



## 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"><li>Correction of full data set</li><li>Review of data</li></ul>

## Trial information

### Trial identification

Sponsor protocol code	RABGRD1005
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### 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)	EMA-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?	
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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
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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
<b>Arm title</b>	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.

<b>Arm title</b>	Part 2: Rabeprazole 2 mg
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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.

<b>Arm title</b>	Part 2: Rabeprazole 3 mg
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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
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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.

<b>Number of subjects in period 1</b>	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<sub>max</sub>) of Rabeprazole and Thioether Metabolite

End point title	Maximum Observed Plasma Concentration (C <sub>max</sub> ) of Rabeprazole and Thioether Metabolite <sup>[1]</sup>
End point description: The C <sub>max</sub> 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 <sup>[2]</sup>	0 <sup>[3]</sup>	0 <sup>[4]</sup>	
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 <sup>[5]</sup>
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End point description:

End point type	Primary
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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
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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
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End point timeframe:

Approximately 8 weeks

## Statistical analyses



No statistical analyses for this end point

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

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End point title	Percentage of Subjects with GERD Symptom Relief Relative to Baseline
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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
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End point timeframe:

Day 5, 10 and 28

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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	

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**Statistical analyses**

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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### Reporting groups

Reporting group title	Part 1: Rabeprazole 1 mg
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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
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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
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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 %

<b>Non-serious adverse events</b>	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 alimmentation 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 <math>\geq 6</math> 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:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported