# Clinical trial results:
# Single and Multiple Dose Pharmacokinetics and Safety Study of Rabeprazole Sodium in 12 to 16 Year Old Subjects

## Summary

| | |
|---|---|
| EudraCT number | 2016-001878-15 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 08 June 2004 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 29 July 2016 |
| First version publication date | 29 July 2016 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | E3810-A001-119 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Eisai Medical Research Inc. |
| Sponsor organisation address | 100 Tice Boulevard, Woodcliff Lake, United States, 07677 |
| Public contact | Eisai Medical Information, Eisai Medical Research Inc., 1 8882742378, esi_medinfo@eisai.com |
| Scientific contact | Eisai Medical Information, Eisai Medical Research Inc., 1 8882742378, esi_medinfo@eisai.com |

Notes:

### Paediatric regulatory details

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMEA-000055-PIP01-07 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 08 June 2004 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 08 June 2004 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To characterize the PK profile of single and repeated doses of rabeprazole sodium in participants 12 to 16 years of age with a diagnosis of, or symptoms of, gastroesophageal reflux disease (GERD).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:
- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal
Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan’s GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 04 September 2003 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 24 |
| Worldwide total number of subjects | 24 |
| EEA total number of subjects | 0 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 24 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Twenty-four children 12 to 16 years of age who had a diagnosis of, or symptoms of, GERD were enrolled into the study. Twelve participants were randomized to the rabeprazole 10-mg group and 12 participants were randomized to the rabeprazole 20-mg group. All 24 participants completed the study; no early terminations or deaths were observed.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | 10 mg Rabeprazole sodium |

Arm description:

On Day 1, after an overnight fast and after completion of pre-dose evaluations (physical examinations, vital signs, electrocardiogram, and clinical laboratory testing), rabeprazole sodium was administered orally with water in the morning. Participants were allowed clear liquids 2 hours after study drug and lunch 4 hours after study drug. Subsequent study drug was administered in the morning on Days 2 to 4, and on Day 5 following an overnight fast. Alternatively, participants could continue taking a single daily dose of rabeprazole on Day 6, fast overnight and return to the site on Day 7 instead of Day 5 for the final dose of study drug and the second pharmacokinetic (PK) blood draw and laboratory testing. Participants returned to the site in a fasted state the morning of Day 6 (or Day 8) for the 24-hour post-dose PK blood draw and laboratory testing. Participants were discharged from the study after the final safety evaluation and study termination procedures were performed.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Rabeprazole sodium |
| Investigational medicinal product code | E3810 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rabeprazole sodium was administered to the participants in an ascending dose fashion, beginning with 10 mg. Administration of the 10 mg dose was completed and preliminary safety data was evaluated before administration of the 20 mg dose was initiated. Each participant participated for a total of up to 3 weeks, including the screening visit, which was scheduled within 2 weeks of study drug administration.

| | |
|---|---|
| **Arm title** | 20 mg Rabeprazole sodium |

Arm description:

On Day 1, after an overnight fast and after completion of pre-dose evaluations (physical examinations, vital signs, electrocardiogram, and clinical laboratory testing), rabeprazole sodium was administered orally with water in the morning. Participants were allowed clear liquids 2 hours after study drug and lunch 4 hours after study drug. Subsequent study drug was administered in the morning on Days 2 to 4, and on Day 5 following an overnight fast. Alternatively, participants could continue taking a single daily dose of rabeprazole on Day 6, fast overnight and return to the site on Day 7 instead of Day 5 for the final dose of study drug and the second pharmacokinetic (PK) blood draw and laboratory testing. Participants returned to the site in a fasted state the morning of Day 6 (or Day 8) for the 24-hour post-dose PK blood draw and laboratory testing. Participants were discharged from the study after the final safety evaluation and study termination procedures were performed.

