Clinical trial results:
A Randomized, Double-Blind, Proof-of-Concept, Phase 2 Study to Evaluate the Efficacy and Safety of Once Daily Oral Vonoprazan 20 mg or Vonoprazan 40 mg Compared to Esomeprazole 40 mg for the Treatment of Subjects With Symptomatic Gastro-Esophageal Reflux Disease Who have a Partial Response Following Treatment with a High Dose of Proton Pump Inhibitor

Summary

EudraCT number	2015-001154-14
Trial protocol	GB EE BE CZ
Global end of trial date	12 October 2018

Results information

Result version number	v1 (current)
This version publication date	11 October 2019
First version publication date	11 October 2019

Trial information

Trial identification

Sponsor protocol code	Vonoprazan-2001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02743949
WHO universal trial number (UTN)	U1111-1172-2373

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Europe Ltd
Sponsor organisation address	61 Aldwych, WC2B 4AE, London, United Kingdom,
Public contact	Medical Director, Takeda, +1 877-825-3327, trialdisclosures@takeda.com
Scientific contact	Medical Director, Takeda, +1 877-825-3327, clinicaltrialregistry@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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the effect of vonoprazan compared to esomeprazole for preventing heartburn symptoms over a 4-week treatment period in participants who have a partial response to treatment with esomeprazole.

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	14 July 2016
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	Belgium: 1
Country: Number of subjects enrolled	Bulgaria: 177
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	Estonia: 11
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	256
EEA total number of subjects	256

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)	0

Adults (18-64 years)	193
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 33 investigative sites in Belgium, Bulgaria, Czech Republic, Estonia, Poland and United Kingdom from 14 July 2014 to 12 October 2018.

Pre-assignment

Screening details:

Participants with a symptomatic gastro-esophageal reflux disease who have a partial response following treatment with a high dose of proton pump inhibitor were enrolled in a 1:1:1 ratio to receive esomeprazole 40 mg, vonoprazan 20 mg, or vonoprazan 40 mg.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Esomeprazole 40 mg

Arm description:

Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by esomeprazole 40 mg, over-encapsulated tablets, orally, once daily for 4 weeks during the active treatment period.

Arm type	Active comparator
Investigational medicinal product name	Esomeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Esomeprazole over-encapsulated tablets

Arm title	Vonoprazan 20 mg

Arm description:

Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by vonoprazan 20 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the treatment period.

Arm type	Experimental
Investigational medicinal product name	Vonoprazan
Investigational medicinal product code	
Other name	TAK-438
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Vonoprazan over-encapsulated capsules

Arm title	Vonoprazan 40 mg

Arm description:

Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by

vonoprazan 40 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the active treatment period.

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

Dosage and administration details:

Vonoprazan over-encapsulated capsules

Number of subjects in period 1	Esomeprazole 40 mg	Vonoprazan 20 mg	Vonoprazan 40 mg
Started	86	85	85
Completed	82	84	82
Not completed	4	1	3
Voluntary Withdrawal	2	1	-
Adverse event, non-fatal	-	-	2
Significant Protocol Deviation	2	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Esomeprazole 40 mg
Reporting group description:	
Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by esomeprazole 40 mg, over-encapsulated tablets, orally, once daily for 4 weeks during the active treatment period.	
Reporting group title	Vonoprazan 20 mg
Reporting group description:	
Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by vonoprazan 20 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the treatment period.	
Reporting group title	Vonoprazan 40 mg
Reporting group description:	
Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by vonoprazan 40 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the active treatment period.	

Reporting group values	Esomeprazole 40 mg	Vonoprazan 20 mg	Vonoprazan 40 mg
Number of subjects	86	85	85
Age categorical Units: Subjects			
Adults (18-64 years)	63	63	67
From 65-84 years	23	22	18
Age Continuous Units: years			
arithmetic mean	53.9	52.0	51.8
standard deviation	± 13.94	± 14.67	± 14.09
Sex: Female, Male Units: Subjects			
Female	48	53	51
Male	38	32	34
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	0	1	0
White	86	84	83
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Smoking Status Units: Subjects			
Participant has never smoked	50	53	53
Participant is a current smoker	21	23	22
Participant is an ex-smoker	15	9	10
Alcohol Classification			

Units: Subjects			
Participant has never drunk	57	49	54
Participant is a current drinker	27	33	30
Participant is an ex-drinker	2	3	1
Alcohol Use Units: Subjects			
Less than 21 units of alcohol per week	27	33	30
Missing	59	52	55
Caffeine Consumption Units: Subjects			
Consumed caffeine	60	67	68
Did not consume caffeine	26	18	17
Is Erosive Esophagitis Present? Units: Subjects			
Present	30	28	17
Not present	56	57	68
If Yes, Grade of Erosive Esophagitis Units: Subjects			
Grade 0	0	1	1
Grade A	30	27	16
Not graded	56	57	68
Did the Endoscopist Visualize Findings Suggestive of Eosinophilic Esophagitis? Units: Subjects			
Not Visualised	86	85	85
H Pylori Status Units: Subjects			
Positive	8	13	8
Negative	78	72	76
Not determined	0	0	1
Region of Enrollment Units: Subjects			
Belgium	0	1	0
Bulgaria	61	55	61
Czech Republic	14	16	10
Estonia	2	5	4
Poland	8	7	7
United Kingdom	1	1	3
Height Units: centimeters (cm)			
arithmetic mean	169.9	168.5	168.1
standard deviation	± 9.17	± 9.07	± 7.81
Weight Units: kilograms (kg)			
arithmetic mean	78.78	77.46	75.81
standard deviation	± 17.003	± 16.353	± 16.126
Body Mass Index (BMI)			
Body Mass Index=weight (kg)/[height (m)^2]			
Units: kg per square meter (kg/m^2)			
arithmetic mean	27.13	27.21	26.76
standard deviation	± 4.611	± 4.854	± 5.076

Hospital Anxiety and Depression Scale (HADS) Anxiety Total			
HADS-A and HADS-D are 7-item subscales that measure the presence and severity of anxiety and depression symptoms, respectively, on a scale of 0 to 3. Total scores ≤ 7: no clinically relevant symptoms; 8 - 10: mild symptoms; 11 - 14: moderate symptoms; and ≥15 (maximum 21): more severe symptoms.			
Units: score on scale			
arithmetic mean	6.5	6.2	7.0
standard deviation	± 3.81	± 3.38	± 3.78
Depression Total			
Units: score on scale			
arithmetic mean	5.9	6.0	6.2
standard deviation	± 3.62	± 3.50	± 3.99

Reporting group values	Total		
Number of subjects	256		
Age categorical			
Units: Subjects			
Adults (18-64 years)	193		
From 65-84 years	63		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	152		
Male	104		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	1		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	1		
White	253		
More than one race	0		
Unknown or Not Reported	0		
Smoking Status			
Units: Subjects			
Participant has never smoked	156		
Participant is a current smoker	66		
Participant is an ex-smoker	34		
Alcohol Classification			
Units: Subjects			
Participant has never drunk	160		
Participant is a current drinker	90		
Participant is an ex-drinker	6		
Alcohol Use			
Units: Subjects			
Less than 21 units of alcohol per week	90		
Missing	166		

Caffeine Consumption Units: Subjects			
Consumed caffeine	195		
Did not consume caffeine	61		
Is Erosive Esophagitis Present? Units: Subjects			
Present	75		
Not present	181		
If Yes, Grade of Erosive Esophagitis Units: Subjects			
Grade 0	2		
Grade A	73		
Not graded	181		
Did the Endoscopist Visualize Findings Suggestive of Eosinophilic Esophagitis? Units: Subjects			
Not Visualised	256		
H Pylori Status Units: Subjects			
Positive	29		
Negative	226		
Not determined	1		
Region of Enrollment Units: Subjects			
Belgium	1		
Bulgaria	177		
Czech Republic	40		
Estonia	11		
Poland	22		
United Kingdom	5		
Height Units: centimeters (cm)			
arithmetic mean			
standard deviation	-		
Weight Units: kilograms (kg)			
arithmetic mean			
standard deviation	-		
Body Mass Index (BMI)			
Body Mass Index=weight (kg)/[height (m)^2]			
Units: kg per square meter (kg/m^2)			
arithmetic mean			
standard deviation	-		
Hospital Anxiety and Depression Scale (HADS) Anxiety Total			
HADS-A and HADS-D are 7-item subscales that measure the presence and severity of anxiety and depression symptoms, respectively, on a scale of 0 to 3. Total scores ≤ 7: no clinically relevant symptoms; 8 - 10: mild symptoms; 11 - 14: moderate symptoms; and ≥15 (maximum 21): more severe symptoms.			
Units: score on scale			
arithmetic mean			
standard deviation	-		
Depression Total			

Units: score on scale			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Esomeprazole 40 mg
Reporting group description:	
Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by esomeprazole 40 mg, over-encapsulated tablets, orally, once daily for 4 weeks during the active treatment period.	
Reporting group title	Vonoprazan 20 mg
Reporting group description:	
Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by vonoprazan 20 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the treatment period.	
Reporting group title	Vonoprazan 40 mg
Reporting group description:	
Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by vonoprazan 40 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the active treatment period.	

Primary: Percentage of Heartburn-Free 24-Hour Periods (Day and Night) During 4 Weeks of Treatment

End point title	Percentage of Heartburn-Free 24-Hour Periods (Day and Night) During 4 Weeks of Treatment
End point description:	
Participants used the Reflux Symptom Questionnaire Electronic Diary (RESQ-eD) every morning upon waking and every evening before going to sleep to document the presence of daytime and nighttime heartburn and regurgitation. The percentage of heartburn-free (HBF) 24-hour periods was calculated for each participant using the following formula: (total 24-hour periods that are heartburn free / total 24-hour periods for which both a daytime and nighttime result is marked) x 100%. The full analysis set (FAS) included all participants randomized to double-blind study medication.	
End point type	Primary
End point timeframe:	
4 Weeks	

End point values	Esomeprazole 40 mg	Vonoprazan 20 mg	Vonoprazan 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	85	85	
Units: percentage of HBF 24-hour periods				
arithmetic mean (standard deviation)	36.54 (± 35.570)	36.69 (± 33.420)	38.43 (± 34.793)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Esomeprazole 40 mg v Vonoprazan 20 mg
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.748 [1]
Method	Wilcoxon rank-sum test
Parameter estimate	Wilcoxon-Mann-Whitney odds estimator
Point estimate	1.0584
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.71
upper limit	1.5778

Notes:

[1] - P-values were obtained using a Pearson chi-square test for each Vonoprazan treatment compared with Esomeprazole.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Esomeprazole 40 mg v Vonoprazan 40 mg
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5985 [2]
Method	Wilcoxon rank-sum test
Parameter estimate	Wilcoxon-Mann-Whitney odds estimator
Point estimate	1.0975
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.7368
upper limit	1.6349

Notes:

[2] - P-values were obtained using a Pearson chi-square test for each Vonoprazan treatment compared with Esomeprazole.

Secondary: Percentage of Participants with ≥1 Sustained Resolution of Heartburn During the 4-Week Treatment Period

End point title	Percentage of Participants with ≥1 Sustained Resolution of Heartburn During the 4-Week Treatment Period

End point description:

≥1 sustained resolution of heartburn is defined as ≥7 consecutive days without both daytime and nighttime heartburn anytime during the 4-week treatment period. Daytime and nighttime heartburn were documented by all participants using the Reflux Symptom Questionnaire Electronic Diary (RESQ-eD). The full analysis set (FAS) included all participants randomized to a double-blind study medication.

End point type	Secondary

End point timeframe:

4 Weeks

End point values	Esomeprazole 40 mg	Vonoprazan 20 mg	Vonoprazan 40 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	86	85	85	
Units: percentage of participants				
number (not applicable)	32.6	30.6	31.8	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Esomeprazole 40 mg v Vonoprazan 20 mg
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.782 [3]
Method	Pearson chi-square
Parameter estimate	Miettinen-Nurminen
Point estimate	0.91
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.44
upper limit	1.91

Notes:

[3] - P-values were obtained using a Pearson chi-square test for each Vonoprazan treatment compared with Esomeprazole.

Statistical analysis title	Statistical Analysis 2
Comparison groups	Esomeprazole 40 mg v Vonoprazan 40 mg
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.912 [4]
Method	Pearson chi-square
Parameter estimate	Miettinen-Nurminen
Point estimate	0.96
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.46
upper limit	2.01

Notes:

[4] - P-values were obtained using a Pearson chi-square test for each Vonoprazan treatment compared with Esomeprazole.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 5 weeks

Adverse event reporting additional description:

Adverse event (AE) is any unfavorable, unintended sign, symptom or disease temporally associated with use of drug, considered related/not related to drug. Treatment-emergent AEs (TEAEs) are reported and defined as any AE that occurred after first dose of study drug during double-blind period and up to 1 week after study completion or withdrawal.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Esomeprazole 40 mg

Reporting group description:

Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by esomeprazole 40 mg, over-encapsulated tablets, orally, once daily for 4 weeks during the active treatment period.

Reporting group title	Vonoprazan 20 mg

Reporting group description:

Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by vonoprazan 20 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the treatment period.

Reporting group title	Vonoprazan 40 mg

Reporting group description:

Esomeprazole 40 mg over-encapsulated tablets, orally, once daily for 4 weeks then esomeprazole placebo-matching capsules, orally, once daily for 2 weeks during the run-in period, followed by vonoprazan 40 mg, over-encapsulated capsules, orally, once daily for 4 weeks during the active treatment period.

Serious adverse events	Esomeprazole 40 mg	Vonoprazan 20 mg	Vonoprazan 40 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	0 / 85 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	0 / 85 (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

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

Non-serious adverse events	Esomeprazole 40 mg	Vonoprazan 20 mg	Vonoprazan 40 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	6 / 85 (7.06%)
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	1 / 86 (1.16%)	0 / 85 (0.00%)	2 / 85 (2.35%)
occurrences (all)	1	0	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 86 (0.00%)	0 / 85 (0.00%)	3 / 85 (3.53%)
occurrences (all)	0	0	3
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 86 (0.00%)	0 / 85 (0.00%)	2 / 85 (2.35%)
occurrences (all)	0	0	2

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.

43 more participants enrolled due to lower screen failure rate in the 5 new sites and the long run in period limited predictability of enrolment in advance. Measures had been implemented maintaining scientific integrity and participant safety.

Notes: