Clinical trial results:
A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of esomeprazole once daily for the treatment of gastroesophageal reflux disease (GERD) in neonatal patients, including premature and up to 1 month corrected age

Summary

EudraCT number	2006-002001-31
Trial protocol	DE GB Outside EU/EEA
Global end of trial date	14 April 2009

Results information

Result version number	v1 (current)
This version publication date	15 July 2016
First version publication date	15 July 2016

Trial information

Trial identification

Sponsor protocol code	D9614C00004

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	1800 Concord Pike, Wilmington, United States, 19850-5437
Public contact	ClinicalTrialTransparency, Astrazeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Marta Illueca, MD, FAAP, AstraZeneca, 1 3028851487, 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	14 April 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 April 2009
Global end of trial reached?	Yes
Global end of trial date	14 April 2009
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the difference between esomeprazole and placebo in the treatment of signs and symptoms of GERD as observed by 8-hour video and cardiorespiratory monitoring in neonatal patients.

Protection of trial subjects:

There was no data monitoring board; however a Data and Safety Monitoring Plan was available for this study. The Clinical Study Physician monitored the SAEs on a continuous basis. A Drug Safety Physician reviewed all serious unexpected reports that were assessed by the investigator to be causally related to study drug within 15 days from AstraZeneca notification of the event. In addition, a safety subteam, consisting of the AstraZeneca Drug Safety Physician(s), Drug Safety Scientist, Clinical Study Physician, Study Delivery, and other Clinical Study Team members met on a regular basis to review blinded study data regarding SAEs, non-serious AEs, discontinuation criteria, clinically significant laboratory data, and vital signs. The safety subteam could request additional evaluations at their discretion from the study center.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Australia: 31
Worldwide total number of subjects	61
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	23
Infants and toddlers (28 days-23 months)	38

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 either full term or those with a gestational age or post-conceptual age ³28 to 44 weeks, and who were inpatients suspected of having the following clinical findings: any 2 (either individually or in any combination) of (1) apnea +/- bradycardia +/- oxygen desaturations, (2) vomiting/gagging, (3) irritability/pain at least every second

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	61
Number of subjects completed	52

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 6
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Study drug was defrosted: 1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Esomeprazole

Arm description:

Esomeprazole 0.5 mg/kg/ day once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.

Arm type	Experimental
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

0.5mg/kg/day administered by oral gavage or nippling

Arm title	Placebo

Arm description:

Placebo once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

0.5mg/kg/day by oral gavage or by nippling

Number of subjects in period 1[1]	Esomeprazole	Placebo
Started	26	26
Completed	25	26
Not completed	1	0
Consent withdrawn by subject	1	-

Notes:

[1] - 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: 61 patients were screened, 52 randomized (=>6 were incorrect enrolled, 2 voluntary discontinuation by parent/guardian, 1 other reason). The baseline numbers reflect the randomized patients.

Period 2

Period 2 title	Study completion to safety follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Esomeprazole

Arm description:

Esomeprazole 0.5 mg/kg/ day once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo

Arm description:

Placebo once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Esomeprazole	Placebo
Started	25	26
Completed	25	25
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Esomeprazole
Reporting group description:	
Esomeprazole 0.5 mg/kg/ day once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	

Reporting group values	Esomeprazole	Placebo	Total
Number of subjects	26	26	52
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	7	9	16
Infants and toddlers (28 days-23 months)	19	17	36
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 | Units: Days			
arithmetic mean	46.5	46.5	
standard deviation	± 30.3	± 31.2	-
Gender, Male/Female Units: Participants			
Female	15	15	30
Male	11	11	22

End points

End points reporting groups

Reporting group title	Esomeprazole
Reporting group description:	
Esomeprazole 0.5 mg/kg/ day once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	
Reporting group title	Esomeprazole
Reporting group description:	
Esomeprazole 0.5 mg/kg/ day once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	

Primary: Change from baseline in normalized number of GERD events observed from video and cardiorespiratory monitoring

End point title	Change from baseline in normalized number of GERD events observed from video and cardiorespiratory monitoring
End point description:	
The number of events are normalized prior to summary to correspond to a complete 8-hour monitoring period. Only patients with data at both baseline and final assessment are included.	
End point type	Primary
End point timeframe:	
Baseline and end of treatment (10-14 days)	

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: Mean Number of Events				
arithmetic mean (standard deviation)	-28.01 (± 77.7)	-24.79 (± 44.25)		

Statistical analyses

Statistical analysis title	ANCOVA of change from baseline
Statistical analysis description:	
change from baseline in log-transformed events, adjusting for treatment and baseline	
Comparison groups	Esomeprazole v Placebo

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9217
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.18
upper limit	14.87

Secondary: Change from baseline in normalized number of GERD events during video and cardiorespiratory monitoring associated with acid reflux

End point title	Change from baseline in normalized number of GERD events during video and cardiorespiratory monitoring associated with acid reflux

End point description:

Event considered associated with reflux if start time of GERD sign/symptom is within 2 minutes of start time of acid reflux. The number of events are normalized prior to summary to correspond to a complete 8-hour monitoring period. Only patients with data at both baseline and final assessment are included.

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	25		
Units: Mean Number of Events				
arithmetic mean (standard deviation)	-21.79 (± 40.37)	-13.49 (± 32.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in number of reflux episodes (acid or non-acid)

End point title	Change from baseline in number of reflux episodes (acid or non-acid)

End point description:

Number of reflux episodes based on 24-hour impedance monitoring data

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Mean Number of Episodes				
arithmetic mean (standard deviation)	-14.55 (± 49.58)	6.27 (± 28.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in number of acidic reflux episodes

End point title	Change from baseline in number of acidic reflux episodes
End point description:	
Number of reflux episodes (pH<4.0) based on 24-hour impedance monitoring data	
End point type	Secondary
End point timeframe:	
Baseline and end of treatment (10-14 days)	

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Mean Number of Episodes				
arithmetic mean (standard deviation)	-37.75 (± 32.38)	2.36 (± 18.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in number of weakly acidic reflux episodes

End point title	Change from baseline in number of weakly acidic reflux episodes
End point description:	
Number of reflux episodes (pH 4.0-6.9) based on 24-hour impedance monitoring data	
End point type	Secondary
End point timeframe:	
Baseline and end of treatment (10-14 days)	

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Mean Number of Episodes				
arithmetic mean (standard deviation)	22.6 (± 45.17)	3.59 (± 21.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in number of non acidic reflux episodes

End point title	Change from baseline in number of non acidic reflux episodes

End point description:

Number of reflux episodes (pH>=7.0) based on 24-hour impedance monitoring data

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Mean Number of Episodes				
arithmetic mean (standard deviation)	0.6 (± 1.14)	0.32 (± 0.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in number of liquid acidic reflux episodes

End point title	Change from baseline in number of liquid acidic reflux episodes

End point description:

Number of reflux episodes based on 24-hour impedance monitoring data

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Mean Number of Episodes				
arithmetic mean (standard deviation)	-19 (± 52.03)	3.05 (± 31.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in number of mixed gas/liquid acidic reflux episodes

End point title	Change from baseline in number of mixed gas/liquid acidic reflux episodes

End point description:

Number of reflux episodes based on 24-hour impedance monitoring data

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Mean Number of Episodes				
arithmetic mean (standard deviation)	4.45 (± 17.44)	3.27 (± 13.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean bolus clearance time

End point title	Change from baseline in mean bolus clearance time

End point description:

Based on 24-hour impedance monitoring data

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Seconds				
arithmetic mean (standard deviation)	-0.29 (± 24.56)	-4.05 (± 25.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean acid clearance time

End point title	Change from baseline in mean acid clearance time

End point description:

Based on 24-hour impedance monitoring data

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Seconds				
arithmetic mean (standard deviation)	5.93 (± 64.32)	-6.36 (± 45.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage time with pH<4.0

End point title	Change from baseline in percentage time with pH<4.0

End point description:

Percentage time with pH<4 during 24-hour pH monitoring

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Percentage				
arithmetic mean (standard deviation)	-10.73 (± 12.63)	2.24 (± 12.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in percentage time with pH within 4.0-6.9

End point title	Change from baseline in percentage time with pH within 4.0-6.9

End point description:

Percentage time with pH 4.0-6.9 during 24-hour pH monitoring

End point type	Secondary

End point timeframe:

Baseline and end of treatment (10-14 days)

End point values	Esomeprazole	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	22		
Units: Percentage				
arithmetic mean (standard deviation)	9.84 (± 12.64)	-2.6 (± 12.18)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During enrollment and randomized treatment period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	
Reporting group title	Esomeprazole
Reporting group description:	
Esomeprazole 0.5 mg/kg/ day once daily 30 minutes prior to a morning feeding during 15 days by oral gavage (using a nasogastric or orogastric tube) or by nippling.	

Serious adverse events	Placebo	Esomeprazole	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 26 (11.54%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Inappropriate Device Signal Detection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradycardia Neonatal			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
alternative dictionary used: MedDRA 12.0			

subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Infantile Apnoeic Attack			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Esomeprazole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 26 (26.92%)	6 / 26 (23.08%)	
Investigations			
Oxygen Saturation Decreased			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	2 / 26 (7.69%)	
occurrences (all)	5	2	
Cardiac disorders			
Cyanosis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia Neonatal			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Oedema Peripheral			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

Ear and labyrinth disorders			
Deafness Neurosensory			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Retinopathy Of Prematurity			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	
occurrences (all)	2	0	
Flatulence			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	1 / 26 (3.85%)	
occurrences (all)	1	1	
Gastrooesophageal Reflux Disease			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	
Diarrhoea			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Neonatal Infection			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	
occurrences (all)	0	1	

Bronchiolitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	
Urinary Tract Infection Neonatal			
alternative dictionary used: MedDRA 12.0			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	
occurrences (all)	1	0	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Because of recruitment challenges, only 52 patients out of the planned 90 were enrolled.

Notes: