days old

** Number in the parenthesis is the actual number for the calculation of the geometric mean clearance

*** Same adult subjects in study SH-QBE-0008

**Table 2 Estimated exposure ($AUC/AUC_{50}$) for 0-1 month neonates ( A value between 3 and 24 indicates a reasonable chance of efficacy and acceptable safety)**

| Study | Weight range | Pounds kg | Age: 5 days | | Age: 10 days | | Age: 15 days | | Age: 20 days | | Age: 25 days | | Age: 30 days | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2.2 | 14.3 | 2.2 | 14.3 | 2.2 | 14.3 | 2.2 | 14.3 | 2.2 | 14.3 | 2.2 | 14.3 |
| | | | 1 | 6.5 | 1 | 6.5 | 1 | 6.5 | 1 | 6.5 | 1 | 6.5 | 1 | 6.5 |
| D9614C00095 | 0.25 mg/kg | $AUC/AUC_{50}$ | 14 | 22 | 7 | 12 | 5 | 8 | 4 | 7 | 4 | 6 | 3 | 5 |
| | 0.50 mg/kg | | 27# | 43# | 15 | 23 | 10 | 17 | 8 | 13 | 7 | 11 | 6 | 10 |
| | 0.75 mg/kg | | 41# | 65# | 22 | 35# | 16 | 25# | 13 | 20 | 11 | 17 | 10 | 15 |
| | 1.0 mg/kg | | 24# | 87# | 29# | 47# | 21 | 33# | 17 | 27# | 14 | 23 | 13 | 20 |

*** Potential insufficient efficacy**
**# Potential safety concern**

**Table 3 Estimated exposure ($AUC/AUC_{50}$) for 1-11 month olds infants ( A value between 3 and 24 indicates a reasonable chance of efficacy and acceptable safety)**

| Age | Weight | | Dose (mg) | | | | |
|---|---|---|---|---|---|---|---|
| | Pounds | KG | 1.5 | 2.5 | 3 | 5 | 10 |
| 2 months | 6.6 | 3 | 6 | 10 | 12 | 20 | 39# |
| | 7.7 | 3.5 | 5 | 9 | 11 | 18 | 35# |
| | 8.8 | 4 | 5 | 8 | 10 | 16 | 32# |
| | 9.9 | 4.5 | 4 | 7 | 9 | 15 | 29# |
| | 11 | 5 | 4 | 7 | 8 | 13 | 27# |
| | 12.1 | 5.5 | 4 | 6 | 8 | 13 | 25# |
| | 13.2 | 6 | 4 | 6 | 7 | 12 | 23 |
| | 14.3 | 6.5 | 3 | 6 | 7 | 11 | 22 |
| 3 months | 6.6 | 3 | 5 | 9 | 11 | 18 | 35# |
| | 7.7 | 3.5 | 5 | 8 | 9 | 16 | 31# |
| | 8.8 | 4 | 4 | 7 | 9 | 14 | 28# |
| | 9.9 | 4.5 | 4 | 7 | 8 | 13 | 26# |
| | 11 | 5 | 4 | 6 | 7 | 12 | 24 |
| | 12.1 | 5.5 | 3 | 6 | 7 | 11 | 22 |
| | 13.2 | 6 | 3 | 5 | 6 | 10 | 21 |
| | 14.3 | 6.5 | 3 | 5 | 6 | 10 | 20 |
| | 15.4 | 7 | 3 | 5 | 6 | 9 | 19 |
| | 16.5 | 7.5 | 3 | 4 | 5 | 9 | 18 |
| 4-11 months | 6.6 | 3 | 5 | 8 | 10 | 17 | 33# |
| | 7.7 | 3.5 | 4 | 7 | 9 | 15 | 29# |
| | 8.8 | 4 | 4 | 7 | 8 | 13 | 27# |
| | 9.9 | 4.5 | 4 | 6 | 7 | 12 | 24 |
| | 11.0 | 5 | 3 | 6 | 7 | 11 | 23 |
| | 12.1 | 5.5 | 3 | 5 | 6 | 10 | 21 |
| | 13.2 | 6 | 3 | 5 | 6 | 10 | 20 |
| | 14.3 | 6.5 | 3 | 5 | 6 | 9 | 18 |
| | 15.4 | 7 | 3 | 4 | 5 | 9 | 17 |
| | 16.5 | 7.5 | 2* | 4 | 5 | 8 | 17 |
| | 17.6 | 8 | 2* | 4 | 5 | 8 | 16 |
| | 18.7 | 8.5 | 2* | 4 | 5 | 8 | 15 |
| | 19.8 | 9 | 2* | 4 | 4 | 7 | 14 |
| | 20.9 | 9.5 | 2* | 3 | 4 | 7 | 14 |
| | 22.0 | 10 | 2* | 3 | 4 | 7 | 13 |
| | 23.1 | 10.5 | 2* | 3 | 4 | 6 | 13 |
| | 24.2 | 11 | 2* | 3 | 4 | 6 | 12 |
| | 25.3 | 11.5 | 2* | 3 | 4 | 6 | 12 |
| | 26.4 | 12 | 2* | 3 | 4 | 6 | 12 |

*** Potential insufficient efficacy**
**# Potential safety concern**

**Table 4 Estimated exposure (AUC/AUC50) for 1-11 year olds children ( A value between 3 and 24 indicates a reasonable chance of efficacy and acceptable safety)**

| Weight | | Dose (mg) | | |
|---|---|---|---|---|
| Pounds | KG | 5 | 10 | 20 |
| 18 | 8 | 8 | 16 | 32# |
| 20 | 9 | 7 | 14 | 29# |
| 22 | 10 | 7 | 13 | 27# |
| 24 | 11 | 6 | 12 | 25# |
| 26 | 12 | 6 | 12 | 23 |
| 29 | 13 | 5 | 11 | 22 |
| 31 | 14 | 5 | 10 | 21 |
| 33 | 15 | 5 | 10 | 20 |
| 44 | 20 | 4 | 8 | 16 |
| 55 | 25 | 3 | 7 | 13 |
| 66 | 30 | 3 | 6 | 12 |
| 77 | 35 | 3 | 5 | 10 |
| 88 | 40 | 2* | 5 | 9 |
| 99 | 45 | 2* | 4 | 9 |
| 110 | 50 | 2* | 4 | 8 |
| 121 | 55 | 2* | 4 | 7 |
| 132 | 60 | 2* | 3 | 7 |

*** Potential insufficient efficacy**
**# Potential safety concern**