

**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<br>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,<br>+353 21 4673500, ClinicalTrialsEU@its.jnj.com |
| Scientific contact           | Clinical Registry Group, Janssen Research & Development,<br>+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)                          | 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 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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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

|                  |   |
|------------------|---|
| <b>Arm title</b> | 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<br>Rabeprazole Sodium<br>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  |

|   |  |
|---|--|
| <b>Period 2</b>   |  |
| 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   |
| <b>Arms</b>   |  |
| Are arms mutually exclusive?                                | Yes                                      |
| <b>Arm title</b>  | 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.        |  |
| <b>Arm title</b>  | 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.  |  |
| <b>Arm title</b>  | 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<br>Placebo | Double-Blind<br>Rabeprazole Sodium<br>5 Mg | Double-Blind<br>Rabeprazole Sodium<br>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<br>Rabeprazole Sodium<br>10 Milligram (mg) | Total |  |
|---|---|-------|--|
| Number of subjects                          | 344   | 344   |  |
| Title for AgeCategorical<br>Units: subjects |   |       |  |
| >= 1 to < 4 Months                          | 175   | 175   |  |
| >= 4 to < 8 Months                          | 124   | 124   |  |
| >= 8 to < 12 Months                         | 45  | 45    |  |
| Title for AgeContinuous<br>Units: years     |   |       |  |
| arithmetic mean                             | 4.6   |       |  |
| standard deviation                          | ± 2.55  | -     |  |
| Title for Gender<br>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:<br>Rabeprazole Sodium capsules once daily in the morning.  |  |
| Reporting group title   | Double-Blind Placebo                             |
| Reporting group description:<br>Matching placebo capsules once daily in the morning.  |  |
| Reporting group title   | Double-Blind Rabeprazole Sodium 5 Mg             |
| Reporting group description:<br>Rabeprazole Sodium 5 mg capsule once daily in the morning.  |  |
| Reporting group title   | Double-Blind Rabeprazole Sodium 10 Mg            |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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

| <b>End point values</b>              | Double-Blind<br>Placebo | Double-Blind<br>Rabeprazole<br>Sodium 5 Mg | Double-Blind<br>Rabeprazole<br>Sodium 10 Mg | Double-Blind<br>Rabeprazole<br>Sodium Total |
|--------------------------------------|-------------------------|--|---|---|
| Subject group type                   | Reporting group         | Reporting group                            | Reporting group                             | Subject analysis set                        |
| Number of subjects analysed          | 89 <sup>[1]</sup>       | 89 <sup>[2]</sup>                          | 87 <sup>[3]</sup>                           | 176 <sup>[4]</sup>                          |
| 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**

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[5]</sup>  |
| 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

| <b>End point values</b>              | 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 <sup>[6]</sup>    | 88 <sup>[7]</sup>                    | 87 <sup>[8]</sup>                     | 176 <sup>[9]</sup>                    |
| 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**

| <b>Statistical analysis title</b>       | 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 <sup>[10]</sup>                                      |
| 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 <sup>[11]</sup>   | 90 <sup>[12]</sup>                   | 88 <sup>[13]</sup>                    | 178 <sup>[14]</sup>                   |
| 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   |

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

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|                 |   |
|-----------------|---|
| 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

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| 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 <sup>[15]</sup>   | 90 <sup>[16]</sup>                   | 88 <sup>[17]</sup>                    | 178 <sup>[18]</sup>                   |
| 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 <sup>[19]</sup>                                       |
| 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.

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

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|   |   |
|---|---|
| End point title   | The Daily Average Number of Episodes Related to Each Volume of Regurgitation During the Double-blind Treatment Period |
| End point description:<br>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:<br>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 <sup>[20]</sup>              | 90 <sup>[21]</sup>                              | 88 <sup>[22]</sup>                               | 89 <sup>[23]</sup>            |
| 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 <sup>[24]</sup>                            | 88 <sup>[25]</sup>                             | 178 <sup>[26]</sup>                              | 178 <sup>[27]</sup>                            |
| 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:<br>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:<br>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 <sup>[28]</sup>   | 88 <sup>[29]</sup>                   | 85 <sup>[30]</sup>                    | 173 <sup>[31]</sup>                   |
| 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 <sup>[32]</sup>                                      |
| 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 <sup>[33]</sup>   | 88 <sup>[34]</sup>                   | 85 <sup>[35]</sup>                    | 173 <sup>[36]</sup>                   |
| 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 <sup>[37]</sup>   | 88 <sup>[38]</sup>                   | 85 <sup>[39]</sup>                    | 173 <sup>[40]</sup>                   |
| 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<br>Rabeprazole Sodium<br>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 %

| <b>Non-serious adverse events</b>                     | Double-Blind<br>Placebo | Double-Blind<br>Rabeprazole Sodium<br>5 Mg | Open-Label<br>Rabeprazole Sodium<br>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<br>occurrences (all)                                     | 0 / 89 (0.00%)<br>0 | 0 / 90 (0.00%)<br>0 | 0 / 344 (0.00%)<br>0   |
| Blood Gastrin Increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 89 (0.00%)<br>0 | 2 / 90 (2.22%)<br>2 | 1 / 344 (0.29%)<br>1   |
| General disorders and administration<br>site conditions                              |                     |                     |                        |
| Irritability<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 89 (1.12%)<br>1 | 0 / 90 (0.00%)<br>0 | 5 / 344 (1.45%)<br>5   |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 89 (2.25%)<br>2 | 6 / 90 (6.67%)<br>9 | 9 / 344 (2.62%)<br>9   |
| Ear and labyrinth disorders  |                     |                     |                        |
| Tympanic Membrane Hyperaemia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 89 (0.00%)<br>0 | 0 / 90 (0.00%)<br>0 | 0 / 344 (0.00%)<br>0   |
| Eye disorders  |                     |                     |                        |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                   | 3 / 89 (3.37%)<br>3 | 0 / 90 (0.00%)<br>0 | 2 / 344 (0.58%)<br>2   |
| Gastrointestinal disorders   |                     |                     |                        |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                        | 4 / 89 (4.49%)<br>4 | 4 / 90 (4.44%)<br>5 | 11 / 344 (3.20%)<br>11 |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 89 (2.25%)<br>2 | 1 / 90 (1.11%)<br>1 | 11 / 344 (3.20%)<br>11 |
| Gastrooesophageal Reflux Disease<br>subjects affected / exposed<br>occurrences (all) | 7 / 89 (7.87%)<br>7 | 2 / 90 (2.22%)<br>2 | 0 / 344 (0.00%)<br>0   |
| Teething<br>subjects affected / exposed<br>occurrences (all)                         | 1 / 89 (1.12%)<br>1 | 2 / 90 (2.22%)<br>2 | 3 / 344 (0.87%)<br>3   |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                         | 5 / 89 (5.62%)<br>5 | 4 / 90 (4.44%)<br>4 | 4 / 344 (1.16%)<br>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               |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>                     | Double-Blind<br>Rabeprazole Sodium<br>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                     | 2 / 88 (2.27%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Constipation                                    |                |  |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Gastrooesophageal Reflux Disease                |                |  |  |
| subjects affected / exposed                     | 4 / 88 (4.55%) |  |  |
| occurrences (all)                               | 4              |  |  |
| Teething  |                |  |  |
| subjects affected / exposed                     | 3 / 88 (3.41%) |  |  |
| occurrences (all)                               | 3              |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Respiratory, thoracic and mediastinal disorders |                |  |  |
| Cough   |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Nasal Congestion                                |                |  |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Skin and subcutaneous tissue disorders          |                |  |  |
| Dermatitis Diaper                               |                |  |  |
| subjects affected / exposed                     | 2 / 88 (2.27%) |  |  |
| occurrences (all)                               | 2              |  |  |
| Intertrigo                                      |                |  |  |
| subjects affected / exposed                     | 0 / 88 (0.00%) |  |  |
| occurrences (all)                               | 0              |  |  |
| Rash  |                |  |  |
| subjects affected / exposed                     | 1 / 88 (1.14%) |  |  |
| occurrences (all)                               | 1              |  |  |
| Infections and infestations                     |                |  |  |
| Bronchitis                                      |                |  |  |
| subjects affected / exposed                     | 4 / 88 (4.55%) |  |  |
| occurrences (all)                               | 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported