Clinical trial results:
A Phase 2 Multicenter, 36-Week Study to Assess the Safety and Effectiveness of Daily Oral Administration of Dexlansoprazole Delayed-Release Capsules for Healing of Erosive Esophagitis and Maintenance of Healed Erosive Esophagitis and Relief of Heartburn, in Adolescent Subjects Aged 12 to 17 Years

Summary

EudraCT number	2012-001681-15
Trial protocol	HU BE PT IT
Global end of trial date	10 November 2014

Results information

Result version number	v1 (current)
This version publication date	04 March 2016
First version publication date	17 June 2015

Trial information

Trial identification

Sponsor protocol code	TAK-390MR_207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01642615
WHO universal trial number (UTN)	U1111-1128-6117

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas, Inc.
Sponsor organisation address	One Takeda Parkway, Deerfield, United States, 60015
Public contact	Study Registration Call Centre, Takeda Global Research & Development Center, Inc., 001 877-825-3327, medicalinformation@tpna.com
Scientific contact	Study Registration Call Centre, Takeda Global Research & Development Center, Inc., 001 877-825-3327, medicalinformation@tpna.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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	13 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2014
Global end of trial reached?	Yes
Global end of trial date	10 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess the safety and effectiveness of treatment with once daily oral administration of dexlansoprazole delayed-release capsules in adolescents with erosive esophagitis (EE) and for maintenance of healed EE and relief of heartburn.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2012
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 States: 22
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Portugal: 4
Worldwide total number of subjects	62
EEA total number of subjects	38

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)	0
Children (2-11 years)	0
Adolescents (12-17 years)	62
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 18 investigative sites in Mexico, Poland, Portugal and the United States from 22 June 2012 (first participant to sign the informed consent) to 10 November 2014.

Pre-assignment

Screening details:

63 adolescents with a diagnosis of erosive esophagitis (EE) were enrolled in the dexlansoprazole delayed release 60 mg capsules open label phase. One participant did not take study drug. Participants with healed EE were randomized into one of 2 treatment groups: dexlansoprazole delayed release 30 mg capsules or placebo in the maintenance phase

Pre-assignment period milestones

Number of subjects started	63[1]
Number of subjects completed	62

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not receive treatment: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1 participant did not receive study medication and therefore was not accounted for in the worldwide number enrolled.

Period 1

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

Arms

Arm title	Healing Phase: Dexlansoprazole 60 mg

Arm description:

Dexlansoprazole 60 mg delayed-release capsules, orally, once daily for up to 8 weeks.

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

Dosage and administration details:

60 mg delayed release capsules

Number of subjects in period 1	Healing Phase: Dexlansoprazole 60 mg
Started	62
Safety Analysis Set	62
Completed	58
Not completed	4
Pretreatment Event/Adverse Event	1
Major Protocol Deviation	1
Voluntary Withdrawal	1
Lost to follow-up	1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance Phase: Dexlansoprazole 30 mg

Arm description:

Participants who are healed at Week 8 will be randomized to receive 30 mg dexlansoprazole delayed-release capsules, orally, once daily for up to 16 weeks.

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

Dosage and administration details:

delayed release capsules

Arm title	Maintenance Phase: Placebo

Arm description:

Participants who are healed at Week 8 will be randomized to receive dexlansoprazole placebo-matching capsules, orally, once daily for up to 16 weeks.

Arm type	Placebo
Investigational medicinal product name	placebo-matching dexlansoprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

dexlansoprazole placebo-matching capsules

Number of subjects in period 2[2]	Maintenance Phase: Dexlansoprazole 30 mg	Maintenance Phase: Placebo
Started	25	26
Completed	18	20
Not completed	7	6
Pretreatment Event/Adverse Event	1	-
Voluntary Withdrawal	5	2
Requires Treatment with Another Drug	-	1
Lack of efficacy	1	3

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Only participants with healing of EE at the end of the Open-Label Phase were eligible to participate in the Maintenance Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Healing Phase: Dexlansoprazole 60 mg
Reporting group description:	
Dexlansoprazole 60 mg delayed-release capsules, orally, once daily for up to 8 weeks.	

Reporting group values	Healing Phase: Dexlansoprazole 60 mg	Total	
Number of subjects	62	62	
Age categorical Units: Subjects			
12 to 14 years	24	24	
15 to 17 years	38	38	
Age continuous Units: years			
arithmetic mean	14.8		
standard deviation	± 1.64	-	
Gender categorical Units: Subjects			
Female	24	24	
Male	38	38	
Race/Ethnicity, Customized Units: Subjects			
Not Hispanic or Latino	16	16	
Hispanic or Latino	6	6	
Not Collected outside the United States	40	40	
Race/Ethnicity, Customized Units: Subjects			
Black or African American	1	1	
White	61	61	
Smoking Classification Units: Subjects			
Never smoked	61	61	
Current smoker	1	1	
Ex-smoker	0	0	
Helicobacter pylori (H. pylori) Status Units: Subjects			
Positive	0	0	
Negative	61	61	
Unknown	1	1	
Erosive Esophagitis Present Units: Subjects			
Yes	62	62	
No	0	0	
[Baseline EE Grade (LA Classification)]			
A=1 (or more) mucosal break 5 mm or less that does not extend between the tops of two mucosal folds, B=1 (or more) mucosal break more than 5 mm-long that does not extend between the tops of two			

mucosal folds, C=1 (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves less than 75% of the circumference and D=1 (or more) mucosal break that involves at least 75% of the esophageal circumference.			
Units: Subjects			
Grade A	34	34	
Grade B	26	26	
Grade C	1	1	
Grade D	1	1	
Region of Enrollment Units: Subjects			
United States	22	22	
Portugal	4	4	
Poland	34	34	
Mexico	2	2	
Height Units: cm			
arithmetic mean	165.5		
standard deviation	± 9.68	-	
Weight Units: kg			
arithmetic mean	61.86		
standard deviation	± 17.06	-	
Body Mass index (BMI)			
BMI is calculated using the weight and height.			
Units: kg/m^2			
arithmetic mean	22.34		
standard deviation	± 5.086	-	

End points

End points reporting groups

Reporting group title	Healing Phase: Dexlansoprazole 60 mg
Reporting group description:	
Dexlansoprazole 60 mg delayed-release capsules, orally, once daily for up to 8 weeks.	
Reporting group title	Maintenance Phase: Dexlansoprazole 30 mg
Reporting group description:	
Participants who are healed at Week 8 will be randomized to receive 30 mg dexlansoprazole delayed-release capsules, orally, once daily for up to 16 weeks.	
Reporting group title	Maintenance Phase: Placebo
Reporting group description:	
Participants who are healed at Week 8 will be randomized to receive dexlansoprazole placebo-matching capsules, orally, once daily for up to 16 weeks.	

Primary: Percentage of Participants Who Experience Each Treatment Emergent Adverse Event Experienced by ≥5% of Participants During the 8-week Healing Treatment Period

End point title	Percentage of Participants Who Experience Each Treatment Emergent Adverse Event Experienced by ≥5% of Participants During the 8-week Healing Treatment Period[1]
End point description:	
An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A Treatment Emergent Adverse Event (TEAE) is defined as an Adverse Event (AE) that starts or worsens on or after Study Day 1, and no more than 30 days after the last dose.	
End point type	Primary
End point timeframe:	
8 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not done.

End point values	Healing Phase: Dexlansoprazole 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: percentage of participants				
number (not applicable)				
Diarrhoea	6.5			
Nasopharyngitis	6.5			
Headache	12.9			
Oropharyngeal pain	8.1			

Statistical analyses

No statistical analyses for this end point

Primary: Percent of Participants Who Experience Each Treatment Emergent Adverse Event Experienced by ≥5% of Participants During the 16-week Maintenance Treatment Period

End point title	Percent of Participants Who Experience Each Treatment Emergent Adverse Event Experienced by ≥5% of Participants During the 16-week Maintenance Treatment Period[2]

End point description:

An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not it is considered related to the drug. A Treatment Emergent Adverse Event (TEAE) is defined as an Adverse Event (AE) that starts or worsens on or after Study Day 1, and no more than 30 days after the last dose.

End point type	Primary

End point timeframe:

From Week 8 to Week 24

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis not done.

End point values	Maintenance Phase: Dexlansoprazole 30 mg	Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: percentage of participants				
number (not applicable)				
Abdominal pain	12	11.5		
Abdominal pain upper	4	7.7		
Erosive oesophagitis	4	7.7		
Diarrhoea	0	7.7		
Pyrexia	0	7.7		
Nasopharyngitis	12	15.4		
Pharyngitis	12	0		
Sinusitis	12	0		
Upper respiratory tract infection	8	0		
Bronchitis	8	3.8		
Headache	24	15.4		
Insomnia	8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Healing of Erosive Esophagitis (EE) by Week 8

End point title	Percentage of Participants With Healing of Erosive Esophagitis (EE) by Week 8

End point description:

Healing of EE was assessed by endoscopy.

End point type	Secondary

End point timeframe:

8 weeks

End point values	Healing Phase: Dexlansoprazole 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: percentage of participants				
number (confidence interval 95%)	87.9 (76.7 to 95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Maintain Healing of EE From Week 8 to Week 24

End point title	Percentage of Participants Who Maintain Healing of EE From Week 8 to Week 24

End point description:

Percentage of participants who maintain healing of EE from Week 8 to Week 24 among the patients who were healed at Week 8 as assessed by endoscopy.

End point type	Secondary

End point timeframe:

From Week 8 to Week 24

End point values	Maintenance Phase: Dexlansoprazole 30 mg	Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: percentage of participants				
number (confidence interval 95%)	81.8 (59.7 to 94.8)	58.3 (36.6 to 77.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Days With Neither Daytime Nor Nighttime Heartburn Over the First 8 Weeks of Treatment

End point title	Percent of Days With Neither Daytime Nor Nighttime Heartburn Over the First 8 Weeks of Treatment

End point description:

Percent of days with neither daytime nor nighttime heartburn over the first 8 weeks of treatment as assessed by electronic daily diary. The percent of days with neither daytime or nighttime heartburn = (total number of days that are heartburn free)/(total number of days for which either a daytime or nighttime result is marked) x 100%.

End point type	Secondary

End point timeframe:

8 weeks

End point values	Healing Phase: Dexlansoprazole 60 mg			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: percent of days				
arithmetic mean (standard deviation)	59.6 (± 30.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Days With Neither Daytime Nor Nighttime Heartburn Over Weeks 8 to 24

End point title	Percent of Days With Neither Daytime Nor Nighttime Heartburn Over Weeks 8 to 24

End point description:

The percent of days with neither daytime nor nighttime heartburn over Weeks 8 to 24 as assessed by electronic daily diary among the participants who were healed at Week 8. The percent of days with neither daytime or nighttime heartburn = (total number of days that are heartburn free)/(total number of days for which either a daytime or nighttime result is marked) x 100%.

End point type	Secondary

End point timeframe:

Weeks 8 to 24

End point values	Maintenance Phase: Dexlansoprazole 30 mg	Maintenance Phase: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	26		
Units: percent of days				

arithmetic mean (standard deviation)	76.7 (± 29.82)	68.9 (± 26.04)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 24 Weeks

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Healing Phase: Dexlansoprazole 60 mg

Reporting group description:

Dexlansoprazole 60 mg delayed-release capsules, orally, once daily for up to 8 weeks.

Reporting group title	Maintenance Phase: Dexlansoprazole 30 mg

Reporting group description:

Participants who are healed at Week 8 will be randomized to receive 30 mg dexlansoprazole delayed-release capsules, orally, once daily for up to 16 weeks.

Reporting group title	Maintenance Phase: Placebo

Reporting group description:

Participants who are healed at Week 8 will be randomized to receive dexlansoprazole placebo-matching capsules, orally, once daily for up to 16 weeks.

Serious adverse events	Healing Phase: Dexlansoprazole 60 mg	Maintenance Phase: Dexlansoprazole 30 mg	Maintenance Phase: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 62 (1.61%)	2 / 25 (8.00%)	1 / 26 (3.85%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 62 (0.00%)	1 / 25 (4.00%)	0 / 26 (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
Gastrointestinal disorders			
Erosive oesophagitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 25 (4.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			

Substance abuse			
subjects affected / exposed	1 / 62 (1.61%)	0 / 25 (0.00%)	0 / 26 (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
Infections and infestations			
H1N1 influenza			
subjects affected / exposed	0 / 62 (0.00%)	0 / 25 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Healing Phase: Dexlansoprazole 60 mg	Maintenance Phase: Dexlansoprazole 30 mg	Maintenance Phase: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 62 (38.71%)	14 / 25 (56.00%)	11 / 26 (42.31%)
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 62 (12.90%)	6 / 25 (24.00%)	4 / 26 (15.38%)
occurrences (all)	9	9	7
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 62 (0.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 62 (4.84%)	3 / 25 (12.00%)	3 / 26 (11.54%)
occurrences (all)	4	3	3
Abdominal pain upper			
subjects affected / exposed	1 / 62 (1.61%)	1 / 25 (4.00%)	2 / 26 (7.69%)
occurrences (all)	1	1	2
Diarrhoea			
subjects affected / exposed	4 / 62 (6.45%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	5	0	2
Erosive oesophagitis			

subjects affected / exposed	0 / 62 (0.00%)	0 / 25 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	5 / 62 (8.06%)	1 / 25 (4.00%)	1 / 26 (3.85%)
occurrences (all)	5	1	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 62 (1.61%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	2	3	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 62 (1.61%)	2 / 25 (8.00%)	1 / 26 (3.85%)
occurrences (all)	1	2	1
Nasopharyngitis			
subjects affected / exposed	4 / 62 (6.45%)	3 / 25 (12.00%)	4 / 26 (15.38%)
occurrences (all)	5	3	4
Pharyngitis			
subjects affected / exposed	3 / 62 (4.84%)	3 / 25 (12.00%)	0 / 26 (0.00%)
occurrences (all)	3	3	0
Sinusitis			
subjects affected / exposed	1 / 62 (1.61%)	3 / 25 (12.00%)	0 / 26 (0.00%)
occurrences (all)	1	3	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 62 (3.23%)	2 / 25 (8.00%)	0 / 26 (0.00%)
occurrences (all)	2	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 April 2012	1. In order to decrease the number of required biopsies and to allow flexibility for standard of care, the duodenal biopsies were removed and a serologic test was specified for use to screen for celiac disease. 2. To ensure compliance with local ethical and regulatory requirements, P450 CYP2C19 genotype testing was not required when local regulations prohibited it. Storage and use of samples were also clarified.
25 April 2013	1. In order to allow for a pre-screening endoscopy to be used for eligibility if all other protocol requirements were met, an allowance was made for the screening endoscopy to have been performed within 1 week prior to signing the informed consent/assent form. 2. In order to add flexibility for the time allowed for screening, a window of 5 days was added to the Screening Period. 3. The number of biopsies required at Screening was reduced in order to increase flexibility and to be aligned with standard of care for biopsy collection. 4. H. pylori test procedures were clarified, particularly for instances in which pre-screening endoscopy results were used to determine eligibility. 5. Exclusion criterion was updated regarding HIV status. 6. Exclusion criterion regarding alcohol use was updated to account for regional differences. 7. Inclusion and exclusion criterion were updated to account for allowance of endoscopies done prior to Screening and other H. pylori test methods. 8. Alternate dosing options were added to accommodate children who could not swallow the capsule.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported