Clinical trial results:
A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Withdrawal Study to Evaluate the Safety and Efficacy of Delayed-Release Rabeprazole in 1- to 11-Month-Old Pediatric Subjects with Symptomatic/Erosive 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	2008-004847-12
Trial protocol	HU BE NL IT BG DK
Global end of trial date	16 November 2011

Results information

Result version number	v2 (current)
This version publication date	01 July 2016
First version publication date	02 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	RABGRD3004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00992589
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International N.V.
Sponsor organisation address	Antwerpseweg 15-17, B-2340 Beerse, Belgium,
Public contact	Clinical Registry Group, Janssen Research & Development, +353 21 4673500, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, +353 21 4673500, 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 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 November 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 November 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and overall safety of rabeprazole sodium at doses of 5.0 milligram (mg) and 10.0 mg relative to placebo in infant subjects with GERD who are 1 to 11 months of age at screening. The primary efficacy endpoint will be measured by the changes from baseline to the end of the study in the Infant Gastroesophageal Reflux Questionnaire-Revised (I-GERQ-R) total score and the Infant Gastroesophageal Reflux Questionnaire-Daily Diary (I-GERQ-DD) total score between the active treatment and placebo groups.

Protection of trial subjects:

Safety assessments were consisting of monitoring and recording all Adverse event (AE) and Serious Adverse events (SAEs), measurement of vital signs, Physical examination and Clinical laboratory assessments (hematology, blood chemistries, and urine values) were assessed throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Bulgaria: 24
Country: Number of subjects enrolled	Hungary: 51
Country: Number of subjects enrolled	Israel: 36
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	United States: 133
Country: Number of subjects enrolled	South Africa: 12
Worldwide total number of subjects	344
EEA total number of subjects	156

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)	344
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:

This is a phase 3 study conducted between 4 November 2009 to 16 November 2011.

Pre-assignment

Screening details:

Four hundred twenty-seven subjects were screened for this study and 83 of these subjects were screening failures. These screening failures included 79 subjects who did not meet entry criteria and 4 subjects who failed for other reasons.

Period 1

Period 1 title	Open Label
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open-Label Rabeprazole Sodium 10 Milligram (mg)

Arm description:

Rabeprazole Sodium capsules once daily in the morning.

Arm type	Experimental
Investigational medicinal product name	Rabeprazole Sodium 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Rabeprazole Sodium 10 mg capsule once daily in the morning.

Number of subjects in period 1	Open-Label Rabeprazole Sodium 10 Milligram (mg)
Started	344
Completed	267
Not completed	77
Physician decision	4
Lost to follow-up	1
Protocol violation	3
Other	6
Adverse event	4
Noncompliance with study drug	2
Withdrawal of consent	20
Did not meet cgi criteria	37

Period 2

Period 2 title	Double Blind
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Placebo

Arm description:

Matching placebo capsules once daily in the morning.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Matching placebo capsules once daily in the morning.

Arm title	Double-Blind Rabeprazole Sodium 5 Mg

Arm description:

Rabeprazole Sodium 5 mg capsule once daily in the morning.

Arm type	Experimental
Investigational medicinal product name	Rabeprazole Sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Rabeprazole Sodium 5 mg capsule once daily in the morning.

Arm title	Double-Blind Rabeprazole Sodium 10 Mg

Arm description:

Rabeprazole Sodium capsules once daily in the morning.

Arm type	Experimental
Investigational medicinal product name	Rabeprazole Sodium 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Granules and solvent for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Rabeprazole Sodium 10 mg capsule once daily in the morning.

Number of subjects in period 2	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg
Started	89	90	88
Completed	76	77	78
Not completed	13	13	10
Consent withdrawn by subject	6	5	2
Other	1	4	3
Adverse event	6	2	3
Noncompliance with study drug	-	2	-
Lost to follow-up	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Open-Label Rabeprazole Sodium 10 Milligram (mg)
Reporting group description:	
Rabeprazole Sodium capsules once daily in the morning.	

Reporting group values	Open-Label Rabeprazole Sodium 10 Milligram (mg)	Total	
Number of subjects	344	344	
Title for AgeCategorical			
Units: subjects			
>= 1 to < 4 Months	175	175	
>= 4 to < 8 Months	124	124	
>= 8 to < 12 Months	45	45	
Title for AgeContinuous			
Units: years			
arithmetic mean	4.6		
standard deviation	± 2.55	-	
Title for Gender			
Units: subjects			
Female	139	139	
Male	205	205	

End points

End points reporting groups

Reporting group title	Open-Label Rabeprazole Sodium 10 Milligram (mg)
Reporting group description:	
Rabeprazole Sodium capsules once daily in the morning.	
Reporting group title	Double-Blind Placebo
Reporting group description:	
Matching placebo capsules once daily in the morning.	
Reporting group title	Double-Blind Rabeprazole Sodium 5 Mg
Reporting group description:	
Rabeprazole Sodium 5 mg capsule once daily in the morning.	
Reporting group title	Double-Blind Rabeprazole Sodium 10 Mg
Reporting group description:	
Rabeprazole Sodium capsules once daily in the morning.	
Subject analysis set title	Intent-to-treat (ITT) population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent to Treat population consisted of all subjects who completed the Open-label period, were randomly assigned to treatment in the Double-blind (DB) period, had taken at least 1 dose of DB study drug, and with evaluable data at each measurement time point.	
Subject analysis set title	Double-Blind Rabeprazole Sodium Total
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Rabeprazole Sodium capsules once daily in the morning.	
Subject analysis set title	Double-Blind Placebo - Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Matching placebo capsules once daily in the morning.	
Subject analysis set title	Double-Blind Rabeprazole Sodium 5 mg - Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Rabeprazole Sodium capsules once daily in the morning.	
Subject analysis set title	Double-Blind Rabeprazole Sodium 10 mg - Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Rabeprazole Sodium capsules once daily in the morning.	
Subject analysis set title	Double-Blind Placebo - Week 8
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Matching placebo capsules once daily in the morning.	
Subject analysis set title	Double-Blind Rabeprazole Sodium 5 mg - Week 8
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Rabeprazole Sodium capsules once daily in the morning.	
Subject analysis set title	Double-Blind Rabeprazole Sodium 10 mg - Week 8
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Rabeprazole Sodium capsules once daily in the morning.	
Subject analysis set title	Double-Blind Rabeprazole Sodium Total - Baseline
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Rabeprazole Sodium capsules once daily in the morning.

Subject analysis set title	Double-Blind Rabeprazole Sodium Total - Week 8
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Rabeprazole Sodium capsules once daily in the morning.

Primary: Change From Baseline in I-GERQ-R Total Score (Double-blind Phase/ Baseline Observation Carried Forward)

End point title	Change From Baseline in I-GERQ-R Total Score (Double-blind Phase/ Baseline Observation Carried Forward)

End point description:

The Infant Gastroesophageal Reflux Questionnaire-Revised (I-GERQ-R) is a 12-item questionnaire that is completed by the primary caregiver at every office or telephonic visit. It has a weekly recall and the items cover the frequency, amount and discomfort attributed to spit-up, refusal or stopping feeding, crying and fussing, hiccups, arching back and stopping breathing or changing color. The total score is calculated as the sum of all 12 scores for the individual questions, and ranges from 0 to 42. A higher value indicates a worse outcome. Here, "Number of Subjects Analysed" is number of subject analysed for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg	Double-Blind Rabeprazole Sodium Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	89[1]	89[2]	87[3]	176[4]
Units: Scores on a scale				
arithmetic mean (standard deviation)	-3.6 (± 6.41)	-3.8 (± 7.5)	-4.1 (± 7)	-3.9 (± 7.24)

Notes:

[1] - ITT Population

[2] - ITT Population

[3] - ITT Population

[4] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Double-Blind Placebo v Double-Blind Rabeprazole Sodium Total
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96 [5]
Method	ANCOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.042
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.615
upper limit	1.7

Notes:

[5] - ANCOVA with Treatment as fixed effect, Region and Age as stratification factors and Change from Open-label (OL) Baseline to OL Endpoint as covariate to test the hypothesis of no difference in change in I-GERQ-R Total Score.

Primary: Change From Baseline in in Weekly Average I-GERQ-DD Total Score (Double-blind Phase/ Baseline Observation Carried Forward)

End point title	Change From Baseline in in Weekly Average I-GERQ-DD Total Score (Double-blind Phase/ Baseline Observation Carried Forward)

End point description:

The Infant Gastroesophageal Reflux Questionnaire-Daily Diary (I-GERQ-DD) is a 9-item daily diary that the primary caregiver will be instructed to complete every evening at the same time interval after the participant has gone to sleep for the night. The I-GERQ-DD contains 3 subscales: the Regurgitation subscale, the Eating Behavior subscale and the Discomfort subscale. Each of the 9 items will be assigned a numeric score. The total score will be calculated as the sum of all 9 items, and ranges from 0 to 37. A higher value indicates a worse outcome. Here, "Number of subject analysed" were the subjects with evaluable data at each measurement time point.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg	Double-Blind Rabeprazole Sodium Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	88[6]	88[7]	87[8]	176[9]
Units: scores on a scale				
arithmetic mean (standard deviation)	-1.9 (± 4.55)	-1.6 (± 4.85)	-2.1 (± 4.9)	-1.9 (± 4.86)

Notes:

[6] - ITT Population

[7] - ITT Population

[8] - ITT Population

[9] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Double-Blind Placebo v Double-Blind Rabeprazole Sodium Total
Number of subjects included in analysis	264
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.968 [10]
Method	ANCOVA
Parameter estimate	Least-Squares Mean Difference [4]
Point estimate	0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.167
upper limit	1.214

Notes:

[10] - Analysis of Covariance with Treatment as fixed effect, Region and Age as stratification factors and Change from Open-label (OL) Baseline to OL Endpoint as covariate to test the hypothesis of no difference in change in Weekly Average I-GERQ-DD Total S

Secondary: Change From Baseline in Average Daily Frequency of Regurgitation (Double-blind Phase/ Baseline Observation Carried Forward)

End point title	Change From Baseline in Average Daily Frequency of Regurgitation (Double-blind Phase/ Baseline Observation Carried Forward)

End point description:

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg	Double-Blind Rabeprazole Sodium Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	89[11]	90[12]	88[13]	178[14]
Units: Frequency of Regurgitation				
arithmetic mean (standard deviation)	-0.8 (± 1.58)	-0.8 (± 1.55)	-1.6 (± 3.63)	-1.2 (± 2.79)

Notes:

[11] - ITT Population

[12] - ITT Population

[13] - ITT Population

[14] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis of Covariance with Treatment as fixed effect, Region and Age as stratification factors and Change from Open-label (OL) Baseline to OL Endpoint as covariate to test the hypothesis of no difference in change in daily average frequency of regurgitation from Double-blind (DB) Baseline to DB Endpoint between rabeprazole sodium total and placebo.

Comparison groups	Double-Blind Placebo v Double-Blind Rabeprazole Sodium Total
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168
Method	ANCOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.449
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.087
upper limit	0.19

Secondary: Change From Baseline in Weight-for-Age Z-Score (Double-blind Phase/ Baseline Observation Carried Forward)

End point title	Change From Baseline in Weight-for-Age Z-Score (Double-blind Phase/ Baseline Observation Carried Forward)

End point description:

Body weight was measured with the participant unclothed and before a feeding during each office visit. In the analysis of weight data, weight will be transformed to the weight-for-age Z-score using World Health Organization Child Growth Standards, taking into account the infant's age and gender (Borghi E, 2006). Here, "Number of Subjects Analysed" is number of subject analysed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg	Double-Blind Rabeprazole Sodium Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	89[15]	90[16]	88[17]	178[18]
Units: Z-score				
arithmetic mean (standard deviation)	0.11 (± 0.329)	0.16 (± 0.322)	0.11 (± 0.264)	0.14 (± 0.295)

Notes:

[15] - ITT Population

[16] - ITT Population

[17] - ITT Population

[18] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Double-Blind Placebo v Double-Blind Rabeprazole Sodium Total
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44 [19]
Method	ANCOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.047
upper limit	0.108

Notes:

[19] - ANCOVA with Treatment as fixed effect, Region and Age as stratification factors and Double-blind (DB) Baseline as covariate to test the hypothesis of no difference in change in Weight-for-Age Z-Score.

Secondary: The Daily Average Number of Episodes Related to Each Volume of Regurgitation During the Double-blind Treatment Period

End point title	The Daily Average Number of Episodes Related to Each Volume of Regurgitation During the Double-blind Treatment Period

End point description:

The Daily Average Number of Episodes Related to Each Volume of Regurgitation During the Double-blind Treatment Period. Here, Number of subject analysed is the subjects is the subjects with evaluable data at each measurement time point.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo - Baseline	Double-Blind Rabeprazole Sodium 5 mg - Baseline	Double-Blind Rabeprazole Sodium 10 mg - Baseline	Double-Blind Placebo - Week 8
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	89[20]	90[21]	88[22]	89[23]
Units: number of episodes				
number (not applicable)				
Less than 1 tablespoon	1.7	1.7	2.7	1.6
1 to 2 tablespoons	1.1	1.2	1.7	1.1
More than 2 tablespoons to 2 fluid oz	0.4	0.3	0.4	0.5
More than 2 fluid oz to 4 fluid oz	0.1	0	0	0.1
More than 4 fluid oz	0	0	0.1	0

Notes:

[20] - ITT Population

[21] - ITT Population

[22] - ITT Population

[23] - ITT Population

End point values	Double-Blind Rabeprazole Sodium 5 mg - Week 8	Double-Blind Rabeprazole Sodium 10 mg - Week 8	Double-Blind Rabeprazole Sodium Total - Baseline	Double-Blind Rabeprazole Sodium Total - Week 8
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	90[24]	88[25]	178[26]	178[27]
Units: number of episodes				
number (not applicable)				
Less than 1 tablespoon	1.6	2.1	2.1	1.8
1 to 2 tablespoons	1	1.4	1.5	1.2
More than 2 tablespoons to 2 fluid oz	0.3	0.4	0.4	0.4
More than 2 fluid oz to 4 fluid oz	0.1	0.1	0	0.1
More than 4 fluid oz	0	0	0.1	0

Notes:

[24] - ITT Population

[25] - ITT Population

[26] - ITT Population

[27] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Weekly Average I-GERQ-DD Regurgitation Subscale Score (Double-blind Phase/ Last Observation Carried Forward)

End point title	Change From Baseline in Weekly Average I-GERQ-DD Regurgitation Subscale Score (Double-blind Phase/ Last Observation Carried Forward)

End point description:

The Infant Gastroesophageal Reflux Questionnaire-Daily Diary (I-GERQ-DD) is a 9-item daily diary that the primary caregiver will be instructed to complete every evening at the same time interval after the participant has gone to sleep for the night. The I-GERQ-DD contains 3 subscales: the Regurgitation subscale, the Eating Behavior subscale and the Discomfort subscale. The Regurgitation subscale will be calculated as the sum of the 3 questions regarding regurgitation (Questions 1, 2, 3) and will range from 0 to 13. For each subscale score, a higher value indicates a worse outcome. Here, number of subject analysed is the number of subject with evaluable data at each measurement time point.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg	Double-Blind Rabeprazole Sodium Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	88[28]	88[29]	85[30]	173[31]
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.8 (± 2.57)	-0.8 (± 2.56)	-1 (± 2.38)	-0.9 (± 2.47)

Notes:

[28] - ITT Population

[29] - ITT Population

[30] - ITT Population

[31] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Double-Blind Placebo v Double-Blind Rabeprazole Sodium Total
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.984 [32]
Method	ANCOVA
Parameter estimate	Difference in least square mean
Point estimate	0.006
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.619
upper limit	0.632

Notes:

[32] - ANCOVA with Treatment as fixed effect, Region and Age as stratification factors and Double-blind (DB) Baseline as covariate to test the hypothesis of no difference in change Weekly Average I-GERQ-DD.

Secondary: Change From Baseline in Weekly Average I-GERQ-DD Eating Behavior Subscale Score (Double-blind Phase/ Last Observation Carried Forward)

End point title	Change From Baseline in Weekly Average I-GERQ-DD Eating Behavior Subscale Score (Double-blind Phase/ Last Observation Carried Forward)

End point description:

The Infant Gastroesophageal Reflux Questionnaire-Daily Diary (I-GERQ-DD) is a 9-item daily diary that the primary caregiver will be instructed to complete every evening at the same time interval after the subject has gone to sleep for the night. The I-GERQ-DD contains 3 subscales: the Regurgitation subscale, the Eating Behavior subscale and the Discomfort subscale. The Eating Behavior subscale score will be calculated as the sum of the 3 questions regarding eating behavior (Questions 4, 5, 6) and will range from 0 to 12. For each subscale score, a higher value indicates a worse outcome. Here, "Number of Subjects Analysed" is number of subject analysed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg	Double-Blind Rabeprazole Sodium Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	88[33]	88[34]	85[35]	173[36]
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.1 (± 2.54)	-0.1 (± 2.19)	-0.4 (± 2.15)	-0.3 (± 2.17)

Notes:

[33] - ITT Population

[34] - ITT Population

[35] - ITT Population

[36] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Rabeprazole Sodium Total
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.498
Method	ANCOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.192
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.751
upper limit	0.366

Secondary: Change From Baseline in Weekly Average I-GERQ-DD Discomfort Subscale Score (Double-blind Phase/ Last Observation Carried Forward)

End point title	Change From Baseline in Weekly Average I-GERQ-DD Discomfort Subscale Score (Double-blind Phase/ Last Observation Carried Forward)

End point description:

The Infant Gastroesophageal Reflux Questionnaire-Daily Diary (I-GERQ-DD) is a 9-item daily diary that the primary caregiver will be instructed to complete every evening at the same time interval after the subject has gone to sleep for the night. The I-GERQ-DD contains 3 subscales: the Regurgitation subscale, the Eating Behavior subscale and the Discomfort subscale. The Discomfort subscale score will be calculated as the sum of the 3 questions regarding discomfort (Questions, 7, 8, 9) and will range from 0 to 12. For each subscale score, a higher value indicates a worse outcome. Here, "Number of Subjects Analysed" is number of subject analysed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Double-Blind Rabeprazole Sodium 10 Mg	Double-Blind Rabeprazole Sodium Total
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	88[37]	88[38]	85[39]	173[40]
Units: scores on a scale				
arithmetic mean (standard deviation)	0 (± 2.24)	-0.1 (± 1.88)	-0.4 (± 1.94)	-0.2 (± 1.9)

Notes:

[37] - ITT population

[38] - ITT Population

[39] - ITT Population

[40] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Double-Blind Placebo v Double-Blind Rabeprazole Sodium Total
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.479
Method	ANCOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.182
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	0.325

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to End of study (Week 8)	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0
Reporting groups	
Reporting group title	Double-Blind Placebo
Reporting group description: Matching placebo capsules once daily in the morning.	
Reporting group title	Double-Blind Rabeprazole Sodium 5 Mg
Reporting group description: Rabeprazole Sodium capsules once daily in the morning.	
Reporting group title	Open-Label Rabeprazole Sodium 10 Mg
Reporting group description: Rabeprazole Sodium capsules once daily in the morning.	
Reporting group title	Double-Blind Rabeprazole Sodium 10 Mg
Reporting group description: Rabeprazole Sodium capsules once daily in the morning.	

Serious adverse events	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Open-Label Rabeprazole Sodium 10 Mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 89 (2.25%)	6 / 90 (6.67%)	5 / 344 (1.45%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Beta 2 Microglobulin Increased			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	0 / 344 (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
Ear and labyrinth disorders			

Hypoacusis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	0 / 344 (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
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Stridor			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	0 / 344 (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
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	0 / 344 (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
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	0 / 344 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 89 (0.00%)	1 / 90 (1.11%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			

subjects affected / exposed	0 / 89 (0.00%)	2 / 90 (2.22%)	0 / 344 (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
Viral Infection			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to Thrive			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic Acidosis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Double-Blind Rabeprazole Sodium 10 Mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 88 (2.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Beta 2 Microglobulin Increased			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Stridor			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper Respiratory Tract Infection			

subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Infection			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral Infection			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Failure to Thrive			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic Acidosis			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Double-Blind Placebo	Double-Blind Rabeprazole Sodium 5 Mg	Open-Label Rabeprazole Sodium 10 Mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 89 (40.45%)	26 / 90 (28.89%)	79 / 344 (22.97%)
Investigations			
Blood Creatinine Increased			

subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	0 / 344 (0.00%)
occurrences (all)	0	0	0
Blood Gastrin Increased			
subjects affected / exposed	0 / 89 (0.00%)	2 / 90 (2.22%)	1 / 344 (0.29%)
occurrences (all)	0	2	1
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	5 / 344 (1.45%)
occurrences (all)	1	0	5
Pyrexia			
subjects affected / exposed	2 / 89 (2.25%)	6 / 90 (6.67%)	9 / 344 (2.62%)
occurrences (all)	2	9	9
Ear and labyrinth disorders			
Tympanic Membrane Hyperaemia			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	0 / 344 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	3 / 89 (3.37%)	0 / 90 (0.00%)	2 / 344 (0.58%)
occurrences (all)	3	0	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 89 (4.49%)	4 / 90 (4.44%)	11 / 344 (3.20%)
occurrences (all)	4	5	11
Constipation			
subjects affected / exposed	2 / 89 (2.25%)	1 / 90 (1.11%)	11 / 344 (3.20%)
occurrences (all)	2	1	11
Gastrooesophageal Reflux Disease			
subjects affected / exposed	7 / 89 (7.87%)	2 / 90 (2.22%)	0 / 344 (0.00%)
occurrences (all)	7	2	0
Teething			
subjects affected / exposed	1 / 89 (1.12%)	2 / 90 (2.22%)	3 / 344 (0.87%)
occurrences (all)	1	2	3
Vomiting			
subjects affected / exposed	5 / 89 (5.62%)	4 / 90 (4.44%)	4 / 344 (1.16%)
occurrences (all)	5	4	4

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 89 (3.37%)	2 / 90 (2.22%)	5 / 344 (1.45%)
occurrences (all)	3	3	5
Nasal Congestion			
subjects affected / exposed	2 / 89 (2.25%)	0 / 90 (0.00%)	3 / 344 (0.87%)
occurrences (all)	2	0	3
Skin and subcutaneous tissue disorders			
Dermatitis Diaper			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences (all)	1	0	1
Intertrigo			
subjects affected / exposed	0 / 89 (0.00%)	2 / 90 (2.22%)	0 / 344 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	2 / 89 (2.25%)	1 / 90 (1.11%)	8 / 344 (2.33%)
occurrences (all)	2	1	8
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 89 (1.12%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences (all)	1	0	1
Bronchiolitis			
subjects affected / exposed	2 / 89 (2.25%)	0 / 90 (0.00%)	2 / 344 (0.58%)
occurrences (all)	2	0	2
Ear Infection			
subjects affected / exposed	3 / 89 (3.37%)	1 / 90 (1.11%)	4 / 344 (1.16%)
occurrences (all)	4	1	4
Nasopharyngitis			
subjects affected / exposed	3 / 89 (3.37%)	2 / 90 (2.22%)	11 / 344 (3.20%)
occurrences (all)	3	2	11
Otitis Media			
subjects affected / exposed	2 / 89 (2.25%)	4 / 90 (4.44%)	6 / 344 (1.74%)
occurrences (all)	2	4	6
Otitis Media Acute			
subjects affected / exposed	2 / 89 (2.25%)	1 / 90 (1.11%)	1 / 344 (0.29%)
occurrences (all)	2	1	1

Pharyngitis			
subjects affected / exposed	0 / 89 (0.00%)	0 / 90 (0.00%)	1 / 344 (0.29%)
occurrences (all)	0	0	1
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 89 (5.62%)	1 / 90 (1.11%)	6 / 344 (1.74%)
occurrences (all)	5	1	6
Rhinitis			
subjects affected / exposed	1 / 89 (1.12%)	2 / 90 (2.22%)	1 / 344 (0.29%)
occurrences (all)	1	2	1

Non-serious adverse events	Double-Blind Rabeprazole Sodium 10 Mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 88 (44.32%)		
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Blood Gastrin Increased			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	7		
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Tympanic Membrane Hyperaemia			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Gastrooesophageal Reflux Disease subjects affected / exposed occurrences (all) Teething subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	2 / 88 (2.27%) 2 2 / 88 (2.27%) 2 4 / 88 (4.55%) 4 3 / 88 (3.41%) 3 1 / 88 (1.14%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Nasal Congestion subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1 2 / 88 (2.27%) 2		
Skin and subcutaneous tissue disorders Dermatitis Diaper subjects affected / exposed occurrences (all) Intertrigo subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	2 / 88 (2.27%) 2 0 / 88 (0.00%) 0 1 / 88 (1.14%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	4 / 88 (4.55%) 4		

Bronchiolitis			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Ear Infection			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	4		
Otitis Media			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	3		
Otitis Media Acute			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Upper Respiratory Tract Infection			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	7		
Rhinitis			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2010	This amendment included reduction of blood sampling volumes, provided additional exclusion criteria, provided clarification concerning the collection of PK samples, provided a larger window for blood draws, added an additional temperature sampling method, and provided additional clarification of symptom management of GERD, criteria for study completion, and data entry.
13 May 2011	This amendment included the addition of an interim analysis to rule out potential futility of continuing the trial in the absence of a positive response, provided clarification of an exclusion criterion (receipt of an investigational drug or use of an investigational device), and clarified PK sampling procedures.
22 August 2011	This amendment changed the method of imputation of missing data for statistical analyses and provided clarification of the definition of how baseline values for the primary endpoints were calculated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported