Clinical trial results:
A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis

Summary

EudraCT number	2019-002579-33
Trial protocol	GB CZ HU PL BG
Global end of trial date	24 August 2021

Results information

Result version number	v1 (current)
This version publication date	22 July 2022
First version publication date	22 July 2022

Trial information

Trial identification

Sponsor protocol code	EE-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04124926
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Phathom Pharmaceuticals, Inc.
Sponsor organisation address	2150 East Lake Cook Road, Suite 800, Buffalo Grove, Illinois, United States, 60089
Public contact	Phathom Medical Information, Phathom Pharmaceuticals, Inc., 1 888-775-PHAT (7428), medicalinformation@phathompharma.com
Scientific contact	Phathom Medical Information, Phathom Pharmaceuticals, Inc., 1 888-775-PHAT (7428), medicalinformation@phathompharma.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	24 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of vonoprazan compared to lansoprazole in participants with erosive esophagitis.

Protection of trial subjects:

This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 (Revision 2) Section 3, Institutional Review Board/Independent Ethics Committee guidelines, Good Clinical Practice regulations and guidelines, and all applicable local regulations.

Background therapy: -

Evidence for comparator:

The regulatory approved doses of lansoprazole 30 mg and 15 mg have been selected for the Healing and Maintenance Phase, respectively, as these are approved therapeutic doses in the United States and Europe.

Actual start date of recruitment	28 October 2019
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	Poland: 213
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Bulgaria: 47
Country: Number of subjects enrolled	Czechia: 70
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	United States: 644
Worldwide total number of subjects	1027
EEA total number of subjects	352

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)	827
From 65 to 84 years	200
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was performed at 111 sites in 6 countries (Bulgaria, Czechia, Hungary, Poland, the United Kingdom and the United States) between 28 October 2019 and 24 August 2021. Of the 4,167 participants screened for the study, 1,027 participants with erosive esophagitis (EE) were randomized in the Healing Phase.

Pre-assignment

Screening details:

Participants were randomized to receive vonoprazan 20 mg once per day (QD) or lansoprazole 30 mg QD using a 1:1 ratio in the Healing Phase. Participants with endoscopic healing of EE at 2 or 8 weeks were re-randomized to receive vonoprazan 10 mg QD, vonoprazan 20 mg QD, or lansoprazole 15 mg QD using a 1:1:1 ratio in the Maintenance Phase.

Period 1

Period 1 title	Healing Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

A double-blind design was employed so that both the investigators and the participants were unaware of the treatment assignment during the entire study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Healing Phase: Vonoprazan 20 mg

Arm description:

Participants received oral vonoprazan 20 mg QD for a maximum of 8 weeks in the Healing Phase.

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

Dosage and administration details:

Vonoprazan was administered orally as over-encapsulated tablets.

Arm title	Healing Phase: Lansoprazole 30 mg

Arm description:

Participants received oral lansoprazole 30 mg QD for a maximum of 8 weeks in the Healing Phase.

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

Dosage and administration details:

Lansoprazole was administered orally as over-encapsulated capsules.

Number of subjects in period 1	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg
Started	514	513
Treated with study drug	514	510
Completed	483	481
Not completed	31	32
Adverse event, non-fatal	3	7
Protocol violation	-	1
Randomized but not treated	-	3
Miscellaneous	8	7
Withdrawal of consent	5	3
Lost to follow-up	5	4
Voluntary withdrawal	10	7

Period 2

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

Blinding implementation details:

A double-blind design was employed so that both the investigators and the participants were unaware of the treatment assignment during the entire study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Maintenance Phase: Vonoprazan 10 mg

Arm description:

Participants received oral vonoprazan 10 mg QD for 24 weeks.

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

Dosage and administration details:

Vonoprazan was administered orally as over-encapsulated tablets.

Arm title	Maintenance Phase: Vonoprazan 20 mg

Arm description:

Participants received oral vonoprazan 20 mg QD for 24 weeks.

Arm type	Experimental

Investigational medicinal product name	Vonoprazan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Vonoprazan was administered orally as over-encapsulated tablets.

Arm title	Maintenance Phase: Lansoprazole 15 mg

Arm description:

Participants received oral lansoprazole 15 mg QD for 24 weeks.

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

Dosage and administration details:

Lansoprazole was administered orally as over-encapsulated capsules.

Number of subjects in period 2[1]	Maintenance Phase: Vonoprazan 10 mg	Maintenance Phase: Vonoprazan 20 mg	Maintenance Phase: Lansoprazole 15 mg
Started	298	298	297
Treated with study drug	296	296	297
Completed	274	269	269
Not completed	24	29	28
Adverse event, non-fatal	3	5	4
Protocol violation	3	-	-
Randomized but not treated	2	2	-
Miscellaneous	1	2	4
Pregnancy	-	1	-
Withdrawal of consent	5	5	5
Lost to follow-up	7	8	9
Voluntary withdrawal	3	6	5
Lack of efficacy	-	-	1

Notes:

[1] - 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 endoscopic healing of EE at 2 or 8 weeks were re-randomized to receive vonoprazan 10 mg QD, vonoprazan 20 mg QD, or lansoprazole 15 mg QD in the Maintenance Phase.

Baseline characteristics

Reporting groups	
Reporting group title	Healing Phase: Vonoprazan 20 mg
Reporting group description:	
Participants received oral vonoprazan 20 mg QD for a maximum of 8 weeks in the Healing Phase.	
Reporting group title	Healing Phase: Lansoprazole 30 mg
Reporting group description:	
Participants received oral lansoprazole 30 mg QD for a maximum of 8 weeks in the Healing Phase.	

Reporting group values	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg	Total
Number of subjects	514	513	1027
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	421	406	827
>=65 years	93	107	200
Gender categorical Units: Subjects			
Female	256	289	545
Male	258	224	482
Ethnicity Units: Subjects			
Hispanic or Latino	62	59	121
Not Hispanic or Latino	450	451	901
Unknown or Not Reported	2	3	5
Race Units: Subjects			
White	474	458	932
Black or African-American	23	41	64
Asian	7	6	13
American Indian or Alaska Native	2	1	3
Native Hawaiian or Other Pacific Islander	1	1	2
Other	5	5	10
Unknown	1	1	2
Not Reported	1	0	1
Adjudicated Los Angeles (LA) Classification of Esophagitis Grading Scale			
LA Classification of Esophagitis Grading Scale: Grade A: One or more mucosal breaks with a length of no longer than 5 mm that did not extend between the tops of 2 mucosal folds. Grade B: One or more mucosal breaks with a length of longer than 5 mm that did not extend between the tops of 2 mucosal folds. Grade C: One or more mucosal breaks that are continuous between the tops of 2 or more mucosal folds, which involves less than 75% of the circumference. Grade D: One or more mucosal breaks, which involves at least 75% of the circumference.			
Units: Subjects			
Grade A or B	337	336	673
Grade C or D	177	174	351

Unknown or Not Reported	0	3	3

End points

End points reporting groups

Reporting group title	Healing Phase: Vonoprazan 20 mg
Reporting group description: Participants received oral vonoprazan 20 mg QD for a maximum of 8 weeks in the Healing Phase.	
Reporting group title	Healing Phase: Lansoprazole 30 mg
Reporting group description: Participants received oral lansoprazole 30 mg QD for a maximum of 8 weeks in the Healing Phase.	
Reporting group title	Maintenance Phase: Vonoprazan 10 mg
Reporting group description: Participants received oral vonoprazan 10 mg QD for 24 weeks.	
Reporting group title	Maintenance Phase: Vonoprazan 20 mg
Reporting group description: Participants received oral vonoprazan 20 mg QD for 24 weeks.	
Reporting group title	Maintenance Phase: Lansoprazole 15 mg
Reporting group description: Participants received oral lansoprazole 15 mg QD for 24 weeks.	

Primary: Healing Phase: Percentage of Participants Who Had Complete Healing of EE by Week 8

End point title	Healing Phase: Percentage of Participants Who Had Complete Healing of EE by Week 8
End point description: A participant was considered to have complete healing of EE if healing was demonstrated during endoscopy. The Modified Intent-to-Treat (MITT) Set (Healing Phase) included all participants randomized into the Healing Phase who had documented EE at baseline and received at least 1 dose of study drug during the Healing Phase. All analyses using the MITT Set grouped subjects according to the randomized treatment.	
End point type	Primary
End point timeframe: Week 8	

End point values	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	514	510		
Units: percentage of participants				
number (not applicable)	92.9	84.6		

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg versus (vs) Lansoprazole 30 mg

Statistical analysis description:

The 2-sided 95% confidence interval (CI) of the difference in EE healing rates between vonoprazan 20 mg and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.

Comparison groups	Healing Phase: Vonoprazan 20 mg v Healing Phase: Lansoprazole 30 mg
Number of subjects included in analysis	1024
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.49
upper limit	12.23

Notes:

[1] - The noninferiority of vonoprazan to lansoprazole was evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in EE rates between treatments (vonoprazan minus lansoprazole).
[2] - 2-sided p-value.

Primary: Maintenance Phase: Percentage of Participants Who Maintained Complete Healing of EE at Week 24

End point title	Maintenance Phase: Percentage of Participants Who Maintained Complete Healing of EE at Week 24

End point description:

A participant was considered to have complete healing of EE if healing was demonstrated during endoscopy. The MITT Set (Maintenance Phase) included all participants randomized into the Maintenance Phase who had healed EE at the end of the Healing Phase and received at least 1 dose of study drug during the Maintenance Phase. All analyses using the MITT Set grouped participants according to the randomized treatment.

End point type	Primary

End point timeframe:

Week 24

End point values	Maintenance Phase: Vonoprazan 10 mg	Maintenance Phase: Vonoprazan 20 mg	Maintenance Phase: Lansoprazole 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	293	291	294	
Units: percentage of participants				
number (not applicable)	79.2	80.7	72.0	

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 15 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in EE maintenance rates between each vonoprazan group and lansoprazole group was calculated via the Miettinen and Nurminen method.

Comparison groups	Maintenance Phase: Vonoprazan 20 mg v Maintenance Phase: Lansoprazole 15 mg
Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	15.53

Notes:

[3] - The noninferiority of each dose group of vonoprazan to lansoprazole was evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in maintenance of healing rates between treatments (vonoprazan minus lansoprazole).
[4] - 2-sided p-value.

Statistical analysis title	Vonoprazan 10 mg vs Lansoprazole 15 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in EE maintenance rates between each vonoprazan group and lansoprazole group was calculated via the Miettinen and Nurminen method.

Comparison groups	Maintenance Phase: Vonoprazan 10 mg v Maintenance Phase: Lansoprazole 15 mg
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	< 0.0001 [6]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	7.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	14.09

Notes:

[5] - The noninferiority of each dose group of vonoprazan to lansoprazole was evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in maintenance of healing rates between treatments (vonoprazan minus lansoprazole).
[6] - 2-sided p-value.

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 15 mg
Comparison groups	Maintenance Phase: Vonoprazan 20 mg v Maintenance Phase: Lansoprazole 15 mg

Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0136 [8]
Method	Farrington and Manning test

Notes:

[7] - The superiority of the vonoprazan 20 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.
[8] - 2-sided p-value.

Statistical analysis title	Vonoprazan 10 mg vs Lansoprazole 15 mg
Comparison groups	Maintenance Phase: Vonoprazan 10 mg v Maintenance Phase: Lansoprazole 15 mg
Number of subjects included in analysis	587
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.0436 [10]
Method	Farrington and Manning test

Notes:

[9] - The superiority of the vonoprazan 10 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.
[10] - 2-sided p-value.

Secondary: Healing Phase: Percentage of 24-hour Heartburn-free Days

End point title	Healing Phase: Percentage of 24-hour Heartburn-free Days

End point description:

A 24-hour heartburn-free day was defined as a day having no heartburn among all diary entries for that day. The percentage of 24-hour heartburn-free days was calculated using all days with at least 1 evening or morning diary entry during the treatment period of this phase. The MITT Set (Healing Phase) including only participants with at least one heartburn diary entry.

End point type	Secondary

End point timeframe:

Day 1 to Week 8

End point values	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	509	507		
Units: percentage of days				
arithmetic mean (standard deviation)	66.8 (± 34.60)	64.1 (± 35.46)		

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 30 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in mean percentage of 24-hour heartburn-free days between vonoprazan 20 mg and lansoprazole 30 mg was calculated from Welch's t-test.

Comparison groups	Healing Phase: Lansoprazole 30 mg v Healing Phase: Vonoprazan 20 mg
Number of subjects included in analysis	1016
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
Parameter estimate	difference in mean percentage
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	7.03

Notes:

[11] - If the lower bound of the CI was greater than -15%, noninferiority would be concluded.

Secondary: Healing Phase: Percentage of Participants With Baseline LA Classification Grades C or D Who Had Complete Healing of EE at Week 2

End point title	Healing Phase: Percentage of Participants With Baseline LA Classification Grades C or D Who Had Complete Healing of EE at Week 2

End point description:

A participant was considered to have complete healing of EE if healing was demonstrated during endoscopy.
LA Classification of Esophagitis Grading Scale:
Grade C: One or more mucosal breaks that are continuous between the tops of 2 or more mucosal folds, which involves less than 75% of the circumference.
Grade D: One or more mucosal breaks, which involves at least 75% of the circumference.
The MITT Set (Healing Phase) including only participants with baseline LA Classification Grades C or D.

End point type	Secondary

End point timeframe:

Week 2

End point values	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	174		
Units: percentage of participants				
number (not applicable)	70.2	52.6		

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 30 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in EE healing rates between vonoprazan 20 mg and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.

Comparison groups	Healing Phase: Vonoprazan 20 mg v Healing Phase: Lansoprazole 30 mg

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.0008 [13]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	17.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.44
upper limit	27.43

Notes:

[12] - The superiority of the vonoprazan 20 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

[13] - 2-sided p-value.

Secondary: Healing Phase: Percentage of Participants With Onset of Sustained Resolution of Heartburn by Day 3

End point title	Healing Phase: Percentage of Participants With Onset of Sustained Resolution of Heartburn by Day 3

End point description:

Sustained resolution was defined as at least 7 consecutive days with no daytime or night time heartburn as assessed by the daily diary. A participant was considered to have sustained resolution of heartburn by Day 3 if the first day of the 7 consecutive days without symptoms was on Days 1, 2, or 3. The MITT Set (Healing Phase) included all participants randomized into the Healing Phase who had documented EE at baseline and received at least 1 dose of study drug during the Healing Phase. All analyses using the MITT Set grouped subjects according to the randomized treatment.

End point type	Secondary

End point timeframe:

Day 1 to maximum of Day 10 (inclusive of 7 day heartburn assessment)

End point values	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	514	510		
Units: percentage of participants				
number (not applicable)	34.4	32.2		

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 30 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in sustained resolution rates between vonoprazan 20 mg and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.

Comparison groups	Healing Phase: Vonoprazan 20 mg v Healing Phase: Lansoprazole 30 mg

Number of subjects included in analysis	1024
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.4392 [15]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	8.04

Notes:

[14] - The superiority of the vonoprazan 20 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

[15] - 2-sided p-value.

Secondary: Healing Phase: Percentage of Participants With Baseline LA Classification Grades C or D Who Had Complete Healing of EE by Week 8

End point title	Healing Phase: Percentage of Participants With Baseline LA Classification Grades C or D Who Had Complete Healing of EE by Week 8

End point description:

A participant was considered to have complete healing of EE if healing was demonstrated during endoscopy.
LA Classification of Esophagitis Grading Scale:
Grade C: One or more mucosal breaks that are continuous between the tops of 2 or more mucosal folds, which involves less than 75% of the circumference.
Grade D: One or more mucosal breaks, which involves at least 75% of the circumference.
The MITT Set (Healing Phase) including only participants with baseline LA Classification Grades C or D.

End point type	Secondary

End point timeframe:

Week 8

End point values	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	177	174		
Units: percentage of participants				
number (not applicable)	91.7	72.0		

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 30 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in EE healing rates between vonoprazan 20 mg and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.

Comparison groups	Healing Phase: Vonoprazan 20 mg v Healing Phase: Lansoprazole 30 mg

Number of subjects included in analysis	351
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	< 0.0001 [17]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	19.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.84
upper limit	27.58

Notes:

[16] - Observed p-value and not a formal test per the preplanned fixed-sequence testing procedure. The superiority of the vonoprazan 20 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

[17] - 2-sided p-value.

Secondary: Healing Phase: Percentage of Participants Who Had Complete Healing of EE at Week 2

End point title	Healing Phase: Percentage of Participants Who Had Complete Healing of EE at Week 2

End point description:

A participant was considered to have complete healing of EE if healing was demonstrated during endoscopy. The MITT Set (Healing Phase) included all participants randomized into the Healing Phase who had documented EE at baseline and received at least 1 dose of study drug during the Healing Phase. All analyses using the MITT Set grouped subjects according to the randomized treatment.

End point type	Secondary

End point timeframe:

Week 2

End point values	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	514	510		
Units: percentage of participants				
number (not applicable)	74.3	68.2		

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 30 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in EE healing rates between vonoprazan 20 mg and lansoprazole 30 mg was calculated via the Miettinen and Nurminen method.

Comparison groups	Healing Phase: Vonoprazan 20 mg v Healing Phase: Lansoprazole 30 mg

Number of subjects included in analysis	1024
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0348 [19]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	11.6

Notes:

[18] - Observed p-value and not a formal test per the preplanned fixed-sequence testing procedure. The superiority of the vonoprazan 20 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

[19] - 2-sided p-value.

Secondary: Maintenance Phase: Percentage of Participants With Baseline LA Classification Grades C or D Who Maintained Complete Healing of EE at Week 24

End point title	Maintenance Phase: Percentage of Participants With Baseline LA Classification Grades C or D Who Maintained Complete Healing of EE at Week 24

End point description:

A participant was considered to have complete healing of EE if healing was demonstrated during endoscopy.
LA Classification of Esophagitis Grading Scale:
Grade C: One or more mucosal breaks that are continuous between the tops of 2 or more mucosal folds, which involves less than 75% of the circumference.
Grade D: One or more mucosal breaks, which involves at least 75% of the circumference.
The MITT Set (Maintenance Phase) including only participants with baseline LA Classification Grades C or D with nonmissing data.

End point type	Secondary

End point timeframe:

Week 24

End point values	Maintenance Phase: Vonoprazan 10 mg	Maintenance Phase: Vonoprazan 20 mg	Maintenance Phase: Lansoprazole 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	95	92	96	
Units: percentage of participants				
number (not applicable)	74.7	77.2	61.5	

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 15 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in maintenance rates between each vonoprazan group and

lansoprazole 15 mg group was calculated via the Miettinen and Nurminen method.

Comparison groups	Maintenance Phase: Vonoprazan 20 mg v Maintenance Phase: Lansoprazole 15 mg
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0196 [21]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	15.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	28.44

Notes:

[20] - The superiority of the vonoprazan 20 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.
[21] - 2-sided p-value.

Statistical analysis title	Vonoprazan 10 mg vs Lansoprazole 15 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in maintenance rates between each vonoprazan group and lansoprazole 15 mg group was calculated via the Miettinen and Nurminen method.

Comparison groups	Maintenance Phase: Vonoprazan 10 mg v Maintenance Phase: Lansoprazole 15 mg
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.049 [23]
Method	Farrington and Manning test
Parameter estimate	difference in percentage
Point estimate	13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	26.14

Notes:

[22] - The superiority of the vonoprazan 10 mg group to lansoprazole group p-value was evaluated with a Farrington and Manning test with the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.
[23] - 2-sided p-value.

Secondary: Maintenance Phase: Percentage of 24-hour Heartburn-free Days

End point title	Maintenance Phase: Percentage of 24-hour Heartburn-free Days

End point description:

A 24-hour heartburn-free day was defined as a day having no heartburn among all diary entries for that day. The percentage of 24-hour heartburn-free days was calculated using all days with at least 1 evening or morning diary entry during the treatment period of this phase. The MITT Set (Maintenance Phase) including only participants with at least one heartburn diary entry.

End point type	Secondary

End point timeframe:

Day 1 to Week 24

End point values	Maintenance Phase: Vonoprazan 10 mg	Maintenance Phase: Vonoprazan 20 mg	Maintenance Phase: Lansoprazole 15 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	291	290	294	
Units: percentage of days				
arithmetic mean (standard deviation)	80.9 (± 28.59)	80.6 (± 29.96)	78.6 (± 27.49)	

Statistical analyses

Statistical analysis title	Vonoprazan 20 mg vs Lansoprazole 15 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in mean percentage of 24-hour heartburn-free days between each vonoprazan group and the lansoprazole group was calculated from Welch's t-test.

Comparison groups	Maintenance Phase: Vonoprazan 20 mg v Maintenance Phase: Lansoprazole 15 mg
Number of subjects included in analysis	584
Analysis specification	Pre-specified
Analysis type	non-inferiority[24]
Parameter estimate	difference in mean percentage
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	6.72

Notes:

[24] - If the lower bound of the CI was greater than -15%, noninferiority would be concluded.

Statistical analysis title	Vonoprazan 10 mg vs Lansoprazole 15 mg

Statistical analysis description:

The 2-sided 95% CI of the difference in mean percentage of 24-hour heartburn-free days between each vonoprazan group and the lansoprazole group was calculated from Welch's t-test.

Comparison groups	Maintenance Phase: Lansoprazole 15 mg v Maintenance Phase: Vonoprazan 10 mg
Number of subjects included in analysis	585
Analysis specification	Pre-specified
Analysis type	non-inferiority[25]
Parameter estimate	difference in mean percentage
Point estimate	2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.27
upper limit	6.84

Notes:

[25] - If the lower bound of the CI was greater than -15%, noninferiority would be concluded.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Healing Phase: Day 1 to Week 8; Maintenance Phase: Day 1 to Week 28

Adverse event reporting additional description:

The Safety Set included all randomized participants who received at least 1 dose of study drug. All analyses using the Safety Set grouped subjects according to the treatment actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Healing Phase: Vonoprazan 20 mg

Reporting group description:

Participants received oral vonoprazan 20 mg QD for a maximum of 8 weeks in the Healing Phase.

Reporting group title	Healing Phase: Lansoprazole 30 mg

Reporting group description:

Participants received oral lansoprazole 30 mg QD for a maximum of 8 weeks in the Healing Phase.

Reporting group title	Maintenance Phase: Vonoprazan 10 mg

Reporting group description:

Participants received oral vonoprazan 10 mg QD for 24 weeks.

Reporting group title	Maintenance Phase: Vonoprazan 20 mg

Reporting group description:

Participants received oral vonoprazan 20 mg QD for 24 weeks.

Reporting group title	Maintenance Phase: Lansoprazole 15 mg

Reporting group description:

Participants received oral lansoprazole 15 mg QD for 24 weeks.

Serious adverse events	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg	Maintenance Phase: Vonoprazan 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 514 (0.58%)	3 / 510 (0.59%)	10 / 296 (3.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer stage I			
subjects affected / exposed	0 / 514 (0.00%)	1 / 510 (0.20%)	0 / 296 (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
Adenocarcinoma			

subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular thyroid cancer			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestine adenocarcinoma			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Gastric bypass			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 514 (0.19%)	0 / 510 (0.00%)	0 / 296 (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
Oedema peripheral			
subjects affected / exposed	1 / 514 (0.19%)	0 / 510 (0.00%)	0 / 296 (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
Chest discomfort			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 514 (0.00%)	1 / 510 (0.20%)	0 / 296 (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
Ligament injury			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic haemothorax			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	1 / 514 (0.19%)	0 / 510 (0.00%)	0 / 296 (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
Syncope			

subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatolithiasis			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Stress urinary incontinence			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 514 (0.19%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 514 (0.00%)	1 / 510 (0.20%)	0 / 296 (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
COVID-19 pneumonia			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Peritonsillar abscess			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	1 / 296 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 514 (0.00%)	0 / 510 (0.00%)	0 / 296 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Maintenance Phase: Vonoprazan 20 mg	Maintenance Phase: Lansoprazole 15 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 296 (4.73%)	7 / 297 (2.36%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer stage I			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Follicular thyroid cancer			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine adenocarcinoma			

subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Gastric bypass			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Animal bite			

subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament injury			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrospinal fluid leakage			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatolithiasis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Stress urinary incontinence			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 296 (0.68%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Influenza			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 296 (0.68%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 296 (0.34%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 296 (0.00%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 296 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Healing Phase: Vonoprazan 20 mg	Healing Phase: Lansoprazole 30 mg	Maintenance Phase: Vonoprazan 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 514 (9.73%)	46 / 510 (9.02%)	72 / 296 (24.32%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 514 (0.58%)	4 / 510 (0.78%)	9 / 296 (3.04%)
occurrences (all)	3	4	9
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 514 (1.17%)	6 / 510 (1.18%)	3 / 296 (1.01%)
occurrences (all)	6	6	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 514 (2.14%)	13 / 510 (2.55%)	3 / 296 (1.01%)
occurrences (all)	11	13	3
Abdominal pain			
subjects affected / exposed	8 / 514 (1.56%)	2 / 510 (0.39%)	4 / 296 (1.35%)
occurrences (all)	9	2	4
Chronic gastritis			
subjects affected / exposed	2 / 514 (0.39%)	1 / 510 (0.20%)	9 / 296 (3.04%)
occurrences (all)	2	1	9
Dyspepsia			
subjects affected / exposed	1 / 514 (0.19%)	3 / 510 (0.59%)	11 / 296 (3.72%)
occurrences (all)	1	3	12
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 514 (1.17%)	2 / 510 (0.39%)	7 / 296 (2.36%)
occurrences (all)	6	2	7
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	2 / 514 (0.39%)	0 / 510 (0.00%)	2 / 296 (0.68%)
occurrences (all)	2	0	2
Back pain			
subjects affected / exposed	2 / 514 (0.39%)	4 / 510 (0.78%)	6 / 296 (2.03%)
occurrences (all)	2	4	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 514 (0.39%)	2 / 510 (0.39%)	2 / 296 (0.68%)
occurrences (all)	2	2	2
COVID-19			
subjects affected / exposed	8 / 514 (1.56%)	6 / 510 (1.18%)	12 / 296 (4.05%)
occurrences (all)	8	6	12
Sinusitis			
subjects affected / exposed	1 / 514 (0.19%)	3 / 510 (0.59%)	7 / 296 (2.36%)
occurrences (all)	1	3	7
Urinary tract infection			
subjects affected / exposed	6 / 514 (1.17%)	4 / 510 (0.78%)	8 / 296 (2.70%)
occurrences (all)	6	4	8

Non-serious adverse events	Maintenance Phase: Vonoprazan 20 mg	Maintenance Phase: Lansoprazole 15 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 296 (27.36%)	74 / 297 (24.92%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 296 (2.70%)	6 / 297 (2.02%)	
occurrences (all)	9	6	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 296 (0.68%)	8 / 297 (2.69%)	
occurrences (all)	2	8	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 296 (2.36%)	13 / 297 (4.38%)	
occurrences (all)	7	14	
Abdominal pain			

subjects affected / exposed	10 / 296 (3.38%)	3 / 297 (1.01%)	
occurrences (all)	12	3	
Chronic gastritis			
subjects affected / exposed	4 / 296 (1.35%)	5 / 297 (1.68%)	
occurrences (all)	4	5	
Dyspepsia			
subjects affected / exposed	12 / 296 (4.05%)	8 / 297 (2.69%)	
occurrences (all)	12	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 296 (3.72%)	6 / 297 (2.02%)	
occurrences (all)	12	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 296 (1.69%)	7 / 297 (2.36%)	
occurrences (all)	5	9	
Back pain			
subjects affected / exposed	8 / 296 (2.70%)	4 / 297 (1.35%)	
occurrences (all)	8	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 296 (0.34%)	7 / 297 (2.36%)	
occurrences (all)	1	8	
COVID-19			
subjects affected / exposed	26 / 296 (8.78%)	18 / 297 (6.06%)	
occurrences (all)	26	18	
Sinusitis			
subjects affected / exposed	4 / 296 (1.35%)	1 / 297 (0.34%)	
occurrences (all)	4	1	
Urinary tract infection			
subjects affected / exposed	1 / 296 (0.34%)	5 / 297 (1.68%)	
occurrences (all)	1	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2019	The purposes of Amendment 1 were to: • Remove double-dummy and placebo from study drugs and other applicable sections. • Change exclusion period for proton pump inhibitors and histamine-2 receptor antagonist from 14 days prior to screening to 14 days prior to screening 13carbon-urea breath test. • Update footnote on table of excluded medications and treatments regarding prohibition period of medications that could have interfered with 13carbon-urea breath test. • Remove 'x' from dispense study drug at Maintenance Week 4 (Maintenance Day 29) in the Schedule of Events. • Update a footnote in the Schedule of Events to clarify that subjects may need to return for study drug administration after Week 2 and Week 8.
01 October 2019	The purposes of Amendment 2 were to: • Remove wording that allowed a subject's legally acceptable representative as a party capable of giving consent for the study. • Add wording allowing the extension of the endoscopy Screening Period to 10 days in rare instances with sponsor approval. • Exclude the use of Cytochrome P450 Family 3 Subfamily A Member 4 substrates with a narrow therapeutic index from 4 days prior to Day 1 through the end of the study. • Add overall study stopping criteria (Appendix 16.1.1; Protocol Section 6.3.1.15). • Clarify requirements for the informed consent process for pharmacogenetic sampling and analysis. • Add collection of smoking status and alcohol use in the Schedule of Events and to include them as variables for subgroup analyses. • Update the protocol with the most recent sample version of the Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 March 2020	New participant screening and enrollment was paused due to the COVID-19 pandemic. Participants already enrolled in the study were allowed to continue at the discretion of the Principal Investigators.	11 May 2020

Notes:

Limitations and caveats

None reported