AstraZeneca

**Clinical Study Report Synopsis**

| | |
|---|---|
| Drug Substance | Esomeprazole sodium |
| Study Code | D9615C00021 |
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# A Phase I, Randomised, Open-Label, Multi-National Study to Evaluate the Pharmacokinetics of Repeated Once-Daily Intravenous Doses of Esomeprazole in Paediatric Patients 0 to 17 Years Old, Inclusive

**Study dates:** First subject enrolled: 13 October 2007
Last subject last visit: 20 October 2009

**Phase of development:** Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

## Study centers

The study was conducted at 10 centers: 7 centers in the United States (30 patients) and 1 center each in Australia (15 patients), Hungary (10 patients), and Sweden (7 patients). A total of 17 centers were initiated; 17 centers received study drug and 10 centers admitted patients.

## Publications

None at the time of writing this report.

## Objectives and criteria for evaluation

**Table S1 Primary and secondary objectives and outcome variables**

| Objectives | Outcome variables |
|---|---|
| **Primary:** To evaluate the pharmacokinetics (PK) of repeated doses of esomeprazole given as a once daily (qd) injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive, by assessment of the total area under the plasma concentration versus time curve within a dosing interval (AUCτ) on Day 4 of the study based on population PK modeling. | **Primary:** AUCτ for esomeprazole on Day 4 of the study |
| **Secondary**: To evaluate the pharmacokinetics of repeated doses of esomeprazole given as a once daily injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive, by assessment of the maximum plasma concentration ($C_{ss,\ max}$), total plasma clearance (CL) and steady-state volume of distribution ($V_{ss}$) on Day 4 of the study based on population PK modeling. | **Secondary:** $C_{ss,\ max}$, CL, and $V_{ss}$ for esomeprazole on Day 4 of the study |
| **Secondary:** To evaluate the pharmacokinetics of the main metabolites of esomeprazole (sulphone metabolite and 5-hydroxy metabolite) after repeated doses of esomeprazole given as a once daily injection over 3 minutes in pediatric patients 0 to 17 years old, inclusive, by assessment of $C_{ss,\ max}$, AUCτ, clearance scaled by fraction metabolized (CL/fm) and steady-state volume of distribution scaled by fraction metabolized ($V_{ss}$/fm) on Day 4 of the study based on population PK modeling. | **Secondary:** $AUC_{\tau}$, $C_{ss,\ max}$, CL/fm and $V_{ss}$/fm on Day 4 of the study for the esomeprazole sulphone metabolite and esomeprazole 5-hydroxy metabolite |
| **Secondary:** To evaluate the safety of esomeprazole given as a once daily injection over 3 minutes for 4 days in pediatric patients 0 to17 years old, inclusive, by assessment of adverse events (AEs), laboratory values, blood pressure, heart rate, respiratory rate, body temperature, and electrocardiogram (ECG). | **Secondary:**<br>• Adverse events<br>• Clinical laboratory evaluation<br>• Vital signs<br>• ECG<br>• Physical examination |

## Study design

This study was a randomized, open-label, multi-national study to evaluate the PK of repeated intravenous doses of once daily esomeprazole in pediatric patients 0 to 17 years old, inclusive (hereafter referred to as 0 to 17 years old).

## Target subject population and sample size

There were 2 amendments to the clinical study protocol (CSP) that affected the study population. In the original CSP, the study population included any hospitalized patient, 0 to 17 years of age, who might benefit from acid suppression therapy. In response to comments made to the Study Design Concept by the FDA, prior to patient recruitment, Amendment 1 more specifically defined the patient population to include only pediatric patients who had a presumptive diagnosis of GERD, which included patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Using this criterion, there was a high rate of screening failure among pre-screened patients and it was determined that this requirement was restrictive to study enrollment. Over a period of 99 weeks (from 30 November 2006 to 22 October 2008), 3151 patients were pre-screened; but only 30 patients were enrolled and 29 were randomized. A total of 652 patients did not meet the GERD criteria (inclusion criterion #4) during this time period. Therefore, Amendment 3 broadened the study population to include pediatric patients who might benefit from intravenous acid suppression therapy, including patients who had a presumptive diagnosis of GERD, which included patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD, since including these additional patients would be anticipated to have no effect on the pharmacokinetics of intravenous esomeprazole.

A "hospitalized patient" was defined as a patient who was anticipated to be in the hospital for at least 4 days. A patient in the age group 0 up to 1 month was defined as a patient with a corrected age of ≥32 complete weeks and < 44 complete weeks where corrected age was the sum of the gestational age and the age after birth in complete weeks. A patient in the age group 1 to 11 months must have had a corrected age of ≥44 complete weeks.

The sample size was not based on statistical considerations, but on the minimum number of patients (aged 0 to 17 years) needed for the PK evaluation in this study, when using population modeling (including characterization of the inter-individual variability and relevant covariate relationships in the pediatric population).

It was estimated that a minimum of 42 patients evaluable for PK analysis were required. This assumed at least 6 patients with evaluable PK (as determined by the pharmacokineticist) in each of the specified treatment groups.

To allow for potential discontinuations prior to PK sampling being performed on Day 4 of dosing or patients with unevaluable PK (as determined by the pharmacokineticist) a maximum of 6 additional patients (12 patients in total per group) could be enrolled into each of the 7 dose groups.

**Investigational product: dosage, mode of administration and batch numbers**

The details of the investigational product are given in Table S2. Vials containing 0.9% NaCl (9 mg/mL) solution for dilution were provided to each investigational site along with instructions for reconstituting the esomeprazole powder to solutions of 8 mg/mL, 2 mg/mL, and 0.2 mg/mL. These solutions were to be used to administer esomeprazole at the doses described in Table S3.

**Table S2 Details of investigational product**

| Investigational product | Dosage strength | Manufacturer | Formulation number |
|---|---|---|---|
| Nexium® IV (esomeprazole sodium) for injection/infusion | 40 mg | AstraZeneca AB, Sweden | H 1516-03-04 |

**Table S3 Investigational product, dosage, and mode of administration**

| Age | Number of evaluable patients needed for PK[a,b] | Dose of esomeprazole IV qd |
|---|---|---|
| 12 to 17 years | 6 | 20 mg |
| | 6 | 40 mg |
| 6 to 11 years | 6 | 10 mg |
| | 6 | 20 mg |
| 1 to 5 years | 6 | 10 mg |
| 1 to 11 months | 6 | 1.0 mg/kg |
| 0 up to 1 month | 6 | 0.5 mg/kg |

[a] An evaluable patient was defined as a patient from whom the pharmacokinetic samples were successfully collected, chemically analyzed, and judged reliable by the pharmacokineticist.

[b] A maximum of 12 patients was randomized to ensure at least 6 patients were evaluable for PK.

PK pharmacokinetics; IV intravenous; qd once daily

**Duration of treatment**

All doses were to be administered once daily for 4 days, between 8:00 AM and 10:00 AM local time to ensure a dosing interval of approximately 24 hours. An infusion pump for the 3-minute injection was necessary to ensure consistent administration across sites for pharmacokinetic data of good quality.

**Criteria for evaluation – Pharmacokinetics (main variables)**

The pharmacokinetic analyses were performed at Uppsala University Department of Pharmacokinetics and Drug Therapy, Institution for Pharmaceutical Biosciences

Box 591S-751 24, Uppsala, Sweden using actual, rather than protocol scheduled, sampling times.

Population modeling was employed for the PK evaluation, using the software NONMEM, with the following variables being estimated:

- $AUC_{\tau}$ for esomeprazole on Day 4 of the study (primary)
- $C_{ss,\ max}$ , CL, and $V_{ss}$ for esomeprazole on Day 4 of the study
- $AUC_{\tau}$, $C_{ss,\ max}$, CL/fm, and $V_{ss}$/fm on Day 4 of the study for the esomeprazole sulphone metabolite and esomeprazole 5-hydroxy metabolite

Mean estimates of structural PK parameters (clearance [CL, for the metabolites: CL/fm] and volume of distribution [$V_{ss}$, for the metabolites: $V_{ss}$/fm]) and between-individual variance were determined.

Empirical Bayes' estimates of the individual PK parameters were generated based on the final structural and variance parameter estimates and the individual plasma concentration measurements, using NONMEM. The PK variable area under the plasma concentration versus time curve within a dosing interval ($AUC_{\tau}$), was derived from the individual PK parameters. In addition the maximum concentration at steady state ($C_{ss,\ max}$ ) and elimination half-life ($t_{1/2}$) could be derived, provided that data were sufficient.

**Criteria for evaluation - Safety (main variables)**

The safety variables included adverse events (AEs), clinical laboratory evaluations, vital signs, EGC, and physical examinations.

**Statistical methods**

The individual PK variables were listed for each patient and also summarized descriptively. In addition, on log transformed values, the means were calculated together with symmetric 95% confidence intervals, based on Student's t distribution. The geometric means were determined by applying the antilogarithm transformation to the obtained confidence intervals. No formal statistical hypothesis testing of the PK data was performed.

The plasma concentrations of esomeprazole, the sulphone metabolite, and the 5-hydroxy metabolite were presented in individual graphs. The lower limit of quantification (LLOQ) was 20 nmol/L and values below the LLOQ were set to LLOQ/2.

All patients who received at least 1 dose of study medication were included in the safety analysis population. Safety analyses consisted of descriptive statistics only. No formal statistical analyses were planned or performed.

## Subject population

The disposition of randomized patients in the study is shown in Table S4. Demographic and baseline characteristics for all patients in the PK evaluable population are presented in Table S5.

**Table S4 Disposition of all randomized patients**

| | Esomeprazole treatment group | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Randomized Not dosed N=2** | **0 to 1 month[a] (0.5 mg/kg) N=6** | **1 to 11 months[b] (1 mg/kg) N=9** | **1 to 5 years (10 mg) N=8** | **6 to 11 years (10 mg) N=8** | **6 to 11 years (20 mg) N=9** | **12 to 17 years (20 mg) N=8** | **12 to 17 years (40 mg) N=9** | **Total N=59** |
| **Category** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| Patients randomized | 2 (100.0) | 6 (100.0) | 9 (100.0) | 8 (100.0) | 8 (100.0) | 9 (100.0) | 8 (100.0) | 9 (100.0) | 59 (100.0) |
| Safety population[c] | 0 | 6 (100.0) | 9(100.0) | 8 (100.0) | 8 (100.0) | 9 (100.0) | 8 (100.0) | 9 (100.0) | 57 (96.6) |
| PK evaluable population[d] | 0 | 6 (100.0) | 7 (77.8) | 7 (87.5) | 8 (100.0) | 8 (88.9) | 6 (75.0) | 8 (88.9) | 50 (84.7) |
| Completed study | 0 | 6 (100.0) | 8 (88.9) | 7 (87.5) | 8 (100.0) | 7 (77.8) | 6 (75.0) | 8 (88.9) | 50 (84.7) |
| Discontinued | 2 (100.0) | 0 | 1 (11.1) | 1 (12.5) | 0 | 2 (22.2) | 2.(25.0) | 1 (11.1) | 9 (15.3) |
| AE | 0 | 0 | 0 | 1 (12.5) | 0 | 1 (11.1) | 0 | 0 | 2 (3.4) |
| Other | 2 (100.0) | 0 | 1 (11.1) | 0 | 0 | 1 (11.1) | 2 (25.0) | 1 (11.1) | 7 (11.9) |

[a] A patient in the age group 0 to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks, where corrected age is the sum of the gestational age and the age after birth in complete weeks.

[b] A patient in the age group 1 to 11 months had ≥44 complete weeks (31 days to <12 months).

[c] The Safety population was defined as all patients who received at least 1 dose of investigational drug and for whom post-dose data were available.

[d] The PK evaluable population was defined as all patients from whom the PK samples were successfully collected, chemically analyzed, and judged reliable by the pharmacokineticist.

**Table S5 Demographic and baseline characteristics, PK evaluable population[a]**

| | | Esomeprazole treatment group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **0 to 1 month[b] (0.5 mg/kg) N=6** | **1 to 11 months[c] (1 mg/kg) N=7** | **1 to 5 years (10 mg) N=7** | **6 to 11 years (10 mg) N=8** | **6 to 11 years (20 mg) N=8** | **12 to 17 years (20 mg) N=6** | **12 to 17 years (40 mg) N=8** |
| **Category** | | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| Age[d] (days/months/years) | Mean (SD) | 9.0 (13.28) | 4.1 (2.04) | 2.6 (1.51) | 7.9 (1.73) | 8.6 (1.85) | 15.0 (1.67) | 15.5 (1.31) |
| | Median | 4.0 | 5.0 | 2.0 | 7.5 | 8.0 | 15.5 | 15.5 |
| | Range | 2 to 36 | 1 to 7 | 1 to 5 | 6 to 11 | 6 to 11 | 13 to 17 | 13 to 17 |
| Corrected age[e] (weeks) | Mean (SD) | 37.8 (3.31) | 56.7 (7.13) | NA | NA | NA | NA | NA |
| | Median | 38.5 | 56.0 | | | | | |
| | Range | 33 to 42 | 45 to 64 | | | | | |
| Sex, n (%) | Male | 4 (66.7) | 5 (71.4) | 5 (71.4) | 5 (62.5) | 5 (62.5) | 4 (66.7) | 2 (25.0) |
| | Female | 2 (33.3) | 2 (28.6) | 2 (28.6) | 3 (37.5) | 3 (37.5) | 2 (33.3) | 6 (75.0) |
| Race, n (%) | White | 4 (66.7) | 7 (100.0) | 5 (71.4) | 8 (100.0) | 6 (75.0) | 4 (66.7) | 7 (87.5) |
| | Black/African American | 1 (16.7) | 0 | 1 (14.3) | 0 | 0 | 1 (16.7) | 0 |
| | Asian | 1 (16.7) | 0 | 0 | 0 | 1 (12.5) | 1 (16.7) | 0 |
| | Other | 0 | 0 | 1 (14.3) | 0 | 1 (12.5) | 0 | 1 (12.5) |
| Length (cm)/ Height (cm) | Mean (SD) | 50.8 (3.76) | 60.7 (4.27) | 95.5 (14.9) | 133.6 (10.9) | 133.7 (13.6) | 164.2 (12.4) | 160.6 (6.9) |
| | Median | 49.5 | 60.0 | 98.0 | 129.5 | 130.8 | 166.5 | 159.0 |
| | Range | 46 to 56 | 56 to 68 | 74 to 117 | 121 to 150 | 115 to 161 | 141 to 175 | 152 to 174 |
| Weight (kg) | Mean (SD) | 3.0 (0.6) | 6.1 (1.1) | 15.3 (5.0) | 33.1 (9.8) | 34.4 (15.6) | 57.6 (12.1) | 52.2 (4.9) |
| | Median | 2.8 | 6.0 | 16.8 | 30.0 | 32.8 | 58.0 | 52.4 |
| | Range | 2 to 4 | 5 to 8 | 9 to 23 | 25 to 50 | 19 to 69 | 38 to 76 | 45 to 60 |
| Head circumference (cm) | Mean (SD) | 33.5 (2.3) | 40.3 (1.9) | NA | NA | NA | NA | NA |
| | Median | 33.5 | 39.5 | | | | | |
| | Range | 31 to 37 | 38 to 43 | | | | | |

**Table S5 Demographic and baseline characteristics, PK evaluable population[a]**

| | | Esomeprazole treatment group | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **0 to 1 month[b] (0.5 mg/kg) N=6** | **1 to 11 months[c] (1 mg/kg) N=7** | **1 to 5 years (10 mg) N=7** | **6 to 11 years (10 mg) N=8** | **6 to 11 years (20 mg) N=8** | **12 to 17 years (20 mg) N=6** | **12 to 17 years (40 mg) N=8** |
| **Category** | | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| BMI[f] ($kg/m^2$) | Mean (SD) | NA | NA | 16.8 (0.8) | 18.1 (3.6) | 18.9 (6.9) | 21.2 (2.1) | 20.1 (1.5) |
| | Median | | | 17.0 | 17.5 | 17.0 | 20.5 | 19.5 |
| | Range | | | 16 to 18 | 14 to 24 | 14 to 35 | 19 to 25 | 19 to 23 |

[a] The PK evaluable population was defined as all patients from whom the PK samples were successfully collected, chemically analyzed, and judged reliable by the pharmacokineticist.

[b] A patient in the age group 0 to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks, where corrected age is the sum of the gestational age and the age after birth in complete weeks.

[c] A patient in the age group 1 to 11 months had ≥44 complete weeks (31 days to <12 months).

[d] For 0 to 1 month, age in days; for 1 to 11 months, age in months; all other ages in years.

[e] Corrected age=(gestational age + age after birth) in weeks.

[f] BMI (body mass index)=weight (kg)/[height (meter) x height (meter)]; BMI calculated only for patients aged 2 or older.

NA not applicable

**Summary of pharmacokinetic results**

Pharmacokinetic data on esomeprazole and its 5-hydroxy and sulphone metabolites, from a total number of 50 patients, 6-8 per dose group, were included in the analysis. The pharmacokinetics of esomeprazole was best described by 2-compartment disposition of the parent compound with elimination routes through 3 pathways: via CYP3A4-mediated metabolism to esomeprazole sulphone metabolite, via CYP2C19-mediated metabolism to esomeprazole 5-hydroxy metabolite, and via CYP2C19-mediated metabolism to the 5 O-desmethyl metabolite (not determined and not analyzed).

The results of the population analysis indicate that the pharmacokinetics of esomeprazole is weight- and age-dependent. In addition to body weight and age, body surface area, serum albumin, presence of gastroesophageal reflux disease (GERD), dose group, and arterial sampling were evaluated as potential covariates. However, there was no indication that any of these covariates significantly influences the pharmacokinetics of esomeprazole. No inferences can be drawn with regards to drug-drug interactions due to the limited number of patients on potentially interacting concomitant medications.

The model was robust and described the data of esomeprazole and its 5-hydroxy and sulphone metabolites well.

The geometric mean $AUC_\tau$ for esomeprazole following repeated dose iv administration of esomeprazole 0.5 mg/kg in 0 to 1 month old (7.5 µmol*h/L) was somewhat lower than that observed with 1.0 mg/kg in 1 to 11 months old (10.5 µmol*h/L), but essentially similar to that observed with 10 mg in 1 to 5 years old (7.9 µmol*h/L), 10 mg in 6 to 11 years old (6.9 µmol*h/L), and 20 mg in 12 to 17 years old (8.1 µmol*h/L).

There was a proportional increase in $AUC_\tau$ when doubling the dose to 20 mg in 6 to 11 years old (14.4 µmol*h/L vs 6.9 µmol*h/L) and when doubling the dose to 40 mg in 12 to 17 years old (17.6 µmol*h/L vs 8.1 µmol*h/L).

The geometric mean observed $C_{ss,max}$ for esomeprazole was lower in the age group 0 to 1 month old (3.71 µmol/L) than in the other age and dose groups (range: 5.60 µmol/L to 10.5 µmol/L), a finding that may be a consequence of the somewhat larger geometric mean $V_{ss}$ observed in this age group (0.38 L/kg) compared to those in the other age and dose groups (range: 0.17 L/kg to 0.25 L/kg).

The geometric mean CL for esomeprazole was higher in the age groups 1 to 11 months old (0.26 L/h/kg) and 1 to 5 years old (0.24 L/h/kg) compared to that in 0 to 1 month old (0.17 L/h/kg) and those in 6 to 17 years old (range: 0.11 L/h/kg to 0.12 L/h/kg).

As expected, the geometric mean $AUC_\tau$ for the sulphone metabolite of esomeprazole was substantially higher (range: 2.6 µmol*h/L to 9.8 µmol*h/L) than that of the 5-hydroxy metabolite (range: 0.33 µmol*h/L to 1.01 µmol*h/L) across all age and dose groups.

The population pharmacokinetic parameters are presented in Table S6. The geometric means of the individual estimates of the esomeprazole pharmacokinetic variables, the 5-hydroxy

esomeprazole pharmacokinetic variables, and the sulphone metabolite pharmacokinetic variables are shown in Table S7, Table S8, and Table S9, respectively.

## Table S6 Estimated population pharmacokinetic parameters

| | | Basic model | | Final model | | Nonparametric bootstrap (N=200) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Parameter** [a] | **Estimate** [b] | **IIV** [c] **%** | **Estimate** | **IIV%** | **Median** | **%RSE** [d] | **IIV%** | **%RSE** [d] |
| Typical population values | $CLeso_{,CYP3A4}$ (L/h/70kg$^{3/4}$) | 3.09 | 76 | 2.55 | 79 | 2.05 | 58.9 | 76 | 44.0 |
| | $CLeso_{,CYP2C19}$ (L/h/70kg$^{3/4}$) | 4.53 | 59 | 5.1 | 57 | 5.03 | 24.6 | 67 | 27.7 |
| | CL/fm5-hyd (L/h/70kg$^{3/4}$) | 36.9 | 53 | 32.9 | 45 | 27.80 | 25.2 | 73 | 27.8 |
| | CL/fmsul (L/h/70kg$^{3/4}$) | 3.14 | 59 | 3.53 | 59 | 3.44 | 49.9 | 50 | 36.0 |
| | Vc (L/70kg) | 2.65 | 60 | 2.65 | 61 | 2.64 | 19.0 | 60 | 44.5 |
| | Q (L/h/70kg$^{3/4}$) | 27.2 | 52 | 27.3 | 52 | 26.70 | 12.9 | 52 | 52.5 |
| | Vp (L/70kg) | 12.8 | 36 | 12.8 | 36 | 12.45 | 5.6 | 38 | 27.1 |
| | $Vss/fm_{,5\text{-}hyd}$ (L/70kg) | 30.4 | 53 | 25.2 | 56 [e] | 21.80 | 46.9 | 62 [e] | 26.6 |
| | $Vss/fm_{,sul}$ (L/70kg) | 20 | 61 | 22.5 | 56 [e] | 22.40 | 25.5 | 62 [e] | 26.6 |
| | Maturation half-life $CL/fm_{5\text{-}hyd}$ (w) | NA | NA | 41.6 | NE | 41.30 | 3.7 | NE | NA |
| | Slope of maturation function | NA | NA | 18.9 | NE | 16.95 | 37.6 | NE | NA |
| Residual variability | $Eso_{prop}$ | 0.19 | 12 | 0.19 | 13 | 0.20 | 18.1 | 15 | 81.0 |
| | $Eso_{add}$ (µmol/L) | 0.01 | NE | 0.01 | NE | 0.01 | 33.3 | NE | NA |
| | $Sul_{prop}$ | 0.11 | NE | 0.11 | NE | 0.12 | 12.9 | NE | NA |
| | $Sul_{add}$ (µmol/L) | 0.03 | NE | 0.03 | NE | 0.03 | 26.2 | NE | NA |
| | $5\text{-}hyd_{prop}$ | 0.08 | NE | 0.08 | NE | 0.07 | 28.6 | NE | NA |
| | $5\text{-}hyd_{add}$ (µmol/L) | 0.01 | NE | 0.01 | NE | 0.02 | 22.0 | NE | NA |

[a] $CLeso_{,CYP3A4,}$ esomeprazole clearance via CYP3A4, $CLeso_{,CYP2C19,}$ esomeprazole clearance via CYP2C19, CL/fm5-hyd, clearance of esomprazole 5-hydroxy metabolite confounded for the fraction metabolized, CL/fmsul, clearance of esomprazole sulphone metabolite confounded for the fraction metabolized, Vc, esomeprazole central volume of distribution, Q , esomeprazole intercompartmental clearance, Vp, esomeprazole peripheral volume of distribution $Vss/fm_{5\text{-}hyd}$, esomprazole 5-hydroxy metabolite volume of distribution, $Vss/fm_{sul}$, esomprazole sulphone metabolite volume of distribution, . $Eso_{prop,}$ esomeprazole proportional residual variability, $Eso_{add,}$ esomeprazole additive residual variability, $Sul_{prop}$, esomeprazole sulphone metabolite proportional residual variability, $Sul_{add}$, esomeprazole sulphone metabolite additive residual variability, $5\text{-}hyd_{prop}$, esomeprazole 5-hydroxy metabolite proportional residual variability, $5\text{-}hyd_{add}$, esomeprazole 5-hydroxy metabolite additive residual variability, $CL/fm_{5\text{-}hyd}$, maturation half-life of esomeprazole 5-hydroxy metabolite clearance

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

[c] IIV, inter-individual variability, given in %; NE, not estimated.

[d] %RSE, relative standard error = (standard estimate of estimate/median estimate) * 100

[e] A single IIV term was estimated for $Vss/fm_{5\text{-}hyd}$ and $Vss/fm_{,sul}$

**Table S7** **Esomeprazole pharmacokinetic variables and exposure estimates at Day 4 across age groups, given as geometric means of individual bayesian estimates from the final population pharmacokinetic model (ranges within brackets)**

| Analyte | Age group | 0-1 month[a] | 1-11 months[b,c] | 1-5 years | 6-11 years[d] | | 12-17 years | |
|---|---|---|---|---|---|---|---|---|
| | Dose group | 0.5 mg/kg (n=6) | 1.0 mg/kg (n=6) | 10 mg (n=7) | 10 mg (n=8) | 20 mg (n=8) | 20 mg (n=6) | 40 mg (n=8) |
| **Patient characteristics** | Median age[e] (range) | 4 days (2-36) | 5.3 months (1.3-7.5) | 2.8 years (1.3-5.2) | 8.3 years (6.3-11.4) | 8.6 years (6.4-11.7) | 16.0 years (13.2-17.6) | 16.2 years (13.2-17.4) |
| | Mean dose (mg/kg) | 0.50 (0.49-0.51) | 1.00 (0.97-1.00) | 0.73 (0.43-1.18) | 0.32 (0.20- 0.42) | 0.67 (0.29-1.08) | 0.36 (0.26-0.53) | 0.77 (0.67-0.89) |
| | Median BW[f] (kg) | 2.8 (2.4-4.1) | 6.1 (5.1-8.0) | 16.8 (8.5-23.0) | 30.0 (24.8-49.7) | 32.8 (18.5-69.0) | 58.0 38.0-76.0) | 52.4 (45.0-60.0) |
| **Pharmacokinetic variables** [g] | $C_{ss,max}$ (µmol/L) | 3.71 (2.73-5.77) | 8.68 (4.51-14) | 9.37 (4.40-17.2) | 5.60 (3.13-13.2) | 8.83 (3.36-29.4) | 7.10 (4.76-9.02) | 10.5 (7.82-14.2)[h] |
| | $AUC_{\tau}$ (µmol*h/L) | 7.5 (4.5-20.5) | 10.5 (4.5-22.2) | 7.9 (2.9-16.6) | 6.9 (3.5-10.9) | 14.4 (7.2-42.3 ) | 8.1 (4.7-15.9 ) | 17.6 (13.1-19.8 ) |
| | CL (L/h) | 0.5 (0.1-1.0) | 1.7 (0.9-3.1 ) | 3.4 (1.6-9.5) | 3.8 (2.7-5.1) | 3.6 (1.1-8.0) | 7.0 (3.4-12.3) | 6.4 (5.5-8.7) |
| | CL (L/h/kg) | 0.17 (0.04-0.32) | 0.26 (0.12-0.58 ) | 0.24 (0.09-0.66) | 0.12 (0.08-0.17) | 0.11 (0.02-0.25) | 0.12 (0.09-0.21) | 0.12 (0.10-0.16) |
| | $V_{ss}$[i] (L) | 1.1 (0.8-2.2) | 1.6 (1.5-1.7) | 3.3 (2.4-4.6) | 6.7 (4.0-14.0) | 6.8 (4.9-10.7) | 9.5 (7.8-11.3) | 10.9 (8.0-15.9) |
| | $V_{ss}$[i] (L/kg) | 0.38 (0.28-0.53) | 0.25 (0.21-0.29) | 0.23 (0.17-0.29) | 0.21 (0.15-0.29) | 0.20 (0.13-0.32) | 0.17 (0.14-0.21) | 0.21 (0.16-0.29) |

[a] A patient in the age group 0 up to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks where corrected age is the sum of the gestational age and the age after birth in complete weeks.

[b] A patient in the age group 1 to 11 months had ≥44 complete weeks (31 days to <12 months).

[c] Estimates for the outlier, ID39 (E1008004), are excluded.

[d] Estimates for ID18 (E4001003) excluded in the calculations of geometric mean/ranges for all variables except $C_{ss,max}$, because only 1 post-dose sample was taken and individual bayesian estimates were therefore deemed uncertain.

[e] Postnatal age.

[f] BW body weight.

[g] $C_{ss,max}$, maximum observed plasma concentration at steady-state; $AUC_{\tau}$, area under the plasma concentration versus time curve during a dosage interval at Day 4; CL, total body clearance; $V_{ss}$ , steady-state volume of distribution.

[h] $C_{ss,max}$ value for ID 1 (E1011001) not included in the analysis, due to contamination of the first sample taken.

[i] $V_{ss}$ sum of individual estimates of central and peripheral volumes of distribution.

**Table S8** **Esomeprazole 5-hydroxy metabolite pharmacokinetic variables and exposure estimates at Day 4, across age groups, given as geometric means of individual bayesian estimates from the final population pharmacokinetic model (ranges within brackets)**

| Analyte | Age group | 0-1 month[a] | 1-11 months[b,c] | 1-5 years | 6-11 years[d] | | 12-17 years | |
|---|---|---|---|---|---|---|---|---|
| | Dose group | 0.5 mg/kg (n=6) | 1.0 mg/kg (n=6) | 10 mg (n=7) | 10 mg (n=8) | 20 mg (n=7) | 20 mg (n=6) | 40 mg (n=8) |
| **Patient characteristics** | Median age[e] (range) | 4 days (2-36) | 5.3 months (1.3-7.5) | 2.8 years (1.3-5.2) | 8.3 years (6.3-11.4) | 8.6 years (6.4-11.7) | 16.0 years (13.2-17.6) | 16.2 years (13.2-17.4) |
| | Mean dose (mg/kg) | 0.50 (0.49-0.51) | 1.00 (0.97-1.00) | 0.73 (0.43-1.18) | 0.32 (0.20- 0.42) | 0.67 (0.29-1.08) | 0.36 (0.26-0.53) | 0.77 (0.67-0.89) |
| | Median BW[f] (kg) | 2.8 (2.4-4.1) | 6.1 (5.1-8.0) | 16.8 (8.5-23.0) | 30.0 (24.8-49.7) | 32.8 (18.5-69.0) | 58.0 38.0-76.0) | 52.4 (45.0-60.0) |
| **Pharmacokinetic variables** [g] | $C_{ss,max,5\text{-}hyd}$ (µmol/L) | 0.11 (0.05-0.17) | 0.40 (0.28-0.57) | 0.30 (0.15-0.55) | 0.22 (0.13-0.34) | 0.28 (0.16-0.46) | 0.24 (0.14-0.34) | 0.38 (0.19-0.73) |
| | $AUC_{\tau,5\text{-}hyd}$ (µmol*h/L) | 0.46 (0.28-0.70) | 0.79 (0.30-2.46 ) | 0.47 (0.21-0.90 ) | 0.33 (0.14-0.65 ) | 0.78 (0.29-1.34 ) | 0.57 (0.32-1.71 ) | 1.01 (0.74-1.85 ) |
| | $CL/fm_{5\text{-}hyd}$ (L/h) | 1.1 (0.3-3.3 ) | 4.8 (2.1-11.4 ) | 13.7 (9.6-25.4 ) | 16.5 (13.1-25.9) | 16.8 (8.8-30.6 ) | 27.0 (10.6-52.6 ) | 26.7 (13.7-40.6 ) |
| | $CL/fm_{5\text{-}hyd}$ (L/h/kg) | 0.36 (0.10-0.80 ) | 0.77 ( 0.32-2.11) | 0.94 (0.54-1.78 ) | 0.52 (0.40-0.60 ) | 0.49 (0.18-0.97 ) | 0.48 (0.28-0.91 ) | 0.52 (0.31-0.84 ) |
| | $V_{ss}/fm_{5\text{-}hyd}$ (L) | 1.7 (0.5-3.6 ) | 3.7 (2.6-7.4 ) | 5.9 (4.0-10.8 ) | 7.1 (3.4-22.5 ) | 12.6 (7.8-28.1 ) | 16.3 (12.1-20.9) | 13.9 (11.0-20.0 ) |
| | $V_{ss}/fm_{5\text{-}hyd}$ (L/kg) | 0.56 (0.20-1.01 ) | 0.59 (0.36-1.37 ) | 0.41 (0.26-0.64 ) | 0.22 (0.07-0.45 ) | 0.36 (0.21-0.84 ) | 0.29 (0.22-0.46 ) | 0.27 (0.24-0.37 ) |

[a] A patient in the age group 0 up to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks where corrected age is the sum of the gestational age and the age after birth in complete weeks.

[b] A patient in the age group 1 to 11 months had ≥44 complete weeks (31 days to <12 months).

c Estimates for the outlier, ID39 (E1008004), are excluded.

d Estimates for ID18 (E4001003) excluded, due to that only 1 post-dose sample was taken and individual bayesian estimates were therefore deemed uncertain. The patient characteristics for ID18 is included in the patient characteristics description in this table.

e Postnatal age.

f BW, body weight.

g $C_{ss,max,5\text{-}hyd}$, maximum observed plasma concentration at steady-state for the 5-hydroxy metabolite; $AUC_{\tau,5\text{-}hyd}$, area under the plasma concentration versus time curve during a dosage interval at day 4 for the 5-hydroxy metabolite; $CL/fm_{,5\text{-}hyd}$,, clearance confounded by fraction metabolized for the 5-hydroxy metabolite, $V_{ss}/fm_{5\text{-}hyd}$ , steady-state volume of distribution confounded by fraction metabolized state for the 5-hydroxy metabolite.

**Table S9** **Esomeprazole sulphone metabolite pharmacokinetic variables and exposure estimates at steady-state, across age groups, given as geometric means of individual bayesian estimates from the final population pharmacokinetic model (ranges within brackets)**

| Analyte | Age group | 0-1 month[a] | 1-11 months[b,c] | 1-5 years | 6-11 years[d] | | 12-17 years | |
|---|---|---|---|---|---|---|---|---|
| | Dose group | 0.5 mg/kg (n=6) | 1.0 mg/kg (n=6) | 10 mg (n=7) | 10 mg (n=8) | 20 mg (n=7) | 20 mg (n=6) | 40 mg (n=8) |
| **Patient characteristics** | Median age[e] (range) | 4 days (2-36) | 5.3 months (1.3-7.5) | 2.8 years (1.3-5.2) | 8.3 years (6.3-11.4) | 8.6 years (6.4-11.7) | 16.0 years (13.2-17.6) | 16.2 years (13.2-17.4) |
| | Mean dose (mg/kg) | 0.50 (0.49-0.51) | 1.00 (0.97-1.00) | 0.73 (0.43-1.18) | 0.32 (0.20- 0.42) | 0.67 (0.29-1.08) | 0.36 (0.26-0.53) | 0.77 (0.67-0.89) |
| | Median BW[f] (kg) | 2.8 (2.4-4.1) | 6.1 (5.1-8.0) | 16.8 (8.5-23.0) | 30.0 (24.8-49.7) | 32.8 (18.5-69.0) | 58.0 38.0-76.0) | 52.4 (45.0-60.0) |
| **Pharmacokinetic variables[g]** | $C_{ss,max,sul}$ (µmol/L) | 1.12 ( 0.20-6.42) | 1.01 (0.25-1.89 ) | 0.87 (0.12-1.71 ) | 0.55 ( 0.18-1.02) | 0.85 ( 0.41-1.52) | 0.52 (0.27-0.96 ) | 1.74 (0.90-2.42 ) |
| | $AUC_{\tau, sul}$ (µmol*h/L) | 6.7 (1.2-41.0 ) | 5.3 (1.2-8.7 ) | 3.0 (0.2-9.6 ) | 2.6 (0.5-5.4 ) | 4.8 ( 2.4-8.2) | 2.7 (1.2-5.0 ) | 9.8 ( 4.9-13.5) |
| | $CL/fm_{sul}$ (L/h) | 0.15 (0.02-0.46 ) | 0.74 (0.39-1.68 ) | 1.57 (0.62-4.60 ) | 1.73 (1.14-2.48 ) | 1.60 (0.45-3.57 ) | 3.31 (1.68-6.23 ) | 2.70 ( 2.12-3.65) |
| | $CL/fm_{sul}$ (L/h/kg) | 0.05 (0.01-0.11 ) | 0.11 (0.05-0.31 ) | 0.11 (0.03-0.32 ) | 0.05 (0.03-0.08 ) | 0.05 (0.01-0.12 ) | 0.06 (0.04-0.11 ) | 0.05 (0.04-0.07 ) |
| | $V_{ss}/fm_{sul}$ (L) | 1.5 ( 0.5-3.2 ) | 3.3 ( 2.3-6.6 ) | 5.3 (3.6-9.7 ) | 6.3 ( 3.1-20.0) | 11.2 (6.9-25.1 ) | 14.5 (10.8-18.7 ) | 12.4 (9.8-17.9 ) |
| | $V_{ss}/fm_{sul}$ (L/kg) | 0.50 (0.17-0.90 ) | 0.53 (0.32-1.23 ) | 0.36 ( 0.23-0.58) | 0.20 (0.07-0.40 ) | 0.33 ( 0.19-0.75) | 0.26 (0.19-0.41 ) | 0.24 ( 0.21-0.33) |

[a] A patient in the age group 0 up to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks where corrected age is the sum of the gestational age and the age after birth in complete weeks.

[b] A patient in the age group 1 to 11 months had ≥44 complete weeks (31 days to <12 months).

[c] Estimates for the outlier, ID39 (E1008004), are excluded.

[d] Estimates for ID18 (E4001003) excluded, due to that only 1 post-dose sample was taken and individual bayesian estimates were therefore deemed uncertain. The patient characteristics for ID18 is included in the patient characteristics description in this table.

[e] Postnatal age.

[f] BW, body weight.

[g] $C_{ss,max,\ sul}$, maximum observed plasma concentration at steady-state for the sulphone metabolite; $AUC_{\tau,\ sul}$, area under the plasma concentration versus time curve during a dosage interval at steady state for the sulphone metabolite; $CL/fm_{sul}$,, clearance confounded by fraction metabolised for the sulphone metabolite, $V_{ss}/fm_{\ sul}$, steady-state volume of distribution confounded by fraction metabolised state for the sulphone metabolite.

**Summary of safety results**

A summary of AEs in each category is presented in Table S10. The most commonly reported adverse events are listed by preferred term in Table S11.

A total of 31 patients (54.4 %) experienced any AE during the study. No deaths occurred during the study. Post-study information revealed that 1 patient died 6-7 weeks after the end of treatment with investigational product. The cause of death was "ataxia telengiectasia with Burkitt's lymphoma," which was also included in the patient's current medical history at study start. The investigator considered that there was no causal relationship between the event and esomeprazole.

Events considered by the investigator to be treatment-related were recorded for 3 patients, all of whom were at the same site: 1 patient each in the 1 to 11 month (1 mg/kg), 1 to 5 year (10 mg), and 12 to 17 year (40 mg) groups.

SAEs were recorded for 6 patients: 2 patients in the 0 to 1 month (0.5 mg/kg) group, and 1 patient each in the 1 to 5 year (10 mg), 6 to 11 year (10 mg), 6 to 11 year (20 mg), and 12 to 17 year (40 mg) groups.

One patient each in the 1 to 5 year (10 mg) and 6 to 11 year (20 mg) groups experienced AEs leading to discontinuation of investigational product (DAEs). None of these AEs was assessed as treatment-related by the investigator.

Overall, the most frequently reported AEs were constipation (10.5%) and pyrexia (8.8%). Out of 11 patients with events included in the General disorders and administration site conditions SOC, 6 patients had events identified as administration site conditions. The events were catheter-related complications (2 patients), infusion site extravasation (2 patients), catheter site swelling (1 patient) and infusion site pain (1 patient).

In this study, 4 patients had pharmacokinetic data suggesting high exposure to esomeprazole. It is important to note that no safety signals were identified for any of these patients, ie, no treatment-related AEs or SAEs were reported and a higher frequency of AEs was not observed for these patients.

No clinically important trends over time in laboratory values, ECG, or vital signs were seen.

In this study, esomeprazole was well tolerated in pediatric patients. No fatal SAE occurred during the study. No clinically important trends over time in laboratory values, ECG, or vital signs were seen. The safety results are consistent with the natural history of health and disease-related events in a pediatric population that was predominantly from hospital intensive care units and with the known safety profile of esomeprazole.

**Table S10 Summary of adverse events by category (Safety population, all patients)**

| | 0 to 1 month[a] (0.5 mg/kg) N=6 | 1 to 11 months[b] (1 mg/kg) N=9 | 1 to 5 years (10 mg) N=8 | 6 to 11 years (10 mg) N=8 | 6 to 11 years (20 mg) N=9 | 12 to 17 years (20 mg) N=8 | 12 to 17 years (40 mg) N=9 | Total N=57 |
|---|---|---|---|---|---|---|---|---|
| **Category of AE** | **n (%) of patients who had an AE in each category[c]** | | | | | | | |
| Any AE | 2 (33.3) | 5 (55.6) | 7 (87.5) | 5 (62.5) | 2 (22.2) | 5 (62.5) | 5 (55.6) | 31 (54.4) |
| SAE leading to death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Any SAE[d] | 2 (33.3) | 0 | 1 (12.5) | 1 (12.5) | 1 (11.1) | 0 | 1 (11.1) | 6 (10.5) |
| Treatment-related AE | 0 | 1 (11.1) | 1 (12.5) | 0 | 0 | 0 | 1 (11.1) | 3 (5.3) |
| DAE | 0 | 0 | 1 (12.5) | 0 | 1 (11.1) | 0 | 0 | 2 (3.5) |
| | **Total number of AEs[e]** | | | | | | | |
| Any AE | 10 | 31 | 25 | 9 | 8 | 23 | 16 | 122 |
| SAE leading to death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Any SAE[d] | 2 | 0 | 1 | 1 | 1 | 0 | 3 | 8 |
| Treatment-related AE | 0 | 1 | 3 | 0 | 0 | 0 | 8 | 12 |
| DAE | 0 | 0 | 1 | 0 | 2 | 0 | 0 | 3 |

[a] A patient in the age group 0 to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks, where corrected age is the sum of the gestational age and the age after birth in complete weeks.

[b] A patient in the age group 1 to 11 months had ≥44 complete weeks (31 days to <12 months).

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

[d] Including SAEs with outcome of death.

[e] Events counted by preferred term, ie, for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

AE adverse event; SAE serious adverse event; DAE premature discontinuation of treatment with investigational product due to an adverse event

**Table S11 Number of patients with most commonly reported[a] adverse events, sorted by decreasing order of frequency[b] (Safety population, all patients)**

| | Esomeprazole treatment group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 to 1 month[c] (0.5 mg/kg) N=6 | 1 to 11 months[d] (1 mg/kg) N=9 | 1 to 5 years (10 mg) N=8 | 6 to 11 years (10 mg) N=8 | 6 to 11 years (20 mg) N=9 | 12 to 17 years (20 mg) N=8 | 12 to 17 years (40 mg) N=9 | Total N=59 |
| **MedDRA preferred term** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| Any AE | 2 (33.3) | 5 (55.6) | 7 (87.5) | 5 (62.5) | 2 (22.2) | 5 (62.5) | 5 (55.6) | 31 (54.4) |
| Constipation | 0 | 2 (22.2) | 2 (25.0) | 1 (12.5) | 0 | 0 | 1 (11.1) | 6 (10.5) |
| Pyrexia | 0 | 1 (11.1) | 1 (12.5) | 0 | 1 (11.1) | 2 (25.0) | 0 | 5 (8.8) |
| Arthralgia | 0 | 0 | 0 | 0 | 0 | 2 (25.0) | 1 (11.1) | 3 (5.3) |
| Erythema | 0 | 3 (33.3) | 0 | 0 | 0 | 0 | 0 | 3 (5.3) |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 2 (25.0) | 1 (1.11) | 3 (5.3) |
| Rash | 0 | 1 (11.1) | 1 (12.5) | 0 | 0 | 0 | 1 (11.1) | 3 (5.3) |
| Tachycardia | 1 (16.7) | 0 | 1 (12.5) | 0 | 0 | 1 (12.5) | 0 | 3 (5.3) |
| Abdominal distension | 0 | 2 (22.2) | 0 | 0 | 0 | 0 | 0 | 2 (3.5) |
| Abdominal pain | 0 | 0 | 2 (25.0) | 0 | 0 | 0 | 0 | 2 (3.5) |
| Agitation | 0 | 0 | 1 (12.5) | 0 | 0 | 1 (12.5) | 0 | 2 (3.5) |
| Anemia | 1 (16.7) | 0 | 0 | 0 | 0 | 1 (12.5) | 0 | 2 (3.5) |
| Catheter related complication | 0 | 1 (1.11) | 1 (12.5) | 0 | 0 | 0 | 0 | 2 (3.5) |
| Diarrhea | 0 | 0 | 1 (12.5) | 1 (12.5) | 0 | 0 | 0 | 2 (3.5) |
| Gastroesophageal reflux disease | 0 | 1 (11.1) | 0 | 0 | 0 | 1 (12.5) | 0 | 2 (3.5) |
| Hypokalemia | 1 (16.7) | 0 | 1 (12.5) | 0 | 0 | 0 | 0 | 2 (3.5) |
| Hyponatremia | 0 | 2 (22.2) | 0 | 0 | 0 | 0 | 0 | 2 (3.5) |
| Infusion site extravasation | 0 | 0 | 1 (12.5) | 0 | 0) | 1 (12.5) | 0 | 2 (3.5) |

**Table S11 Number of patients with most commonly reported[a] adverse events, sorted by decreasing order of frequency[b] (Safety population, all patients)**

| | Esomeprazole treatment group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 to 1 month[c] (0.5 mg/kg) N=6 | 1 to 11 months[d] (1 mg/kg) N=9 | 1 to 5 years (10 mg) N=8 | 6 to 11 years (10 mg) N=8 | 6 to 11 years (20 mg) N=9 | 12 to 17 years (20 mg) N=8 | 12 to 17 years (40 mg) N=9 | Total N=59 |
| **MedDRA preferred term** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| Nausea | 0 | 0 | 0 | 1 (12.5) | 1 (11.1) | 0 | 0 | 2 (3.5) |
| Pneumonia | 0 | 1 (1.11) | 0 | 0 | 1 (1.11) | 0 | 0 | 2 (3.5) |
| Vomiting | 0 | 0 | 1 (12.5) | 0 | 1 (11.1) | 0 | 0 | 2 (3.5) |

[a] This table includes only those events that occurred in at least 2 patients during the study.

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

[c] A patient in the age group 0 to 1 month is defined as a patient with a corrected age of ≥32 complete weeks and <44 complete weeks, where corrected age is the sum of the gestational age and the age after birth in complete weeks.

[d] A patient in the age group 1 to 11 months had ≥44 complete weeks (31 days to <12 months).

## Date of the report

23 February 2010