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Rabeprazole sodium |
| Investigational medicinal product code | E3810 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rabeprazole sodium was administered to the participants in an ascending dose fashion, beginning with 10 mg. Administration of the 10 mg dose was completed and preliminary safety data was evaluated before administration of the 20 mg dose was initiated. Each participant participated for a total of up to 3 weeks, including the screening visit, which was scheduled within 2 weeks of study drug administration.

| **Number of subjects in period 1** | 10 mg Rabeprazole sodium | 20 mg Rabeprazole sodium |
|---|---|---|
| Started | 12 | 12 |
| Completed | 12 | 12 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | 10 mg Rabeprazole sodium |
| Reporting group description: | |
| On Day 1, after an overnight fast and after completion of pre-dose evaluations (physical examinations, vital signs, electrocardiogram, and clinical laboratory testing), rabeprazole sodium was administered orally with water in the morning. Participants were allowed clear liquids 2 hours after study drug and lunch 4 hours after study drug. Subsequent study drug was administered in the morning on Days 2 to 4, and on Day 5 following an overnight fast. Alternatively, participants could continue taking a single daily dose of rabeprazole on Day 6, fast overnight and return to the site on Day 7 instead of Day 5 for the final dose of study drug and the second pharmacokinetic (PK) blood draw and laboratory testing. Participants returned to the site in a fasted state the morning of Day 6 (or Day 8) for the 24-hour post-dose PK blood draw and laboratory testing. Participants were discharged from the study after the final safety evaluation and study termination procedures were performed. | |
| Reporting group title | 20 mg Rabeprazole sodium |
| Reporting group description: | |
| On Day 1, after an overnight fast and after completion of pre-dose evaluations (physical examinations, vital signs, electrocardiogram, and clinical laboratory testing), rabeprazole sodium was administered orally with water in the morning. Participants were allowed clear liquids 2 hours after study drug and lunch 4 hours after study drug. Subsequent study drug was administered in the morning on Days 2 to 4, and on Day 5 following an overnight fast. Alternatively, participants could continue taking a single daily dose of rabeprazole on Day 6, fast overnight and return to the site on Day 7 instead of Day 5 for the final dose of study drug and the second pharmacokinetic (PK) blood draw and laboratory testing. Participants returned to the site in a fasted state the morning of Day 6 (or Day 8) for the 24-hour post-dose PK blood draw and laboratory testing. Participants were discharged from the study after the final safety evaluation and study termination procedures were performed. | |

| Reporting group values | 10 mg Rabeprazole sodium | 20 mg Rabeprazole sodium | Total |
|---|---|---|---|
| Number of subjects | 12 | 12 | 24 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 0 |
| Newborns (0-27 days) | | | 0 |
| Infants and toddlers (28 days-23 months) | | | 0 |
| Children (2-11 years) | | | 0 |
| Adolescents (12-17 years) | | | 0 |
| Adults (18-64 years) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 13.9 | 14.5 | |
| full range (min-max) | 12 to 16 | 12 to 16 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 8 | 5 | 13 |
| Male | 4 | 7 | 11 |

## Primary: Mean Area Under the Plasma Concentration-Time Curve from zero to Time t (AUC (0-t))

| End point title | Mean Area Under the Plasma Concentration-Time Curve from zero to Time t (AUC (0-t))[1] |
|---|---|

End point description:

Blood samples were obtained pre-dose and post-dose, at specified time points. Rabeprazole plasma concentration and its metabolite, rabeprazole thioether (PTBI), was measured by a validated liquid chromatography/tandem mass spectrometry system (LC/MS/MS). The pharmacokinetic (PK) parameter, AUC was calculated by the linear/log trapezoidal rule and analyzed using non-compartmental methods.

| End point type | Primary |
|---|---|

End point timeframe:

Day 1 (pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours post-dose); Days 2, 3 & 4 (pre-dose); Day 5 (or 7) (time points same as for Day 1); Day 6 (or 8) post-dose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

| **End point values** | E3810 (10 mg Group) | PTBI (10 mg Group) | E3810 (20 mg Group) | PTBI (20 mg Group) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: ng*hr/mL | | | | |
| geometric mean (standard error) | | | | |
| Day 1 (n = 8, 8, 11, 8) | 305 (± 37.91) | 228.9 (± 42.84) | 557.8 (± 109.8) | 823.4 (± 205.2) |
| Day 5 or 7 (n = 9, 10, 9, 9) | 249.8 (± 31.74) | 184.6 (± 40.1) | 828.4 (± 176.1) | 727.1 (± 231.4) |

### Statistical analyses

No statistical analyses for this end point

## Primary: Mean Maximum Drug Plasma Concentration (Cmax)

| End point title | Mean Maximum Drug Plasma Concentration (Cmax)[2] |
|---|---|

End point description:

Cmax was obtained directly from the data with and without interpolation.

| End point type | Primary |
|---|---|

End point timeframe:

Day 1 (pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours post-dose); Days 2, 3 & 4 (pre-dose); Day 5 (or 7) (time points same as for Day 1); Day 6 (or 8) post-dose

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

| **End point values** | E3810 (10 mg Group) | PTBI (10 mg Group) | E3810 (20 mg Group) | PTBI (20 mg Group) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: ng/mL | | | | |
| geometric mean (standard error) | | | | |

| | | | | |
|---|---|---|---|---|
| Day 1 (n = 12, 12, 12, 12) | 186.6 (± 25.46) | 39.12 (± 5.767) | 319 (± 48.38) | 108.8 (± 19.48) |
| Day 5 or 7 (n = 11, 11, 12, 12) | 184.1 (± 26.58) | 31.37 (± 3.627) | 460.4 (± 85.82) | 120.3 (± 19.96) |

### Statistical analyses

No statistical analyses for this end point

### Primary: Mean Time to Peak Concentration (Tmax)

| | |
|---|---|
| End point title | Mean Time to Peak Concentration (Tmax)[3] |

End point description:

T max was obtained directly from the data with and without interpolation.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Day 1 (pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours post-dose); Days 2, 3 & 4 (pre-dose); Day 5 (or 7) (time points same as for Day 1); Day 6 (or 8) post-dose

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

| **End point values** | E3810 (10 mg Group) | PTBI (10 mg Group) | E3810 (20 mg Group) | PTBI (20 mg Group) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: Hours | | | | |
| geometric mean (standard error) | | | | |
| Day 1 (n = 12, 12, 12, 12) | 3.333 (± 0.322) | 4.625 (± 0.37) | 3.958 (± 0.199) | 5.5 (± 0.275) |
| Day 5 or 7 (n = 11, 11, 12, 12) | 3.409 (± 0.517) | 4.273 (± 0.464) | 4.125 (± 0.449) | 5.75 (± 0.656) |

### Statistical analyses

No statistical analyses for this end point

### Primary: Mean Apparent Elimination Half-life (t1/2)

| | |
|---|---|
| End point title | Mean Apparent Elimination Half-life (t1/2)[4] |

End point description:

The elimination half-life is the time it takes for the concentration of study drug to drop to 50% of its value in plasma. The apparent elimination half-life (t1/2) during the terminal disposition phase was defined as 0.693λz.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Day 1 (pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours post-dose); Days 2, 3 & 4 (pre-dose); Day 5 (or 7) (time points same as for Day 1); Day 6 (or 8) post-dose

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

| **End point values** | E3810 (10 mg Group) | PTBI (10 mg Group) | E3810 (20 mg Group) | PTBI (20 mg Group) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: Hour | | | | |
| geometric mean (standard error) | | | | |
| Day 1 (n = 8, 8, 11, 8) | 0.545 (± 0.042) | 2.151 (± 0.192) | 1.01 (± 0.247) | 4.5 (± 0.683) |
| Day 5 or 7 (n = 9, 10, 9, 9) | 0.56 (± 0.059) | 2.49 (± 0.355) | 0.99 (± 0.166) | 3.06 (± 0.491) |

## Statistical analyses

No statistical analyses for this end point

## Primary: Mean Apparent Oral Clearance by Weight (CL/F/Wt)

| End point title | Mean Apparent Oral Clearance by Weight (CL/F/Wt)[5] |
|---|---|

End point description:

Blood samples were obtained pre-dose and at specified time points. CL/F was calculated based on the last day of multiple dosing. On Day 1 E3810 and PTBI was not calculated as n = 0, therefore zero was added as a placeholder.

| End point type | Primary |
|---|---|

End point timeframe:

Day 1 (pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours post-dose); Days 2, 3 & 4 (pre-dose); Day 5 (or 7) (time points same as for Day 1); Day 6 (or 8) post-dose

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

| **End point values** | E3810 (10 mg Group) | PTBI (10 mg Group) | E3810 (20 mg Group) | PTBI (20 mg Group) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: mL/minute/kg | | | | |
| geometric mean (standard error) | | | | |
| Day 1 (n = 0, 0, 0, 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) |
| Day 5 or 7 (n = 9, 10, 9, 9) | 12.58 (± 1.826) | 21.04 (± 3.938) | 10.14 (± 2.302) | 14.41 (± 4.372) |

## Statistical analyses

No statistical analyses for this end point

## Primary: Mean Volume of Distribution for Extravascular Administration (Vz/F)

| End point title | Mean Volume of Distribution for Extravascular Administration |
|---|---|

| | |
|---|---|
| | (Vz/F)[6] |

End point description:

Vz/F was calculated based on the last day of multiple dosing. On Day 1, E3810 and PTBI was not calculated as n = 0, therefore zero was added as a placeholder.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Day 1 (pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours post-dose); Days 2, 3 & 4 (pre-dose); Day 5 (or 7) (time points same as for Day 1); Day 6 (or 8) post-dose

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

| **End point values** | E3810 (10 mg Group) | PTBI (10 mg Group) | E3810 (20 mg Group) | PTBI (20 mg Group) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 12 | 12 | 12 | 12 |
| Units: mL | | | | |
| geometric mean (standard error) | | | | |
| Day 1 (n = 0, 0, 0, 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) |
| Day 5 or 7 (n = 9, 10, 9, 9) | 33907 (± 3357) | 230000 (± 24309) | 39600 (± 5994) | 169000 (± 27317) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs)

| | |
|---|---|
| End point title | Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs) |

End point description:

Safety variables assessed included: occurrence of AEs, SAEs, and Treatment-Emergent Signs and Symptoms (TESS), and changes in physical examination findings, clinical laboratory test results, vital signs, and electrocardiogram (ECG) evaluations. AEs were tabulated as TESS for this study. The incidence of TESS were summarized by body system, and by severity and relationship to study drug. A participant having the same TESS more than once over the course of the study was counted only once in the incidence calculation for that TESS. Also, if a participant had more than one TESS in a single body system, the participants was counted only once in the total number of participants with TESS for that body system. If a participant had a TESS more than once in the study, the occurrence with the maximum severity was used in the calculation of the incidence of individual TESS by severity. For drug relationship, the TESS considered most closely related to study drug was used.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Screening Visit, Days 1 through 6 (or Day 8, as appropriate)

| **End point values** | 10 mg Rabeprazole sodium | 20 mg Rabeprazole sodium | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Total TESS | 6 | 5 | | |
| Total Treatment Related TESS | 3 | 2 | | |
| Total SAEs | 0 | 0 | | |
| Withdrawn due to AEs | 0 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for approximately 9 months.

Adverse event reporting additional description:

Safety variables assessed during this study consisted of the following: occurrence of AEs, serious AEs, and Treatment-emergent Signs an Symptoms (TESS), and changes in physical examination findings, clinical laboratory test results, vital signs and electrocardiogram (ECG) evaluations.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 6.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | 20 mg Rabeprazole sodium |

Reporting group description:

On Day 1, after an overnight fast and after completion of pre-dose evaluations (physical examinations, vital signs, electrocardiogram, and clinical laboratory testing), rabeprazole sodium was administered orally with water in the morning. Participants were allowed clear liquids 2 hours after study drug and lunch 4 hours after study drug. Subsequent study drug was administered in the morning on Days 2 to 4, and on Day 5 following an overnight fast. Alternatively, participants could continue taking a single daily dose of rabeprazole on Day 6, fast overnight and return to the site on Day 7 instead of Day 5 for the final dose of study drug and the second pharmacokinetic (PK) blood draw and laboratory testing. Participants returned to the site in a fasted state the morning of Day 6 (or Day 8) for the 24-hour post-dose PK blood draw and laboratory testing. Participants were discharged from the study after the final safety evaluation and study termination procedures were performed.

| | |
|---|---|
| Reporting group title | 10 mg Rabeprazole sodium |

Reporting group description:

On Day 1, after an overnight fast and after completion of pre-dose evaluations (physical examinations, vital signs, electrocardiogram, and clinical laboratory testing), rabeprazole sodium was administered orally with water in the morning. Participants were allowed clear liquids 2 hours after study drug and lunch 4 hours after study drug. Subsequent study drug was administered in the morning on Days 2 to 4, and on Day 5 following an overnight fast. Alternatively, participants could continue taking a single daily dose of rabeprazole on Day 6, fast overnight and return to the site on Day 7 instead of Day 5 for the final dose of study drug and the second pharmacokinetic (PK) blood draw and laboratory testing. Participants returned to the site in a fasted state the morning of Day 6 (or Day 8) for the 24-hour post-dose PK blood draw and laboratory testing. Participants were discharged from the study after the final safety evaluation and study termination procedures were performed.

| **Serious adverse events** | 20 mg Rabeprazole sodium | 10 mg Rabeprazole sodium | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 12 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | 20 mg Rabeprazole sodium | 10 mg Rabeprazole sodium | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 6 / 12 (50.00%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 12 (25.00%) | |
| occurrences (all) | 1 | 3 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Periorbital oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Renal and urinary disorders | | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 11 February 2004 | •The number of study centers was revised from up to 8 to up to 9 study centers due to slower than anticipated subject enrollment.<br>•The requirement that pretest evaluations be performed and study drug be administered at 8 AM was changed to "in the morning" on Day 1, Days 3 and 4, and Days 5 and 6, from 8 AM to "approximately the same time in the morning as on Day 1." This change was also made for subjects who returned to the site on Day 7 (8 AM in the original protocol was changed to "approximately the same time as on Day 1"). This revision was made to allow for the variability in subjects' schedule, especially during the school year.<br>•Inclusion criterion #7 that required normal laboratory findings in the original Study Protocol was deleted in Amendment 01. This change was made to allow screening of subjects whose laboratory test results values were outside the defined normal range but considered to be "normal" for that subject or were values that were not clinically significant.<br>•Because of the high frequency of smoking and alcohol use encountered the population under study, Exclusion criterion 3 was modified. The original Study Protocol stated that subjects with a known or suspected history of tobacco use, alcohol, or drug misuse within the past three months were excluded. Amendment 01 changed this to the following: "subjects who were unwilling or unable to refrain from smoking or drinking alcohol starting from 48 hours prior to screening and dosing, through the end of the study, and/or a positive urine drug screen were excluded."<br>•Based on the change to Exclusion criterion 3, Section 4.4 (Prohibitions and Restrictions during the Study) of the Study Protocol, had the following addition in Amendment 01: "subjects may not receive any recreational drugs, tobacco, and alcohol during study participation and within 48 hours of admission to the clinical site." |
| 11 February 2004 | Continuation of Amendment 1:<br>• Based on the change to Section 4.4 of the Study Protocol noted above, the following statement was deleted from Section 4.5 (Concomitant Medications): "subjects may not receive any recreational drugs and alcohol during study participation and within 72 hours of admission to the clinical site."<br>• The list of drug substances to be assayed in the urine drug screen (Section 7.5.4 of the Study Protocol, Appendix 16.1.1) was modified to exclude nicotine/cotinine in Amendment 0 l.<br>• Appendix 5 was added in Amendment 01 to provide the procedure for processing samples for CYP2C 19 genotyping.<br>• In Amendment 01, revisions for the processing, storage, and shipping of the blood samples for PK assays were made to Appendix IV. The laboratory processing these samples was changed from PRACS Institute, Ltd. to Quest Pharmaceutical Services, L.C.C.<br>• New contact information for responsible EMR personnel was provided in Amendment 01.<br>There were no changes to the planned analyses. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported