

**Clinical trial results:****A Pharmacokinetic, Pharmacodynamic and Short-term Safety Study of Single and Multiple Day Doses of Rabeprazole Sodium in Neonates and Pre-term Infants with a Corrected Age of Less than 44 Weeks with a Presumptive Diagnosis of Gastroesophageal Reflux Disease (GERD)**

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2009-015885-75 |
| Trial protocol | GB DE |
| Global end of trial date | 14 January 2012 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 01 July 2016 |
| First version publication date | 01 August 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set• Review of data |

Trial information**Trial identification**

| | |
|-----------------------|------------|
| Sponsor protocol code | RABGRD1005 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00855361 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Johnson and Johnson Pharmaceutical Research and Development, L.L.C. |
| Sponsor organisation address | 1125 Trenton-Harbourton Rd, Titusville, New Jersey, United States, 08560 |
| Public contact | Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.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 | Yes |

| | |
|--------------------------------|--|
| 1901/2006 apply to this trial? | |
|--------------------------------|--|

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 January 2012 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 January 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the pharmacokinetics (PK) using population PK methods, pharmacodynamics (PD) (intraesophageal and intragastric pH, assessment of the overall treatment effect [OTE] [overall GERD symptom relief]) and the short-term safety of rabeprazole after single and multiple dose administration for up to 28 days at one low dose level (Part 1) and two presumed effective dose levels (Part 2) in neonates and pre-term infants, with a corrected age of less than 44 weeks at the time of the first dose, who have been diagnosed with GERD.

Protection of trial subjects:

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP) and all applicable regulatory and legal requirements. The safety evaluations were based on the following Reports of Adverse effects (AEs) and serious adverse effects (SAEs) : Clinical laboratory tests (hematology, serum chemistry, and urinalysis), Vital sign measurements (blood pressure [systolic and diastolic], pulse rate, and respiratory rate, and body temperature)

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 21 February 2010 |
| 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 Kingdom: 3 |
| Country: Number of subjects enrolled | Poland: 38 |
| Country: Number of subjects enrolled | United States: 28 |
| Worldwide total number of subjects | 69 |
| EEA total number of subjects | 41 |

Notes:

Subjects enrolled per age group

| | |
|----------|---|
| In utero | 0 |
|----------|---|

| | |
|---|----|
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 15 |
| Infants and toddlers (28 days-23 months) | 54 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Total 69 subjects were enrolled in study from 22 sites in 4 countries.

Pre-assignment

Screening details:

A total of 69 neonates and pre-term infants having a presumptive diagnosis of GERD; including 19 subjects in Part 1 (rabeprazole 1 mg) and 50 subjects in Part 2 (25 subjects each in rabeprazole 2-mg and 3-mg treatment groups) were enrolled.

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 | Part 1: Rabeprazole 1 milligram (mg) |

Arm description:

Subject received 1 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 1). The study drug was administered through a nasogastric or orogastric tube.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rabeprazole Sodium |
| Investigational medicinal product code | R128546 |
| Other name | |
| Pharmaceutical forms | Granules |
| Routes of administration | Oral use |

Dosage and administration details:

Dose of 1.0 milligram [mg] rabeprazole sodium every 24 hours for a minimum of 5 days and a maximum of 28 days.

| | |
|------------------|--------------------------|
| Arm title | Part 2: Rabeprazole 2 mg |
|------------------|--------------------------|

Arm description:

Subject received 2 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug was administered through a nasogastric or orogastric tube.

| | |
|--|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rabeprazole sodium |
| Investigational medicinal product code | R128546 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Dose of 2.0 milligram [mg] rabeprazole sodium every 24 hours for a minimum of 5 days and a maximum of 28 days.

| | |
|------------------|--------------------------|
| Arm title | Part 2: Rabeprazole 3 mg |
|------------------|--------------------------|

Arm description:

one single daily dose of rabeprazole sodium 3 mg as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug will be administered through a nasogastric or orogastric tube.

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

| | |
|--|--------------------|
| Investigational medicinal product name | Rabeprazole sodium |
| Investigational medicinal product code | R128546 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Dose of 3.0 milligram [mg] rabeprazole sodium every 24 hours for a minimum of 5 days and a maximum of 28 days.

| Number of subjects in period 1 | Part 1: Rabeprazole 1 milligram (mg) | Part 2: Rabeprazole 2 mg | Part 2: Rabeprazole 3 mg |
|---------------------------------------|---|-----------------------------|-----------------------------|
| Started | 19 | 25 | 25 |
| Completed | 1 | 0 | 0 |
| Not completed | 18 | 25 | 25 |
| Physician decision | 14 | 23 | 21 |
| Consent withdrawn by subject | - | 1 | - |
| Adverse Event | 1 | - | 1 |
| Other | 2 | 1 | 2 |
| Lack of efficacy | 1 | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Part 1: Rabeprazole 1 milligram (mg) |
|-----------------------|--------------------------------------|

Reporting group description:

Subject received 1 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 1). The study drug was administered through a nasogastric or orogastric tube.

| | |
|-----------------------|--------------------------|
| Reporting group title | Part 2: Rabeprazole 2 mg |
|-----------------------|--------------------------|

Reporting group description:

Subject received 2 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug was administered through a nasogastric or orogastric tube.

| | |
|-----------------------|--------------------------|
| Reporting group title | Part 2: Rabeprazole 3 mg |
|-----------------------|--------------------------|

Reporting group description:

one single daily dose of rabeprazole sodium 3 mg as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug will be administered through a nasogastric or orogastric tube.

| Reporting group values | Part 1: Rabeprazole 1 milligram (mg) | Part 2: Rabeprazole 2 mg | Part 2: Rabeprazole 3 mg |
|---|--------------------------------------|--------------------------|--------------------------|
| Number of subjects | 19 | 25 | 25 |
| Title for AgeCategorical Units: subjects | | | |
| Newborns (0-27 days) | 2 | 5 | 8 |
| infants and toddlers(28 - 135 days) | 17 | 20 | 17 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 52.5 | 58.3 | 46.4 |
| standard deviation | ± 26.99 | ± 33.52 | ± 26.74 |
| Title for Gender Units: subjects | | | |
| Female | 7 | 13 | 13 |
| Male | 12 | 12 | 12 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 69 | | |
| Title for AgeCategorical Units: subjects | | | |
| Newborns (0-27 days) | 15 | | |
| infants and toddlers(28 - 135 days) | 54 | | |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | | | |
| Title for Gender Units: subjects | | | |
| Female | 33 | | |
| Male | 36 | | |

End points

End points reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Part 1: Rabeprazole 1 milligram (mg) |
|-----------------------|--------------------------------------|

Reporting group description:

Subject received 1 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 1). The study drug was administered through a nasogastric or orogastric tube.

| | |
|-----------------------|--------------------------|
| Reporting group title | Part 2: Rabeprazole 2 mg |
|-----------------------|--------------------------|

Reporting group description:

Subject received 2 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug was administered through a nasogastric or orogastric tube.

| | |
|-----------------------|--------------------------|
| Reporting group title | Part 2: Rabeprazole 3 mg |
|-----------------------|--------------------------|

Reporting group description:

one single daily dose of rabeprazole sodium 3 mg as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug will be administered through a nasogastric or orogastric tube.

Primary: Maximum Observed Plasma Concentration (C_{max}) of Rabeprazole and Thioether Metabolite

| | |
|-----------------|--|
| End point title | Maximum Observed Plasma Concentration (C _{max}) of Rabeprazole and Thioether Metabolite ^[1] |
|-----------------|--|

End point description:

The C_{max} is the maximum observed plasma concentration.

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

End point timeframe:

Up to Day 5

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: Descriptive statistics were done, no inferential statistical analyses were performed

| End point values | Part 1: Rabeprazole 1 milligram (mg) | Part 2: Rabeprazole 2 mg | Part 2: Rabeprazole 3 mg | |
|--|--|--------------------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | 0 ^[4] | |
| Units: Nanogram per milliliter [ng/ml] | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

[2] - Data not reported as only sparse PK sampling was done no quantitative analysis were performed.

[3] - Data not reported as only sparse PK sampling was done no quantitative analysis were performed.

[4] - Data not reported as only sparse PK sampling was done no quantitative analysis were performed.

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Intraesophageal pH concentration and intragastric pH Concentration

| | |
|-----------------|---|
| End point title | Change From Baseline in Intraesophageal pH concentration and intragastric pH Concentration ^[5] |
|-----------------|---|

End point description:

End point type Primary

End point timeframe:

Baseline, Day 5

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: Descriptive statistics were done, no inferential statistical analyses were performed

| End point values | Part 1: Rabeprazole 1 milligram (mg) | Part 2: Rabeprazole 2 mg | Part 2: Rabeprazole 3 mg | |
|--|--|--------------------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 19 | 25 | 25 | |
| Units: millimole. hour per liter (mmol.h/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline: Intragastric pH | 31.43 (± 22.8523) | 35.539 (± 18.3496) | 44.357 (± 22.9909) | |
| Baseline: Intraesophageal pH | 4.179 (± 5.4933) | 6.946 (± 9.6122) | 18.232 (± 24.1211) | |
| Change at Day 5: Intragastric pH | -19.394 (± 30.3668) | -35.645 (± 19.5423) | -23.055 (± 20.5577) | |
| Change at Day 5: Intraesophageal pH | -1.555 (± 7.8498) | -5.541 (± 10.5261) | -17.512 (± 23.9473) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Serious and Non-Serious Adverse Events

End point title Number of Participants With Serious and Non-Serious Adverse Events

End point description:

Safety and tolerability was measured by number of reported adverse events (serious and non-serious) and repeated clinical evaluation of physical examinations, vital signs, 12-lead electrocardiogram (ECG), 24-hour continuous cardiac monitoring, and laboratory tests (hematology/blood chemistry/urinalysis).

End point type Secondary

End point timeframe:

Approximately 8 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with GERD Symptom Relief Relative to Baseline

| | |
|-----------------|--|
| End point title | Percentage of Subjects with GERD Symptom Relief Relative to Baseline |
|-----------------|--|

End point description:

Overall Treatment Effectiveness was reported by assessing the overall GERD symptom relief as compared to baseline. Here, number of subject analysed is the subject analysed for this outcome measure and "n" is number of subjects analysed at specific time point.

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

End point timeframe:

Day 5, 10 and 28

| End point values | Part 1: Rabeprazole 1 milligram (mg) | Part 2: Rabeprazole 2 mg | Part 2: Rabeprazole 3 mg | |
|---|--|--------------------------------|--------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 18 | 25 | 25 | |
| Units: percentage of subject number (not applicable) | | | | |
| Day 5: Better (n=18, 25, 25) | 13 | 20 | 20 | |
| Day 5: No change (n=18, 25, 25) | 4 | 5 | 4 | |
| Day 5: Worse (n=18, 25, 25) | 1 | 0 | 1 | |
| Day 10: Better (n=9, 7, 11) | 8 | 7 | 9 | |
| Day 10: No Change (n=9, 7, 11) | 1 | 7 | 2 | |
| Day 10: Worse (n=9, 7, 11) | 0 | 0 | 0 | |
| Day 28: Better (n=1, 0, 0) | 1 | 0 | 0 | |
| Day 28: No Change (1, 0, 0) | 0 | 0 | 0 | |
| Day 28: Worse (n=1, 0, 0) | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Day 28

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 14.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Part 1: Rabeprazole 1 mg |
|-----------------------|--------------------------|

Reporting group description:

Subject received 1 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 1). The study drug was administered through a nasogastric or orogastric tube.

| | |
|-----------------------|--------------------------|
| Reporting group title | Part 2: Rabeprazole 3 mg |
|-----------------------|--------------------------|

Reporting group description:

Subject received 3 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug was administered through a nasogastric or orogastric tube.

| | |
|-----------------------|--------------------------|
| Reporting group title | Part 2: Rabeprazole 2 mg |
|-----------------------|--------------------------|

Reporting group description:

Subject received 2 mg of rabeprazole sodium as a microgranule formulation for up to 28 consecutive days (Part 2). The study drug was administered through a nasogastric or orogastric tube.

| Serious adverse events | Part 1: Rabeprazole 1 mg | Part 2: Rabeprazole 3 mg | Part 2: Rabeprazole 2 mg |
|---|--------------------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 4 / 25 (16.00%) | 1 / 25 (4.00%) |
| number of deaths (all causes) | 0 | 1 | 0 |
| number of deaths resulting from adverse events | | | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 19 (5.26%) | 0 / 25 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral Atrophy | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinopathy of Prematurity | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 19 (0.00%) | 2 / 25 (8.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Necrotising Colitis | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 2 / 19 (10.53%) | 0 / 25 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory Failure | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal Failure | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Renal Necrosis | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Infections and infestations | | | |
| Sepsis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 19 (0.00%) | 2 / 25 (8.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

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

| Non-serious adverse events | Part 1: Rabeprazole 1 mg | Part 2: Rabeprazole 3 mg | Part 2: Rabeprazole 2 mg |
|---|-----------------------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 6 / 19 (31.58%) | 16 / 25 (64.00%) | 12 / 25 (48.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 0 / 25 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal Congestion | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 0 / 25 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Apnoea | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 1 / 25 (4.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 2 | 2 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 0 / 25 (0.00%) | 2 / 25 (8.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Investigations | | | |
| Haematocrit Decreased | | | |
| subjects affected / exposed | 0 / 19 (0.00%) | 0 / 25 (0.00%) | 1 / 25 (4.00%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|----------------------|----------------------|
| Haemoglobin Decreased subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Oxygen Saturation Decreased subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 25 (4.00%) 2 | 0 / 25 (0.00%) 0 |
| Head Circumference Abnormal subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 25 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Red Blood Cell Count Decreased subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Injury, poisoning and procedural complications Feeding Tube Complication subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Congenital, familial and genetic disorders Atrial Septal Defect subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 2 / 25 (8.00%) 3 | 1 / 25 (4.00%) 1 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 6 / 25 (24.00%) 6 | 5 / 25 (20.00%) 5 |
| Anaemia Neonatal subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Eye disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Conjunctival Disorder subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 25 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 2 | 1 / 25 (4.00%) 1 | 2 / 25 (8.00%) 2 |
| Retinopathy of Prematurity subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 2 / 25 (8.00%) 2 | 0 / 25 (0.00%) 0 |
| Eye Discharge subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 1 / 25 (4.00%) 2 |
| Gastrointestinal disorders | | | |
| Apthous Stomatitis subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 25 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Constipation subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 1 / 25 (4.00%) 1 |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Impaired Gastric Emptying subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Infantile Colic subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Inguinal Hernia | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Umbilical Hernia subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis Diaper subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 25 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Skin Lesion subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 25 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteopenia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Infections and infestations | | | |
| Candidiasis subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Herpes Virus Infection subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Paronychia subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Respiratory Tract Infection subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |
| Pneumonia | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 1 / 25 (4.00%) 1 |
| Rhinitis subjects affected / exposed occurrences (all) | 2 / 19 (10.53%) 2 | 0 / 25 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 1 / 19 (5.26%) 1 | 0 / 25 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Urinary Tract Infection subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 2 / 25 (8.00%) 2 |
| Metabolism and nutrition disorders Feeding Disorder Neonatal subjects affected / exposed occurrences (all) | 0 / 19 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 25 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 15 November 2010 | <p>The amendment was implemented after completion of Part 1 of the study, but before study drug administration began in Part 2 of the study. The important changes in the amendment included the following: participants need to be admitted to NICU or step-down unit prior to alimentation by a feeding tube (6 F NG or OG); Clarification on minimum number of subjects needed in Part 2 of study and</p> <p>undergoing pHmetry; Clarification on changes made to reflect the selection of 2 dose levels and formulation for Part 2. Dosing instructions for Part 2 were updated; Clarification on certain assessments done in subjects undergoing or not undergoing pHmetry in the Part 2 of study; Additional exclusion criteria for continuous feeding, and mothers taking PPIs and breast feeding; In Part 1 of the study, for serum laboratory assessment, the safety laboratory parameters were changed to: Hemoglobin, hematocrit, sodium, potassium, chloride, calcium, bicarbonate, AST, ALT, total bilirubin, direct bilirubin, albumin, BUN, glucose, creatinine, and total protein; Clarification on certain medications allowed or disallowed during the study; Capillary sampling for PK was allowed; but venous collection was preferable; Blood volume for PK evaluation was reduced to 0.4 mL per sample; Indication that the PK samples collected between 2- to 3-hours postdose and 3- to 4-hours postdose should be separated by at least 1 hour.</p> |
| 18 May 2011 | <p>The amendment was implemented in Part 2 of the study before study drug administration which began for 21 participants. The important changes in amendment included the following:</p> <p>Instead of 6 F NG or OG feeding tube only, a ≥ 6 F NG or OG feeding tube may be used; 6.5 F silicone NG or OG tubes should be avoided. Due to dosing issues with vehicle tablet (described below), vehicle granules supplied in sachets instead of vehicle tablets were used for dosing in Part 2 -directions for dose preparation were updated The reason for this amendment was the occurrence of clogging of NG or OG tube in 5 participants (participants 1175001, 1085003, 1105002, 1085004 and 1455001) who had been randomized to the 3 mg dose group of rabeprazole. In one participants (participants 1105002), the occurrence of tube clogging was reported as a study-drug related TEAE. This dose (3 mg) of study drug required 2 vehicle tablets to be added to water in order to form suspension with the rabeprazole granules. Participants randomized to the 2 mg dose only required one vehicle tablet to form the suspension and did not experience NG or OG tube clogging. After reports of difficulty with infusion of the study drug during the first administration in some participants receiving the 3 mg dose, several mitigation strategies were employed including avoidance of 6.5 F silicone NG or OG tubes (more adherence of suspension in silicone tubes vs. tubes made of other materials); vigorous shaking of the suspension in syringe just prior to infusion via NG or OG tube; Use of an interval water flush midway through the infusion of the suspension; and changing to an 8 F feeding tube in infants with a 6 F tube in place. With these mitigation strategies, full timely doses of study drug were able to be administered to participants. Protocol Amendment INT-2 substituted the vehicle granules as suspending agent instead of the vehicle tablet.</p> |
| 13 September 2011 | <p>The amendment was implemented in Part 2 of the study before study drug administration began for 18 participants. This included a further clarification on the feeding regimens for participants undergoing pHmetry and not undergoing pHmetry.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported