

VONOPRAZAN FOR THE TREATMENT OF HEARTBURN IN NON-EROSIVE REFLUX DISEASE: A RANDOMIZED TRIAL

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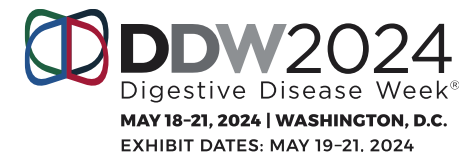
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INTRODUCTION

GERD is a common GI disorder: U.S. pooled prevalence 21%

- Most patients do not have endoscopic evidence of erosive esophagitis
- GERD-like symptoms (heartburn, regurgitation) without erosive esophagitis: diagnosed as non-erosive reflux disease (NERD)

PPIs most commonly prescribed medication for GERD

- Mainstay of treatment for both erosive esophagitis and NERD

INTRODUCTION

Potassium-competitive acid blockers (PCABs) provide more potent and prolonged inhibition of gastric acid than PPIs

Small observational study reported 18 (69%) of 26 patients with PPI-resistant NERD had symptom improvement when changing to vonoprazan

Two Japanese RCTs in NERD failed to show a significant difference for vonoprazan vs. placebo in primary endpoint (median % heartburn-free days)

Placebo	Vonoprazan 10mg	Vonoprazan 20mg
7.4%	10.3%	12.0%
<i>1-week run-in: ≥ 2 days $\geq$ moderate heartburn while on antacids $\geq 75\%$ of week</i>		
61.5%	72.3% (p=0.06)	

INTRODUCTION

We performed a double-blind randomized trial of U.S. patients diagnosed with NERD to assess heartburn control with vonoprazan vs. placebo over 4 weeks followed by a 20-week active treatment extension period to assess longer-term treatment effect of vonoprazan

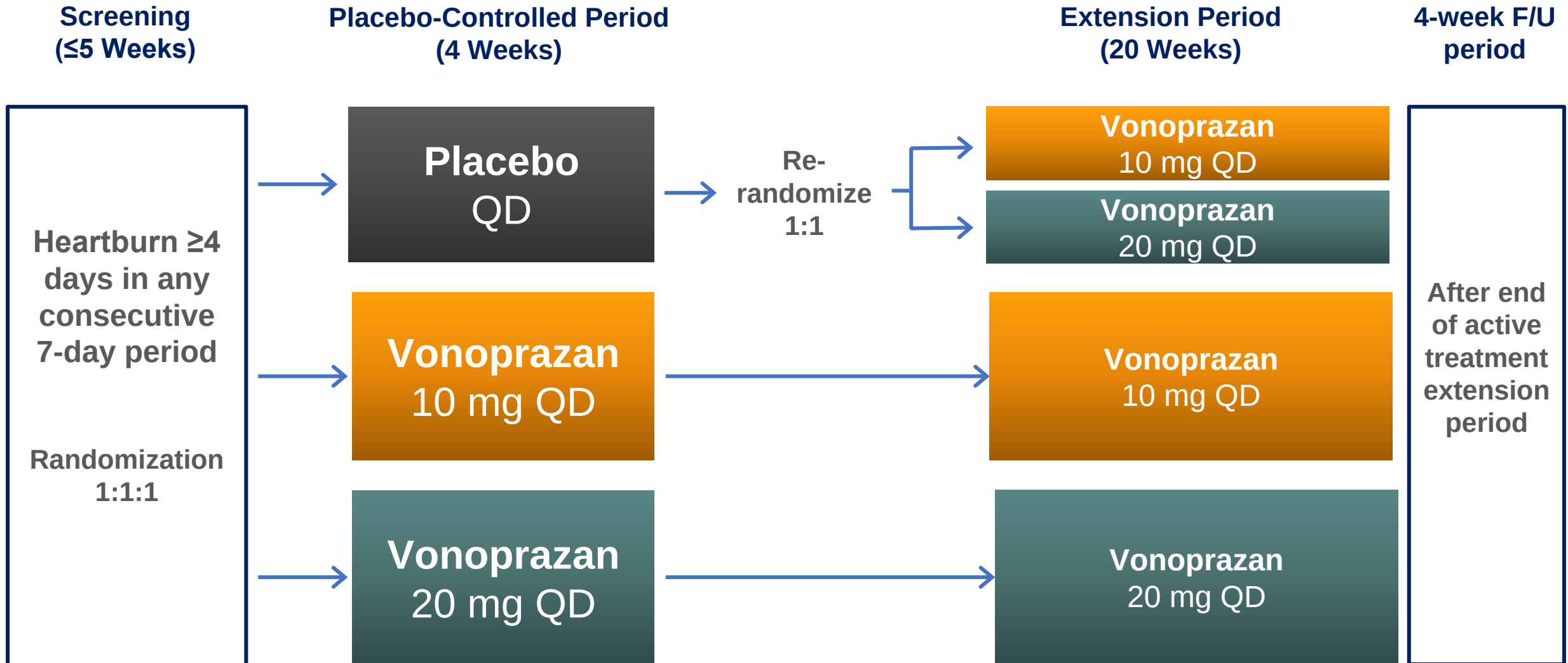
METHODS

Subjects

- **Adults diagnosed with symptomatic GERD**
 - Heartburn predominant symptom, onset $\geq$ 6 months prior to screening
 - No erosive esophagitis or Barrett's on screening endoscopy
 - *H. pylori* negative (tested during screening)
- **Subjects received rescue antacid to use as needed for heartburn**
- **Subjects completed electronic diary in morning and before bedtime to record heartburn (0-4 scale) and rescue antacid use**
- **The trial was performed at 91 U.S. sites**

METHODS

Study Flow



METHODS

Efficacy Endpoints: Placebo-Controlled Period

- **Primary**
 - Percentage of 24-hour heartburn-free days
 - Morning and evening diary entries: no heartburn and no rescue antacid use
- **Secondary**
 - Percentage of days without rescue antacid use
- **Exploratory**
 - Percentage of days without daytime heartburn
 - Percentage of days without nighttime heartburn
 - Mean severity of heartburn

METHODS

Efficacy Endpoints: Extension Period

Exploratory

- Percentage of 24-hour heartburn-free days
- Percentage of days without rescue antacid use
- Percentage of days without daytime heartburn
- Percentage of days without nighttime heartburn
- Mean severity of heartburn

PRIMARY AND SECONDARY ENDPOINTS ASSESSED USING A FIXED-SEQUENCE TESTING PROCEDURE

Population: All Randomized Subjects Who Received ≥ 1 Dose of Study Drug

Vonoprazan 20 mg vs. placebo for percentage of 24-hour heartburn-free days



Vonoprazan 10 mg vs. placebo for percentage of 24-hour heartburn-free days



Vonoprazan 20 mg vs. placebo for percentage of days without rescue antacid



Vonoprazan 10 mg vs. placebo for percentage of days without rescue antacid

2-sided comparisons performed at $\alpha=0.05$ level in the prespecified order until a test not significant

SELECTED BASELINE CHARACTERISTICS: PLACEBO-CONTROLLED PERIOD

	Placebo (N=258)	Vonoprazan 10mg (N=257)	Vonoprazan 20mg (N=257)
Age, mean yrs	51.5	51.0	50.4
Female sex	179 (69.4%)	182 (70.8%)	166 (64.6%)
Race			
White	205 (79.5%)	186 (72.4%)	185 (72.0%)
Black	33 (12.8%)	38 (14.8%)	52 (20.2%)
Asian	12 (4.7%)	22 (8.6%)	11 (4.3%)
Other/unknown	8 (3.1%)	11 (4.3%)	9 (3.5%)
Latino ethnicity	77 (29.8%)	87 (33.9%)	80 (31.1%)
BMI, mean kg/m²	30.4	30.5	29.9
Current smoker	35 (13.6%)	29 (11.3%)	34 (13.2%)
Prior PPI	164 (63.6%)	182 (70.8%)	162 (63.0%)
Mean heartburn severity (0-4)	1.4	1.4	1.4

PRIMARY AND SECONDARY ENDPOINTS ASSESSED USING A FIXED-SEQUENCE TESTING PROCEDURE

Vonoprazan 20 mg vs. placebo for percentage of 24-hour heartburn-free days

LS means: 44.4% vs. 27.7%, Difference = 16.7%, $p < 0.0001$



Vonoprazan 10 mg vs. placebo for percentage of 24-hour heartburn-free days

LS means: 44.8% vs. 27.7%, Difference = 17.1%, $p < 0.0001$



Vonoprazan 20 mg vs. placebo for percentage of days without rescue antacid

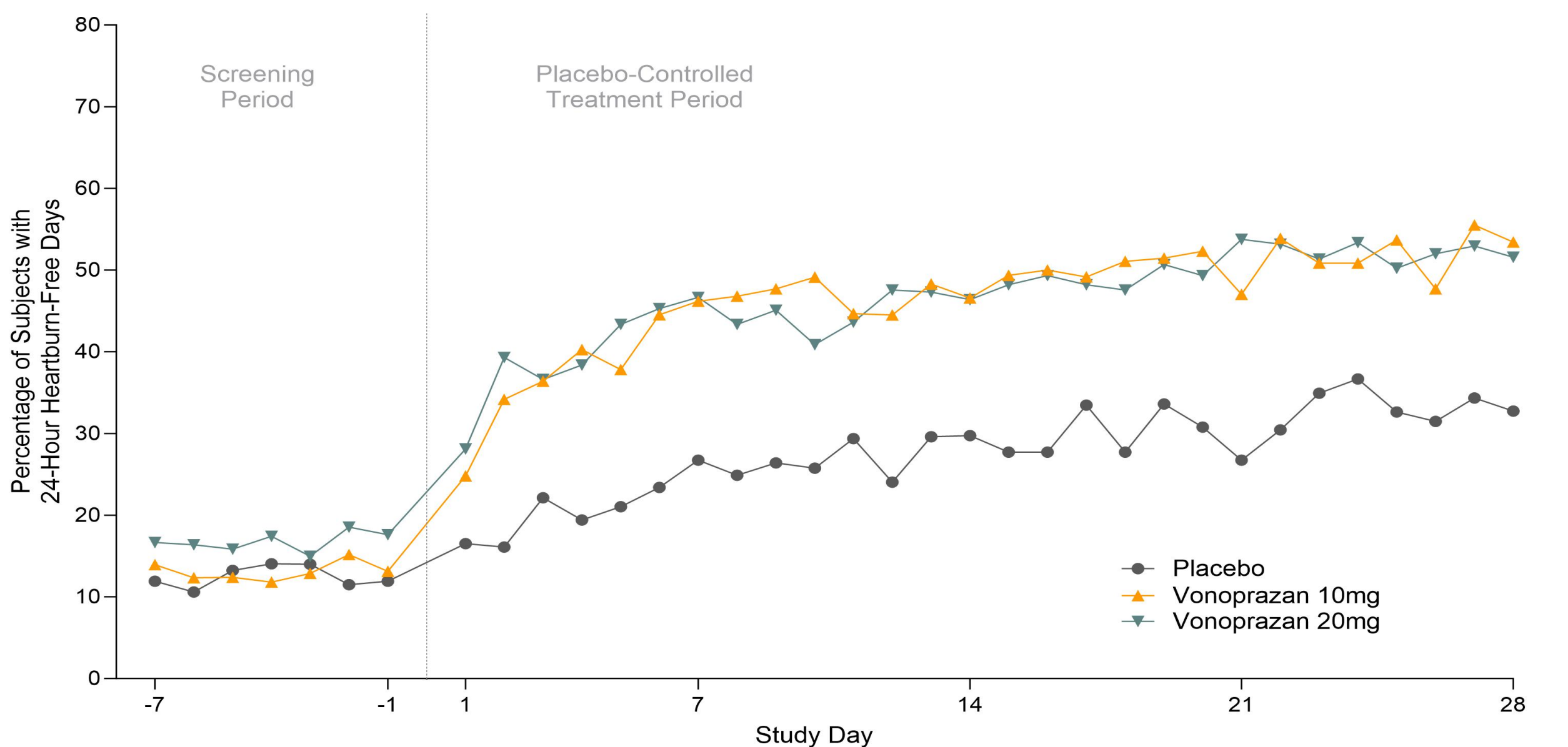
LS means: 61.2% vs. 47.6%, Difference = 13.7%, $p < 0.0001$



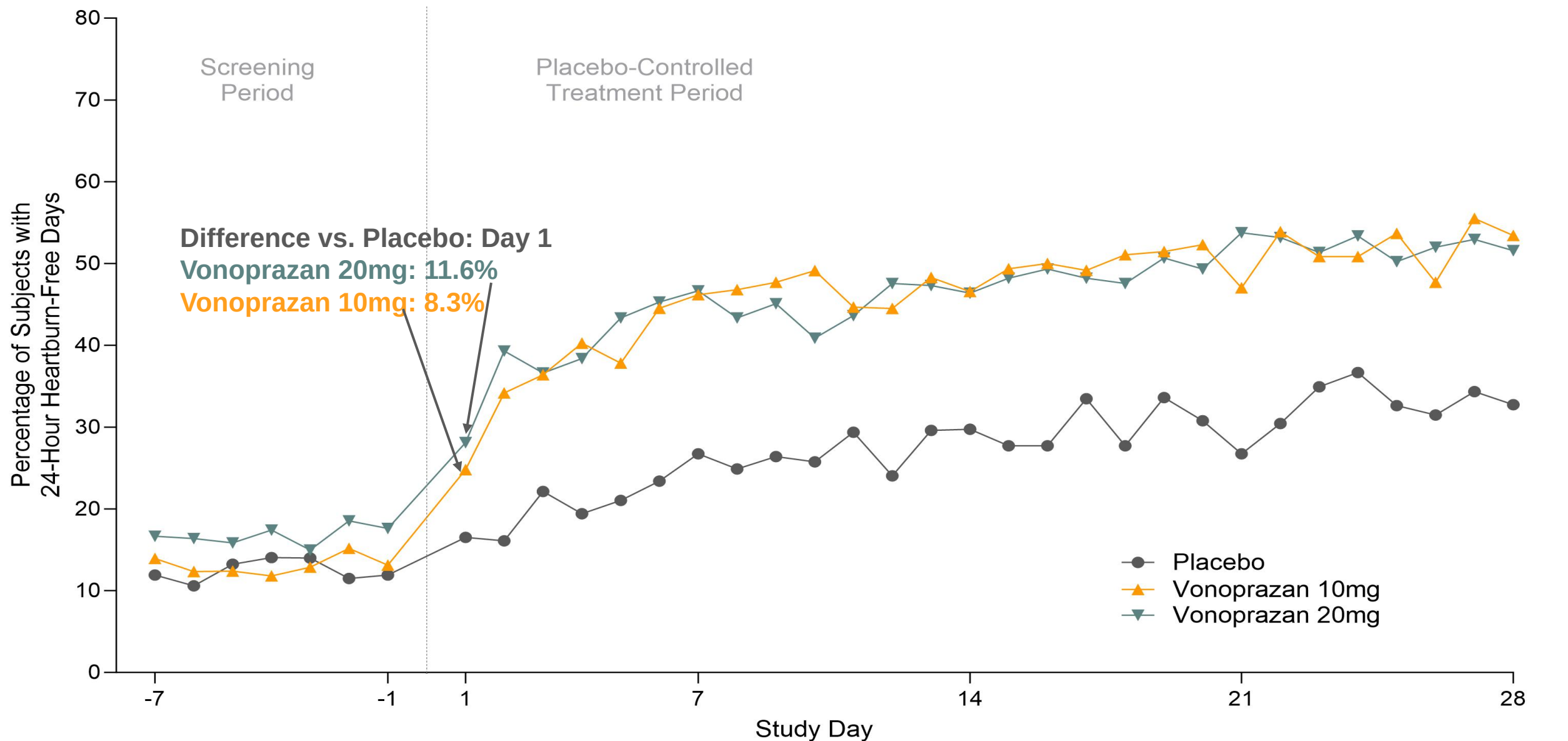
Vonoprazan 10 mg vs. placebo for percentage of days without rescue antacid

LS means: 63.3% vs. 47.6%, Difference = 15.8%, $p < 0.0001$

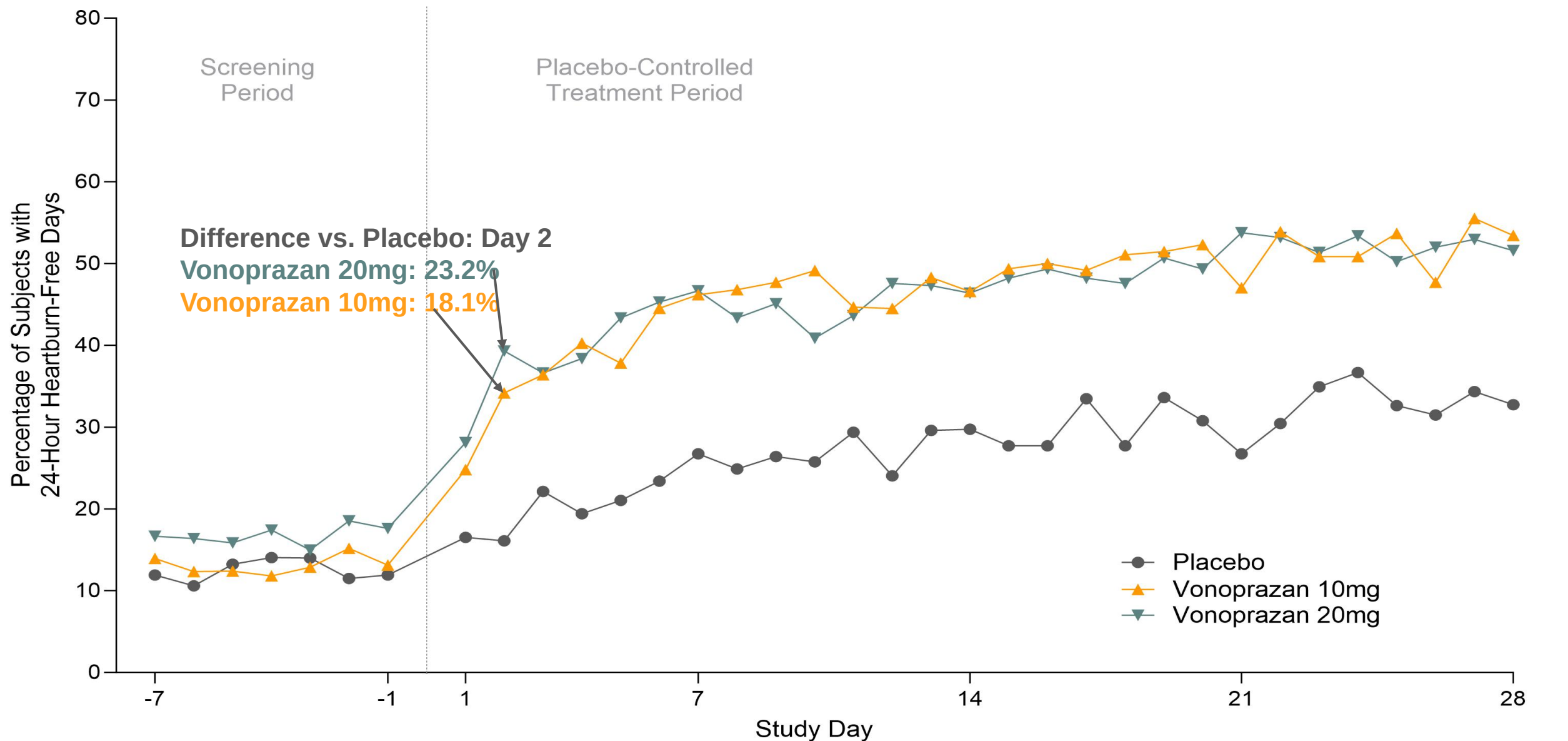
PERCENTAGE OF SUBJECTS WITHOUT HEARTBURN ON EACH DAY OF THE LAST WEEK OF THE SCREENING PERIOD AND THE PLACEBO-CONTROLLED PERIOD



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PERCENTAGE OF SUBJECTS WITHOUT HEARTBURN ON EACH DAY OF THE LAST WEEK OF THE SCREENING PERIOD AND THE PLACEBO-CONTROLLED PERIOD



RESULTS: PLACEBO-CONTROLLED PERIOD

	Placebo (N=258)		Vonoprazan 10mg (N=257)		Vonoprazan 20mg (N=257)		LS Mean Difference Vonoprazan 10mg vs. Placebo	LS Mean Difference Vonoprazan 20mg vs. Placebo
	LS Mean	Median	LS Mean	Median	LS Mean	Median		
24-hr heartburn-free days	27.7%	16.7%	44.8%	48.1%	44.4%	46.4%	17.1%*	16.7%*
24-hr days without rescue antacid	47.6%	50.0%	63.3%	75.9%	61.2%	73.9%	15.8%*	13.7%*

* p<0.0001

RESULTS: PLACEBO-CONTROLLED PERIOD

	Placebo (N=258)		Vonoprazan 10mg (N=257)		Vonoprazan 20mg (N=257)		LS Mean Difference Vonoprazan 10mg vs. Placebo	LS Mean Difference Vonoprazan 20mg vs. Placebo
	LS Mean	Median	LS Mean	Median	LS Mean	Median		
24-hr heartburn-free days	27.7%	16.7%	44.8%	48.1%	44.4%	46.4%	17.1%*	16.7%*
24-hr days without rescue antacid	47.6%	50.0%	63.3%	75.9%	61.2%	73.9%	15.8%*	13.7%*
Days without daytime heartburn	38.9%	33.3%	53.3%	62.1%	53.6%	66.7%	14.4%*	14.8%*
Days without nighttime heartburn	43.3%	45.5%	59.9%	70.4%	56.4%	71.0%	16.5%*	13.1%*
Heartburn severity (0-4)	1.0	0.8	0.7	0.4	0.7	0.4	-0.4*	-0.3*

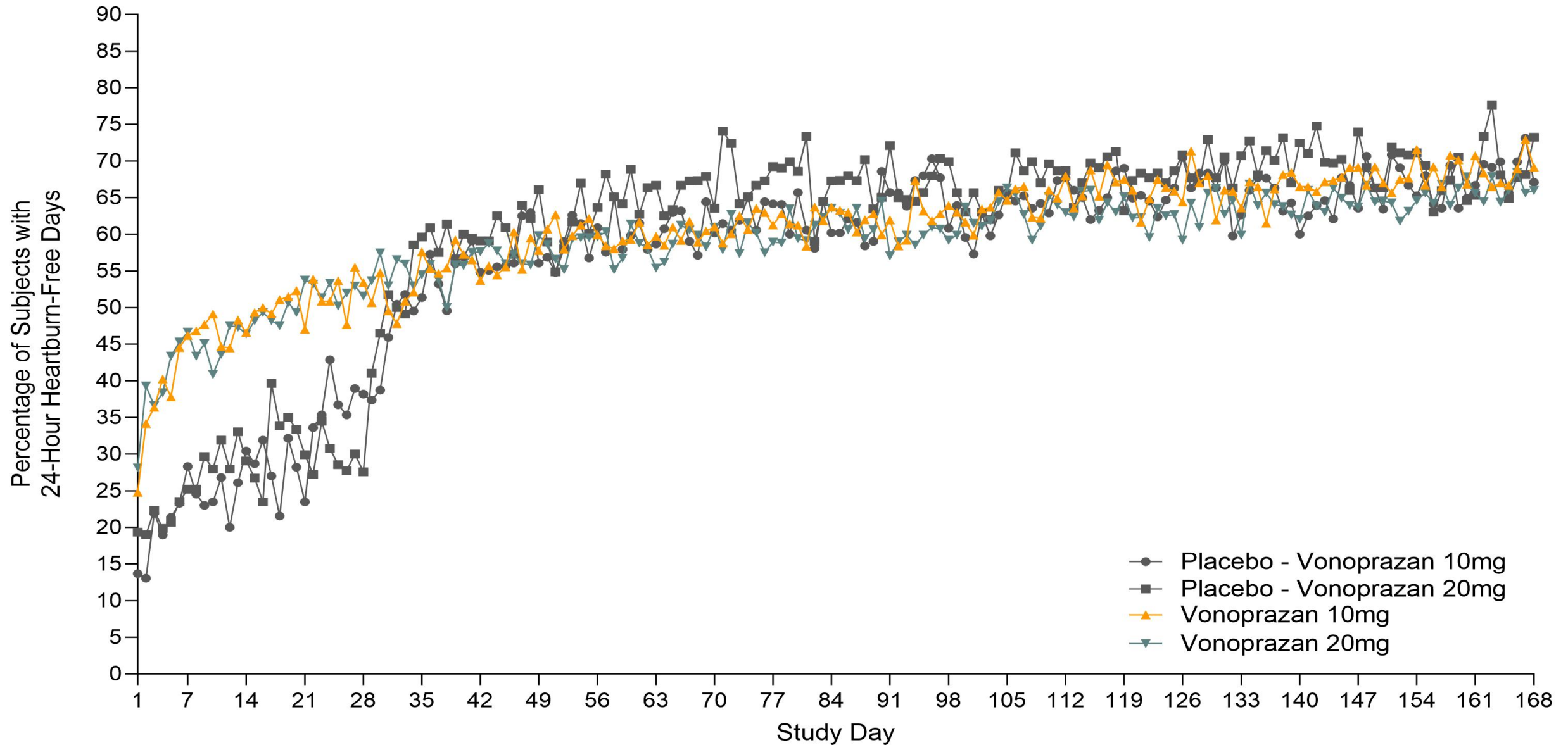
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RESULTS: PLACEBO-CONTROLLED PERIOD

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24-hr days without rescue antacid	47.6%	50.0%	63.3%	75.9%	61.2%	73.9%	15.8%*	13.7%*
Days without daytime heartburn	38.9%	33.3%	53.3%	62.1%	53.6%	66.7%	14.4%*	14.8%*
Days without nighttime heartburn	43.3%	45.5%	59.9%	70.4%	56.4%	71.0%	16.5%*	13.1%*
Heartburn severity (0-4)	1.0	0.8	0.7	0.4	0.7	0.4	-0.4*	-0.3*

* p<0.0001

PERCENTAGE OF SUBJECTS WITHOUT HEARTBURN ON EACH DAY OF THE PLACEBO-CONTROLLED PERIOD AND EXTENSION PERIOD



RESULTS: EXTENSION PERIOD

	Placebo to Vonoprazan 10mg (N=119)		Placebo to Vonoprazan 20mg (N=122)		Vonoprazan 10mg to 10mg (N=247)		Vonoprazan 20mg to 20mg (N=235)	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
24-hr heartburn-free days	61.9%	78.3%	62.9%	76.2%	62.6%	77.7%	60.7%	79.4%
24-hr days without rescue antacid	73.1%	91.5%	76.9%	93.2%	73.7%	90.0%	72.5%	91.7%
Days without daytime heartburn	70.5%	88.5%	71.2%	87.4%	69.8%	85.9%	68.0%	90.1%
Days without nighttime heartburn	70.7%	88.2%	71.2%	89.1%	72.5%	88.4%	70.2%	91.5%
Heartburn severity (0-4)	0.4	0.1	0.4	0.2	0.4	0.1	0.4	0.1

RESULTS: EXTENSION PERIOD

	Placebo to Vonoprazan 10mg (N=119)		Placebo to Vonoprazan 20mg (N=122)		Vonoprazan 10mg to 10mg (N=247)		Vonoprazan 20mg to 20mg (N=235)	
	Mean	Median	Mean	Median	Mean	Median	Mean	Median
24-hr heartburn-free days	61.9%	78.3%	62.9%	76.2%	62.6%	77.7%	60.7%	79.4%
24-hr days without rescue antacid	73.1%	91.5%	76.9%	93.2%	73.7%	90.0%	72.5%	91.7%
Days without daytime heartburn	70.5%	88.5%	71.2%	87.4%	69.8%	85.9%	68.0%	90.1%
Days without nighttime heartburn	70.7%	88.2%	71.2%	89.1%	72.5%	88.4%	70.2%	91.5%
Heartburn severity (0-4)	0.4	0.1	0.4	0.2	0.4	0.1	0.4	0.1

MEAN SERUM GASTRIN LEVELS THROUGHOUT STUDY

	Placebo to Vonoprazan 10mg	Placebo to Vonoprazan 20mg	Vonoprazan 10mg to 10mg	Vonoprazan 20mg to 20mg
Baseline, placebo- controlled period	43.9 (N=114)	58.9 (N=113)	50.4 (N=230)	43.7 (N=219)
Baseline, extension period	36.1 (N=118)	61.8 (N=120)	156.8 (N=247)	211.5 (N=235)
End of extension period	199.5 (N=97)	257.4 (N=95)	218.9 (N=203)	296.7 (N=196)
End of follow-up period	65.6 (N=101)	63.3 (N=96)	65.9 (N=205)	68.3 (N=199)

CONCLUSIONS

- **Strengths**

- **Double-blind, randomized design**
- **20-week active treatment extension for all subjects enrolled**
 - Scant evidence from prior prospective trials of antisecretory therapy in NERD over longer periods and only in selected patients with symptomatic relief prior to entry
- **Generalizability to U.S. population**
 - High proportions of Black (16%) and Latino (32%) subjects

- **Limitations**

- **Likely not all subjects had acid reflux as cause of symptoms**
 - May have had other etiologies: e.g., functional heartburn, weakly acid/non-acid reflux
 - No reflux testing required for enrollment--simulating real-world practice

CONCLUSIONS

The PCAB vonoprazan was efficacious in reducing heartburn symptoms in patients diagnosed with NERD

- Benefit appeared to begin as early as the first day of therapy
- Treatment effect persisted after the initial 4-week placebo-controlled period throughout the 20-week extension period
- The two vonoprazan doses (10 and 20mg) similar in efficacy