



Clinical trial results:

A Phase III, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel group, Treatment-withdrawal Study to Evaluate the Efficacy and Safety of Esomeprazole for the Treatment of Gastroesophageal Reflux Disease (GERD) in Infants Aged 1 to 11 Months, Inclusive

Summary

EudraCT number	2006-005212-27
Trial protocol	FR DE Outside EU/EEA
Global end of trial date	23 September 2008

Results information

Result version number	v1 (current)
This version publication date	18 November 2016
First version publication date	18 November 2016

Trial information

Trial identification

Sponsor protocol code	D9614C00096
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca LP
Sponsor organisation address	1800 Concord Pike, Wilmington, Delaware, United States, 19850
Public contact	AZ Clinical Trial Transparency group, AstraZeneca R&D, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Gerard Lynch, AstraZeneca R&D, AZTrial_Results_Posting@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000331-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2008
Global end of trial reached?	Yes
Global end of trial date	23 September 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of once daily esomeprazole for reducing the esophageal and supraesophageal signs and symptoms of infantile gastroesophageal reflux disease (GERD).

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics. The final clinical study protocol (CSP), including the final version of the Informed Consent Form, was approved or given a favorable opinion in writing by an Ethics Committee as appropriate. The investigator submitted written approval to AstraZeneca before he or she enrolled any patient into the study. The principal investigator(s) at each center ensured that the patient's parent/guardian was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The parent/guardian was also notified that they were free to discontinue his/her child from the study at any time. The patient's parent/guardian was given the opportunity to ask questions and allowed time to consider the information provided.

The parent/guardian's signed and dated informed consent was obtained before conducting any procedure specifically for the study.

Patients could be discontinued from study treatment and assessments at any time, at the discretion of the investigator(s).

Background therapy:

PPI within 7 days, or H2RAs or prokinetics within 24 hours prior to enrollment in the open label treatment phase were exclusion criteria.

Evidence for comparator:

No comparator

Actual start date of recruitment	12 April 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	98
EEA total number of subjects	61

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)	98
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:

Participants aged 1 to 11 months inclusive with a clinical diagnosis of suspected Gastroesophageal Reflux Disease (GERD), symptomatic GERD, or endoscopically proven GERD enrolled

First patient enrolled: 12 April 2007

Last patient completed: 4 June 2008

Pre-assignment

Screening details:

Of 103 patients screened for this study, 5 patients failed to be eligible.

In total, 98 patients were entered into the open-label esomeprazole phase. Of these, 80 were randomized into the double-blind randomized phase.

Period 1

Period 1 title	Open-label treatment phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open Label Esomeprazole
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Arm description:

Open-label daily esomeprazole (2.5mg, 5mg or 10mg daily during open-label phase of the study, according to baseline weight). Eligible participants from the Open Label phase were randomized to the the double blind withdrawal phase.

Arm type	Experimental
Investigational medicinal product name	Esomeprazole magnesium
Investigational medicinal product code	
Other name	NEXIUM
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.5-1.3 mg/kg od orally

Number of subjects in period 1	Open Label Esomeprazole
Started	98
Completed	80
Not completed	18
AE(5);Lack of efficacy(9); W/Consent(4)	18

Period 2

Period 2 title	Double-blind, treatment-withdrawal phase
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Double Blind Esomeprazole
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	Esomeprazole magnesium
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Investigational medicinal product code	
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Other name	NEXIUM
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Pharmaceutical forms	Capsule
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Routes of administration	Oral use
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Dosage and administration details:

0.5-1.3 mg/kg od orally

Arm title	Double Blind Placebo
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Arm description: -

Arm type	Placebo
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Investigational medicinal product name	Placebo
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Investigational medicinal product code	
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Other name	Placebo
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Pharmaceutical forms	Capsule
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Routes of administration	Oral use
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Dosage and administration details:

0.5-1.3 mg/kg od orally

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Amongst the 98 patients who entered the open-label period 18 did not qualify to be randomized into the double-blinded period. All baseline characteristics were reported on the 80 patients randomized into the Double-Blind Randomized Period

Number of subjects in period 2^[2]	Double Blind Esomeprazole	Double Blind Placebo
Started	39	41
Completed	29	24
Not completed	10	17
Adverse event, non-fatal	2	-
Lack of efficacy	8	17

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Amongst the 98 patients who entered the open-label period 18 did not qualify to be randomized into the double-blinded period. All baseline characteristics were reported on the 80 patients randomized into the Double-Blind Randomized Period

Baseline characteristics

Reporting groups

Reporting group title	Double Blind Esomeprazole
Reporting group description: -	
Reporting group title	Double Blind Placebo
Reporting group description: -	

Reporting group values	Double Blind Esomeprazole	Double Blind Placebo	Total
Number of subjects	39	41	80
Age categorical			
Units: Subjects			
Newborns (0-27 days)	1	3	4
Infants and toddlers (28 days-23 months)	38	38	76
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Age in months			
Units: months			
arithmetic mean	4.9	4.9	
standard deviation	± 2.6	± 3.2	-
Gender, Male/Female			
Units: Participants			
Female	9	14	23
Male	30	27	57

Subject analysis sets

Subject analysis set title	Open label treatment phase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Open label treatment phase	
Subject analysis set title	Double-blind phase esomeprazole
Subject analysis set type	Intention-to-treat
Subject analysis set description: Double-blind phase esomeprazole	
Subject analysis set title	Double-blind phase placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Double-blind phase placebo	

Reporting group values	Open label treatment phase	Double-blind phase esomeprazole	Double-blind phase placebo
Number of subjects	98	39	41

Age categorical			
Units: Subjects			
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	98	39	41
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Age in months			
Units: months			
arithmetic mean	4.8	4.9	4.9
standard deviation	± 2.9	± 2.6	± 3.2
Gender, Male/Female			
Units: Participants			
Female	35	9	14
Male	63	30	27

End points

End points reporting groups

Reporting group title	Open Label Esomeprazole
Reporting group description: Open-label daily esomeprazole (2.5mg, 5mg or 10mg daily during open-label phase of the study, according to baseline weight). Eligible participants from the Open Label phase were randomized to the the double blind withdrawal phase.	
Reporting group title	Double Blind Esomeprazole
Reporting group description: -	
Reporting group title	Double Blind Placebo
Reporting group description: -	
Subject analysis set title	Open label treatment phase
Subject analysis set type	Intention-to-treat
Subject analysis set description: Open label treatment phase	
Subject analysis set title	Double-blind phase esomeprazole
Subject analysis set type	Intention-to-treat
Subject analysis set description: Double-blind phase esomeprazole	
Subject analysis set title	Double-blind phase placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: Double-blind phase placebo	

Primary: Number of participants discontinuing due to symptom worsening in the randomized treatment withdrawal phase (Treatment withdrawal phase endpoint)

End point title	Number of participants discontinuing due to symptom worsening in the randomized treatment withdrawal phase (Treatment withdrawal phase endpoint)
End point description: Number of participants discontinuing during the 4-week of randomized double-blind withdrawal phase that met the pre-set definition of symptom worsening criteria.	
End point type	Primary
End point timeframe: Treatment-withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study)	

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	39	41	39	41
Units: Participants				
Week 1	1	6	1	6
Week 2	7	6	7	6
Week 3	2	1	2	1
Week 4	5	7	5	7

Statistical analyses

Statistical analysis title	Analysis of time to discontinuation
Statistical analysis description: Analysis of time to discontinuation due to symptom worsening.	
Comparison groups	Double Blind Esomeprazole v Double Blind Placebo v Double-blind phase esomeprazole v Double-blind phase placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2751
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Number of participants discontinuing due to any reason, including symptom worsening, in the randomized treatment withdrawal phase (Treatment withdrawal phase endpoint)

End point title	Number of participants discontinuing due to any reason, including symptom worsening, in the randomized treatment withdrawal phase (Treatment withdrawal phase endpoint)
End point description: Number of participants discontinuing due to any reason was identical to the number of participants discontinuing due to symptom worsening (the primary assessment) when no participants discontinued due to reason other than symptom worsening.	
End point type	Secondary
End point timeframe: Treatment withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study)	

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	39	41	39	41
Units: Participants				
Week 1	1	6	1	6
Week 2	7	6	7	6
Week 3	2	1	2	1
Week 4	5	7	5	7

Statistical analyses

Statistical analysis title	Time to discontinuation due to any reason
Comparison groups	Double Blind Esomeprazole v Double Blind Placebo v Double-blind phase esomeprazole v Double-blind phase placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2751
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.4

Secondary: Treatment successes at the end of the 4-week double-blind treatment withdrawal phase (Treatment withdrawal phase endpoint).

End point title	Treatment successes at the end of the 4-week double-blind treatment withdrawal phase (Treatment withdrawal phase endpoint).
End point description:	The number of participants reaching the end of the treatment withdrawal phase without discontinuing from the study (for any reason) or showing symptom worsening in the physician global assessment of Gastroesophageal Reflux Disease (GERD) symptoms. Based on the severity of symptoms reported by the parent/guardian in IVRS, the investigator provided the overall clinical impression of the patient's GERD-related symptoms over the last 7 days as: None Mild Moderate Severe
End point type	Secondary
End point timeframe:	Treatment withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study)

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	39	41	39	41
Units: Participants	24	21	24	21

Statistical analyses

Statistical analysis title	Analysis of the number of responders
Statistical analysis description:	
Analysis of the number of treatment responders at the end of the double-blind phase	
Comparison groups	Double Blind Esomeprazole v Double Blind Placebo v Double-blind phase esomeprazole v Double-blind phase placebo
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3524
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.524
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.626
upper limit	3.709
Variability estimate	Standard error of the mean
Dispersion value	0.45

Secondary: Physician's Global Assessment (PGA) of Gastroesophageal Reflux Disease (GERD) symptoms (Treatment withdrawal phase endpoint)

End point title	Physician's Global Assessment (PGA) of Gastroesophageal Reflux Disease (GERD) symptoms (Treatment withdrawal phase endpoint)
End point description:	
Percentage of participants with Physician's Global Assessment (PGA) score at the final treatment withdrawal assessment in following categories: None (no symptoms), Mild, Moderate or Severe. The worst post-randomization Physician's Global Assessment (PGA) assessment during double blind phase is taken into account.	
End point type	Secondary
End point timeframe:	
Treatment withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study)	

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	39	41	39	41
Units: Percentage of participants				
number (not applicable)				
None	0	0	0	0
Mild	2.6	7.3	2.6	7.3
Moderate	76.9	78	76.9	78
Severe	20.5	14.6	20.5	14.6

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of Vomiting/regurgitation symptoms as reported by the parent/guardian (Treatment withdrawal phase endpoint)

End point title	Severity of Vomiting/regurgitation symptoms as reported by the parent/guardian (Treatment withdrawal phase endpoint)
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End point description:

Change from baseline in symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, final severity score is the mean severity in the final 7-days, while baseline is the mean severity in the 7-day period up to and including randomization. Changes less than zero indicate improved severity versus baseline. Participants needed baseline measure and one additional post baseline measure to be included in analysis.

End point type	Secondary
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End point timeframe:

Treatment withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study) Change was calculated from baseline to last measure obtained

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	37	40	37	40
Units: Units on a scale				
arithmetic mean (standard deviation)	0.04 (± 0.56)	0.09 (± 0.61)	0.04 (± 0.56)	0.09 (± 0.61)

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of irritability crying/fussing symptoms as reported by the parent/guardian (Treatment withdrawal phase endpoint)

End point title	Severity of irritability crying/fussing symptoms as reported by the parent/guardian (Treatment withdrawal phase endpoint)
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End point description:

Change from baseline in symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, final severity score is the mean severity in the final 7-days, while baseline is the mean severity in the 7-day period up to and including randomization. Changes less than zero indicate improved severity versus baseline. Participants needed baseline measure and one additional post baseline measure to be included in analysis.

End point type	Secondary
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End point timeframe:

Treatment withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study) Change was calculated from baseline to last measure obtained

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	37	40	37	40
Units: Units on a scale				
arithmetic mean (standard deviation)	0.06 (± 0.58)	0.19 (± 0.59)	0.06 (± 0.58)	0.19 (± 0.59)

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of supraesophageal/respiratory disturbances (coughing/wheezing,labored breathing) as reported by parent/guardian (Treatment withdrawal phase endpoint)

End point title	Severity of supraesophageal/respiratory disturbances (coughing/wheezing,labored breathing) as reported by parent/guardian (Treatment withdrawal phase endpoint)
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End point description:

Change from baseline in symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, final severity score is the mean severity in the final 7-days, while baseline is the mean severity in the 7-day period up to and including randomization. Changes less than zero indicate improved severity versus baseline. Participants needed baseline measure and one additional post baseline measure to be included in analysis.

End point type	Secondary
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End point timeframe:

Treatment withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study) Change was calculated from baseline to last measure obtained

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	37	40	37	40
Units: Units on a scale				
arithmetic mean (standard deviation)	0.12 (± 0.48)	0.03 (± 0.58)	0.12 (± 0.48)	0.03 (± 0.58)

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of feeding difficulties reported by parent/guardian (Treatment withdrawal phase endpoint)

End point title	Severity of feeding difficulties reported by parent/guardian (Treatment withdrawal phase endpoint)
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End point description:

Change from baseline in symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, final severity score is the mean severity in the final 7-days, while baseline is the mean severity in the 7-day period up to and including randomization. Changes less than zero indicate improved severity versus baseline. Participants needed baseline measure and one additional post baseline measure to be included in analysis.

End point type	Secondary
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End point timeframe:

Treatment withdrawal phase (up to 4 weeks following randomization, or until earlier discontinuation from the study) Change was calculated from baseline to last measure obtained

End point values	Double Blind Esomeprazole	Double Blind Placebo	Double-blind phase esomeprazole	Double-blind phase placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	37	40	37	40
Units: Units on a scale				
arithmetic mean (standard deviation)	0.09 (± 0.48)	0.1 (± 0.61)	0.09 (± 0.48)	0.1 (± 0.61)

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in Physician's Global Assessment (PGA) following open-label esomeprazole (Open-label phase endpoint)

End point title	Improvement in Physician's Global Assessment (PGA) following open-label esomeprazole (Open-label phase endpoint)
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End point description:

Number of patients who had an improvement of at least one category in the PGA at the end of open-label treatment with esomeprazole compared to baseline. Improvement in PGA was a pre-requisite for randomization into the randomized treatment withdrawal phase. Only patients with PGA at baseline and end of open-label are analyzed here.

End point type	Secondary
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End point timeframe:

Open-label treatment period (2 weeks)

End point values	Open Label Esomeprazole	Open label treatment phase		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	98	98		
Units: Participants	81	81		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of Vomiting/regurgitation symptoms as reported by the parent/guardian (Open-label phase)

End point title	Severity of Vomiting/regurgitation symptoms as reported by the parent/guardian (Open-label phase)			
End point description:	Symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, The score is the mean severity in each 7-day period.			
End point type	Secondary			
End point timeframe:	Open Label phase (Screening plus two weeks)			

End point values	Open Label Esomeprazole	Open label treatment phase		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	98	98		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Screening	1.42 (± 0.76)	1.42 (± 0.76)		
Week 1	1.14 (± 0.67)	1.14 (± 0.67)		
Week 2	1 (± 0.72)	1 (± 0.72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of irritability crying/fussing symptoms as reported by the parent/guardian (Open-label phase endpoint)

End point title	Severity of irritability crying/fussing symptoms as reported by the parent/guardian (Open-label phase endpoint)			
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End point description:

Symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, The score is the mean severity in each 7-day period.

End point type Secondary

End point timeframe:

Open Label Phase (Screening plus two weeks)

End point values	Open Label Esomeprazole	Open label treatment phase		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	98	98		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Screening	1.5 (± 0.67)	1.5 (± 0.67)		
Week 1	1.22 (± 0.68)	1.22 (± 0.68)		
Week 2	1.02 (± 0.74)	1.02 (± 0.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of supraesophageal/respiratory disturbances (coughing/wheezing,labored breathing) as reported by parent/guardian (Open-label phase endpoint)

End point title Severity of supraesophageal/respiratory disturbances (coughing/wheezing,labored breathing) as reported by parent/guardian (Open-label phase endpoint)

End point description:

Symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, The score is the mean severity in each 7-day period.

End point type Secondary

End point timeframe:

Open Label Phase (Screening plus two weeks)

End point values	Open Label Esomeprazole	Open label treatment phase		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	98	98		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Screening	0.54 (± 0.69)	0.54 (± 0.69)		
Week 1	0.48 (± 0.61)	0.48 (± 0.61)		
Week 2	0.44 (± 0.69)	0.44 (± 0.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of feeding difficulties as reported by parent/guardian (Open-label phase endpoint)

End point title	Severity of feeding difficulties as reported by parent/guardian (Open-label phase endpoint)
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End point description:

Symptom severity (Severity is scored as 0-4 [none, mild moderate, severe]). For each participant, The score is the mean severity in each 7-day period.

End point type	Secondary
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End point timeframe:

Open Label Phase (Screening plus two weeks)

End point values	Open Label Esomeprazole	Open label treatment phase		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	98	98		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Screening	1.16 (± 0.76)	1.16 (± 0.76)		
Week 1	0.94 (± 0.71)	0.94 (± 0.71)		
Week 2	0.83 (± 0.76)	0.83 (± 0.76)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During openlabel phase 2 weeks and doubleblind randomised treatment 4 weeks.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	11.0
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Reporting groups

Reporting group title	Open-label phase
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Reporting group description:

Open-label daily esomeprazole (2.5mg, 5mg or 10mg daily during open-label phase of the study, according to baseline weight).

Reporting group title	Double Blind Esomeprazole
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Reporting group description:

Eligible participants from the Open Label phase were randomized to the the double blind withdrawal phase.

Reporting group title	Double Blind Placebo
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Reporting group description:

Eligible participants from the Open Label phase were randomized to the the double blind withdrawal phase.

Serious adverse events	Open-label phase	Double Blind Esomeprazole	Double Blind Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 98 (4.08%)	3 / 39 (7.69%)	0 / 41 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Poor Peripheral Circulation			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 98 (0.00%)	1 / 39 (2.56%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	0 / 98 (0.00%)	1 / 39 (2.56%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchospasm alternative dictionary used: MedDRA 11.0 subjects affected / exposed	0 / 98 (0.00%)	1 / 39 (2.56%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Chlamydial Infection alternative dictionary used: MedDRA 11.0 subjects affected / exposed	1 / 98 (1.02%)	1 / 39 (2.56%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Syncytial Virus Bronchiolitis alternative dictionary used: MedDRA 11.0 subjects affected / exposed	0 / 98 (0.00%)	1 / 39 (2.56%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotavirus Infection alternative dictionary used: MedDRA 11.0 subjects affected / exposed	1 / 98 (1.02%)	0 / 39 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection alternative dictionary used: MedDRA 11.0 subjects affected / exposed	1 / 98 (1.02%)	0 / 39 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure To Thrive alternative dictionary used: MedDRA 11.0 subjects affected / exposed	1 / 98 (1.02%)	0 / 39 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Open-label phase	Double Blind Esomeprazole	Double Blind Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 98 (47.96%)	23 / 39 (58.97%)	27 / 41 (65.85%)
General disorders and administration site conditions			
Pyrexia			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 98 (4.08%)	5 / 39 (12.82%)	3 / 41 (7.32%)
occurrences (all)	47	23	27
Gastrointestinal disorders			
Constipation			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 98 (1.02%)	1 / 39 (2.56%)	4 / 41 (9.76%)
occurrences (all)	47	23	27
Diarrhoea			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	3 / 98 (3.06%)	4 / 39 (10.26%)	2 / 41 (4.88%)
occurrences (all)	47	23	27
Flatulence			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	1 / 98 (1.02%)	2 / 39 (5.13%)	1 / 41 (2.44%)
occurrences (all)	47	23	27
Teething			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	4 / 98 (4.08%)	3 / 39 (7.69%)	2 / 41 (4.88%)
occurrences (all)	47	23	27
Vomiting			
alternative dictionary used: MedDRA 11.0			
subjects affected / exposed	2 / 98 (2.04%)	2 / 39 (5.13%)	2 / 41 (4.88%)
occurrences (all)	47	23	27
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 11.0			

<p>subjects affected / exposed occurrences (all)</p> <p>Pharyngolaryngeal Pain alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)</p>	<p>3 / 98 (3.06%) 47</p> <p>0 / 98 (0.00%) 47</p>	<p>3 / 39 (7.69%) 23</p> <p>2 / 39 (5.13%) 23</p>	<p>4 / 41 (9.76%) 27</p> <p>0 / 41 (0.00%) 27</p>
<p>Skin and subcutaneous tissue disorders Rash alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)</p>	<p>1 / 98 (1.02%) 47</p>	<p>2 / 39 (5.13%) 23</p>	<p>1 / 41 (2.44%) 27</p>
<p>Infections and infestations Bronchitis alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)</p> <p>Nasopharyngitis alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)</p> <p>Otitis Media alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)</p> <p>Rhinitis alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)</p> <p>Upper Respiratory Tract Infection alternative dictionary used: MedDRA 11.0 subjects affected / exposed occurrences (all)</p> <p>Ear Infection alternative dictionary used: MedDRA 11.0</p>	<p>4 / 98 (4.08%) 47</p> <p>2 / 98 (2.04%) 47</p> <p>2 / 98 (2.04%) 47</p> <p>3 / 98 (3.06%) 47</p> <p>5 / 98 (5.10%) 47</p>	<p>3 / 39 (7.69%) 23</p> <p>4 / 39 (10.26%) 23</p> <p>2 / 39 (5.13%) 23</p> <p>4 / 39 (10.26%) 23</p> <p>6 / 39 (15.38%) 23</p>	<p>2 / 41 (4.88%) 27</p> <p>3 / 41 (7.32%) 27</p> <p>1 / 41 (2.44%) 27</p> <p>3 / 41 (7.32%) 27</p> <p>4 / 41 (9.76%) 27</p>

subjects affected / exposed	0 / 98 (0.00%)	2 / 39 (5.13%)	1 / 41 (2.44%)
occurrences (all)	47	23	27

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported