GI ReConnect

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Napa Valley, California

GI Health Foundation

GI ReConnect

What's New in GI Pharmacology

Philip Schoenfeld, MD, MSED, MSc (Epi)

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Faculty Disclosure

Philip Schoenfeld, MD, MSEd, MSc (Epi)-Potential Conflict of Interest Statement

- Ironwood Pharmaceuticals-Consultant, Advisory Board Member, Speaker Bureau
- AbbVie Pharmaceuticals- Consultant, Advisory Board Member, Speaker Bureau
- Salix Pharmaceuticals- Consultant, Advisory Board Member, Speaker Bureau
- Takeda Pharmaceuticals-Advisory Board Member
- Phathom Pharmaceuticals-Consultant, Advisory Board Member
- Alnylam Pharmaceuticals-Speaker Bureau

pHALCON-HP Study: Vonoprazan for Treatment of H.Pylori

- Vonoprazan: Potassium-competitive acid blocker
  - Competitively blocks availability of potassium to hydrogen-potassium ATPase.

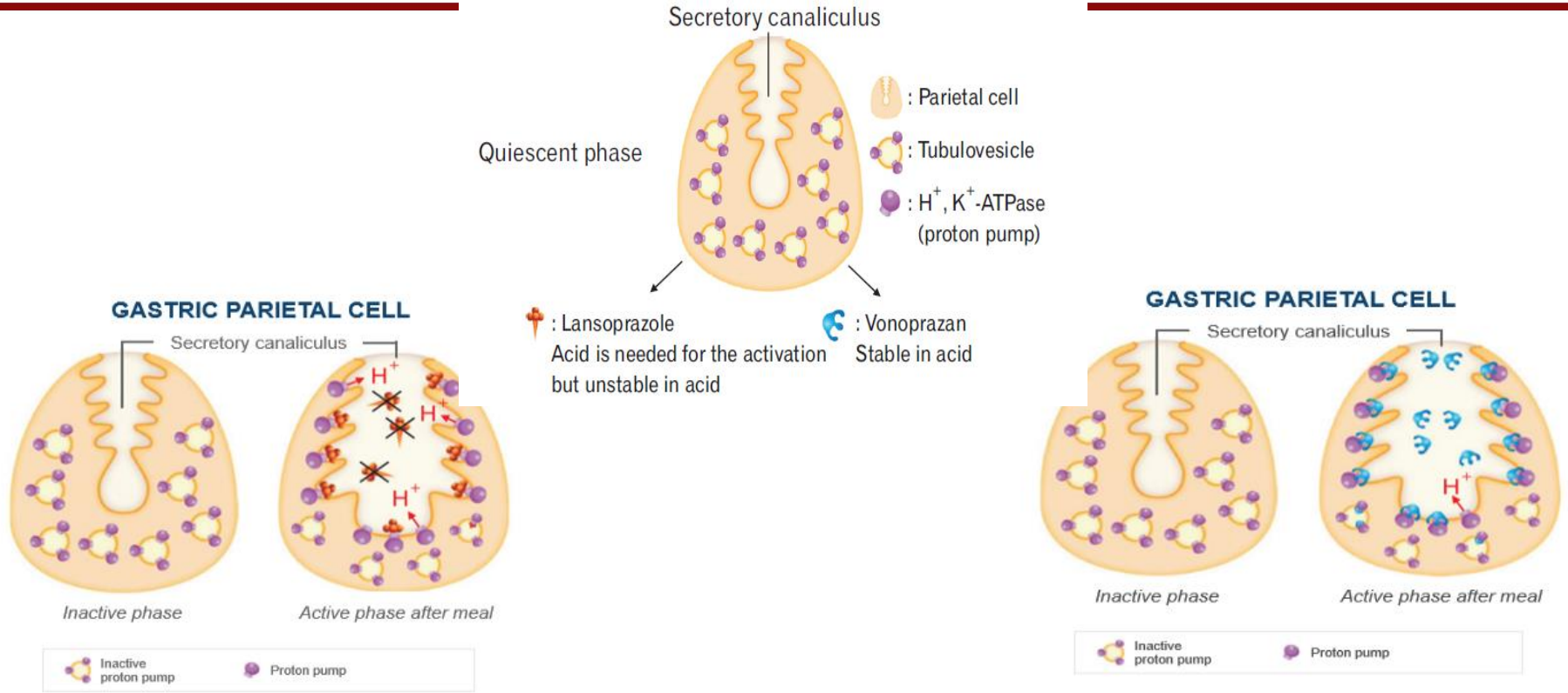
- Potential Benefits over Current PPIs:
  - Longer ½ life
  - More potent acid inhibition

Accessed at www.phathompharma.com-june 10 2021

Mechanism of Action: PPIs vs P-CABs

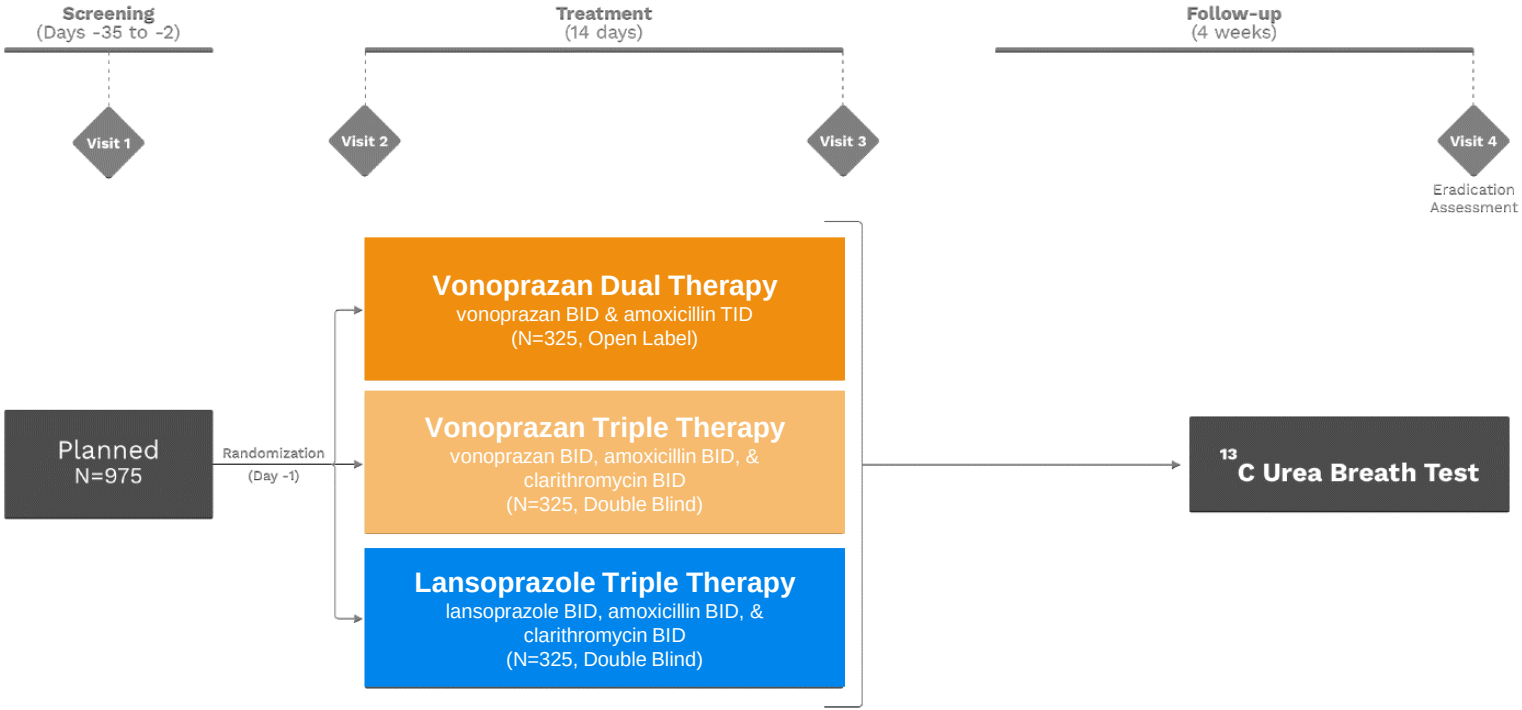
Proton Pump Inhibitors (PPIs) MOA

Potassium-Competitive Acid Blocker (P-CAB) MOA



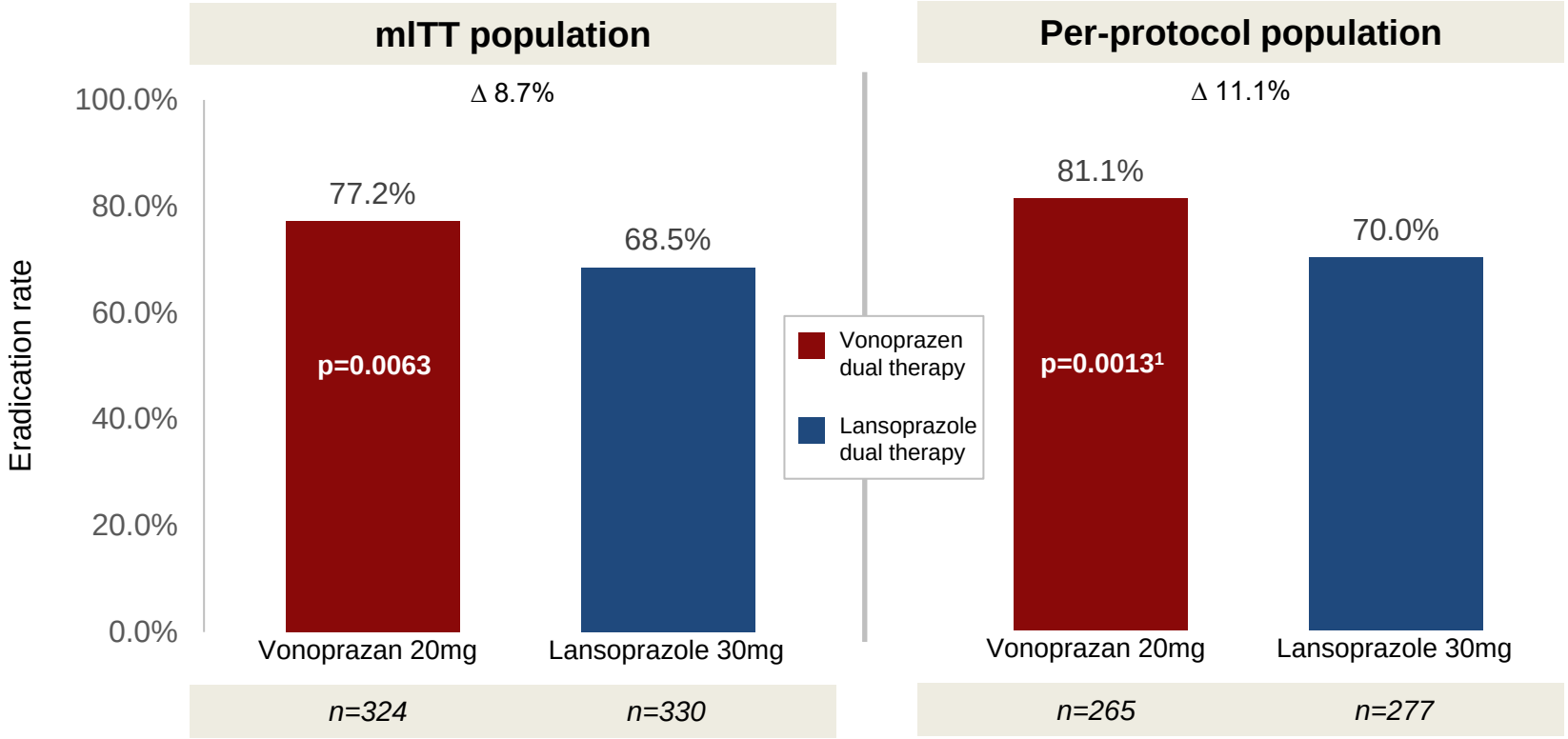
Oshima T, Miwa H. J Neurogastroenterol Motil. 2018;24(3):334-344.

pHALCON-HP Study: Vonoprazan Treatment of H.Pylori



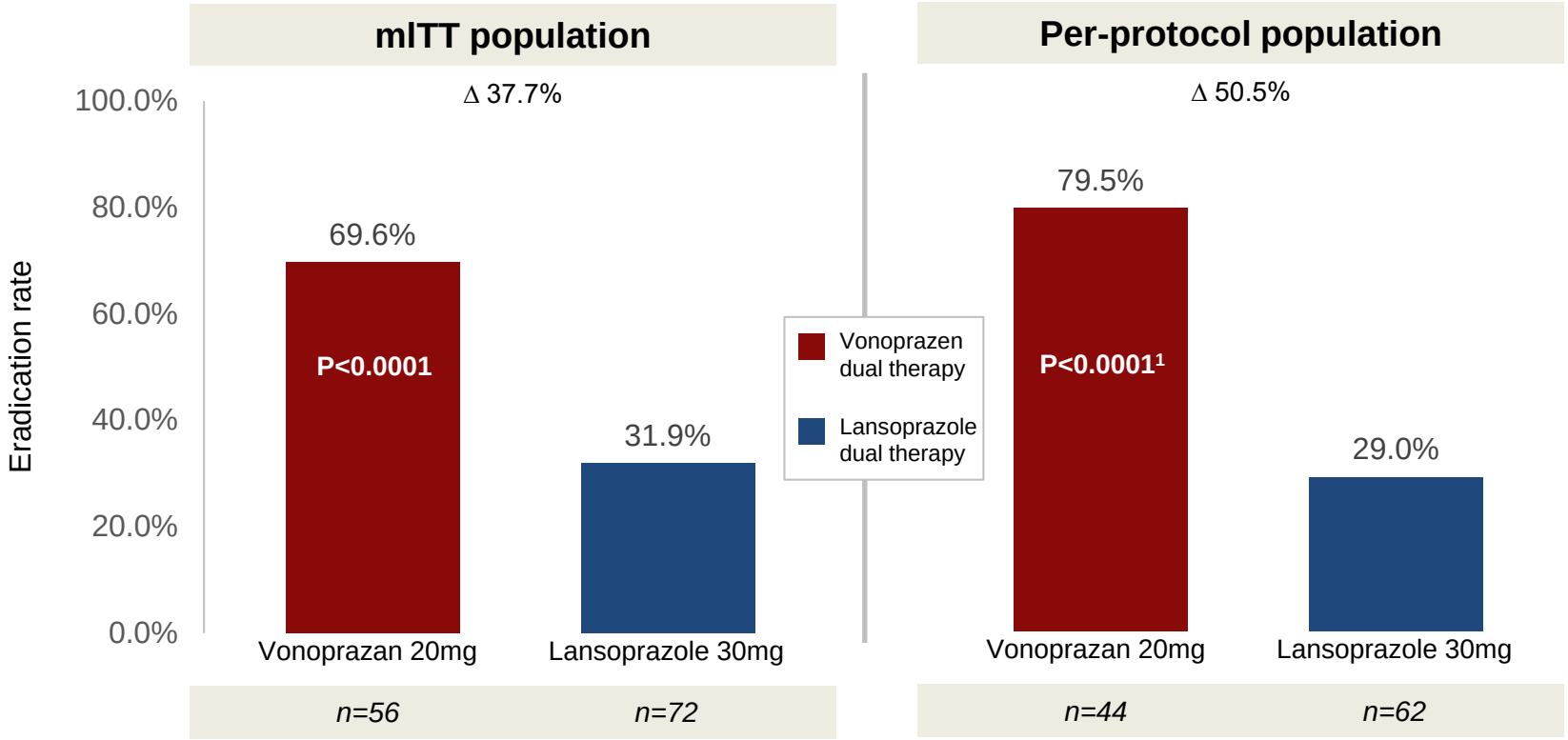
HP = *Helicobacter Pylori*; BID = twice daily; TID = three times daily.
Dosing: Vonoprazan 20 mg, amoxicillin 1000 mg, clarithromycin 500 mg, lansoprazole 30 mg.

Vonoprazan dual therapy vs Lansoprazole-All Subjects



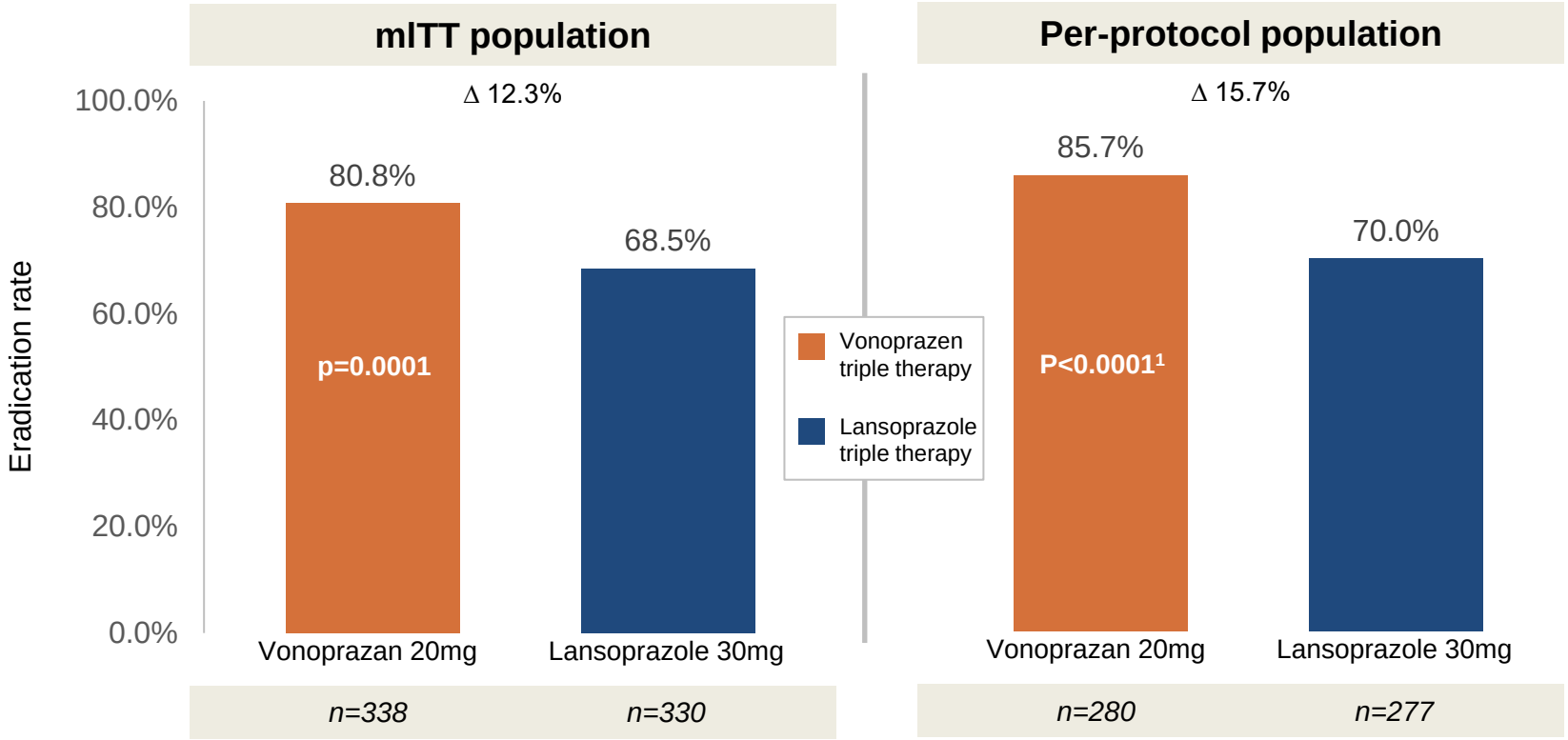
[1] *Not adjusted for multiple comparisons*

Vonoprazan dual therapy vs Lansoprazole-Clarithromycin resistant strains



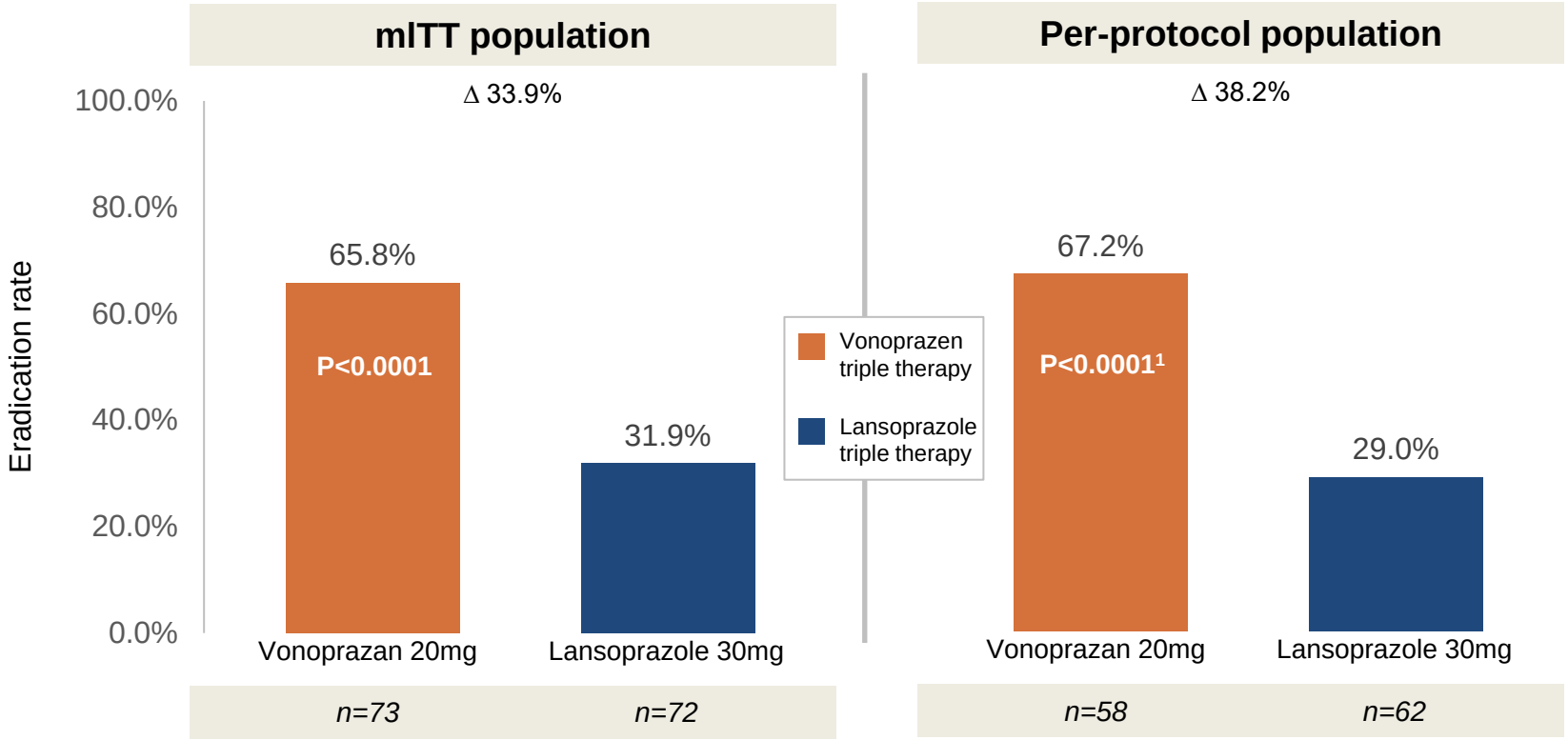
[1] *Not adjusted for multiple comparisons*

Vonoprazan triple therapy vs Lansoprazole- all subjects



[1] *Not adjusted for multiple comparisons*

Vonoprazan triple therapy vs Lansoprazole-clarithromycin resistant strains



[1] *Not adjusted for multiple comparisons*

Safety Profile

% (n) with adverse event	Vonoprazan triple therapy (n=346)	Vonoprazan dual therapy (n=348)	Lansoprazole triple therapy (n=345)
Diarrhea	4.0% (14)	5.2% (18)	9.6% (33)
Nausea	1.7% (6)	1.7% (6)	2.6% (9)
Dysgeusia	4.3% (15)	0.6% (2)	6.1% (21)
Headache	2.6% (9)	1.4% (5)	1.4% (5)
Vaginal infection	2.3% (8)	0.9% (3)	0.3% (1)

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Once-Weekly Semaglutide in Adults with Overweight or Obesity

METHODS

In this double-blind trial, we enrolled 1961 adults with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand (a precise description of the treatment effect reflecting the objective of the clinical trial) assessed effects regardless of treatment discontinuation or rescue interventions.

RESULTS

The mean change in body weight from baseline to week 68 was −14.9% in the semaglutide group as compared with −2.4% with placebo, for an estimated treatment difference of −12.4 percentage points (95% confidence interval [CI], −13.4 to −11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was −15.3 kg in the semaglutide group as compared with −2.6 kg in the placebo group (estimated treatment difference, −12.7 kg; 95% CI, −13.7 to −11.7). Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in participant-reported physical functioning from baseline than those who received placebo. Nausea and diarrhea were the most common adverse events with semaglutide; they were typically transient and mild-to-moderate in severity and subsided with time. More participants in the semaglutide group than in the placebo group discontinued treatment owing to gastrointestinal events (59 [4.5%] vs. 5 [0.8%]).

Michigan Ave., Suite 530, Chicago, IL 60611, or at rkushner@northwestern.edu.

*A complete list of investigators in the STEP 1 trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 10, 2021, at NEJM.org.

N Engl J Med 2021;384:989-1002.
DOI: 10.1056/NEJMoa2032183

Once Weekly Semaglutide in Adults for Overweight and Obesity

- Double-blind, RCT (2:1 randomization)
- 1961 non-diabetic patients with BMI $\geq$ 30
- Intervention: Semaglutide 2.4mg subq qweek or placebo plus lifestyle intervention X 68 weeks
- Co-primary endpoint: (a) % change in body weight; (b) weight reduction $\geq$ 5%

N Engl J Med 2021; 384: 989-1002.

Once Weekly Semaglutide in Adults for Overweight and Obesity: Results

- Mean change in body weight: 14.9% vs 2.4%, respectively, $p < 0.001$

  Treatment Effect: 12.5% reduction (95% CI: 11.5-13.4%)

- Weight reduction $\geq$ 5% body weight: 86.4% vs 31.5%, $p < 0.001$

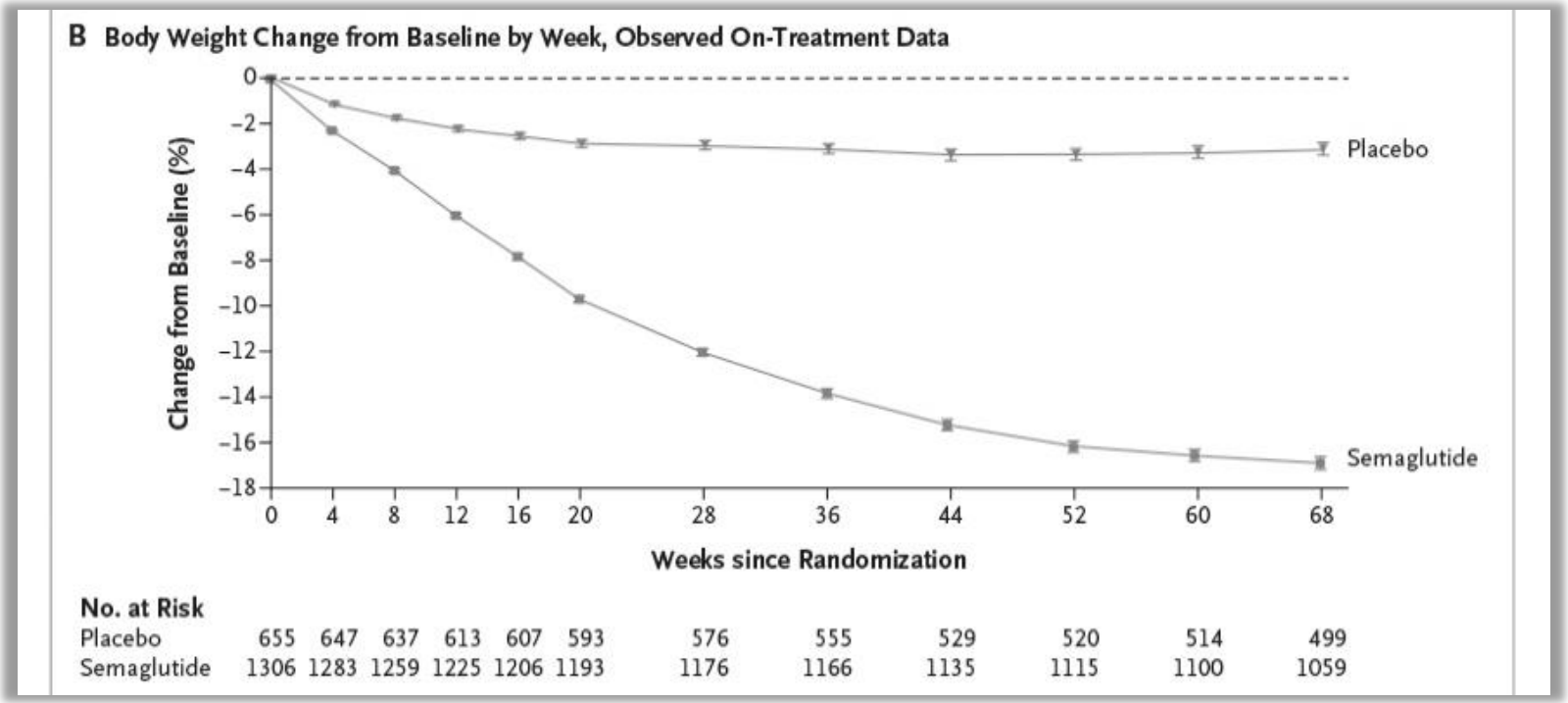
  $\geq$ 15% body weight reduction: 50.5% vs 4.9%, $p < 0.001$

- Mean weight reduction: 33.7 lbs vs 5.7 lbs, $p < 0.001$

  Treatment Effect: 28 lbs reduction vs placebo (95% CI: 30.1 vs 25.7 lbs)

N Engl J Med 2021; 384: 989-1002.

Once-Weekly Semaglutide for Treatment of Overweight and Obesity



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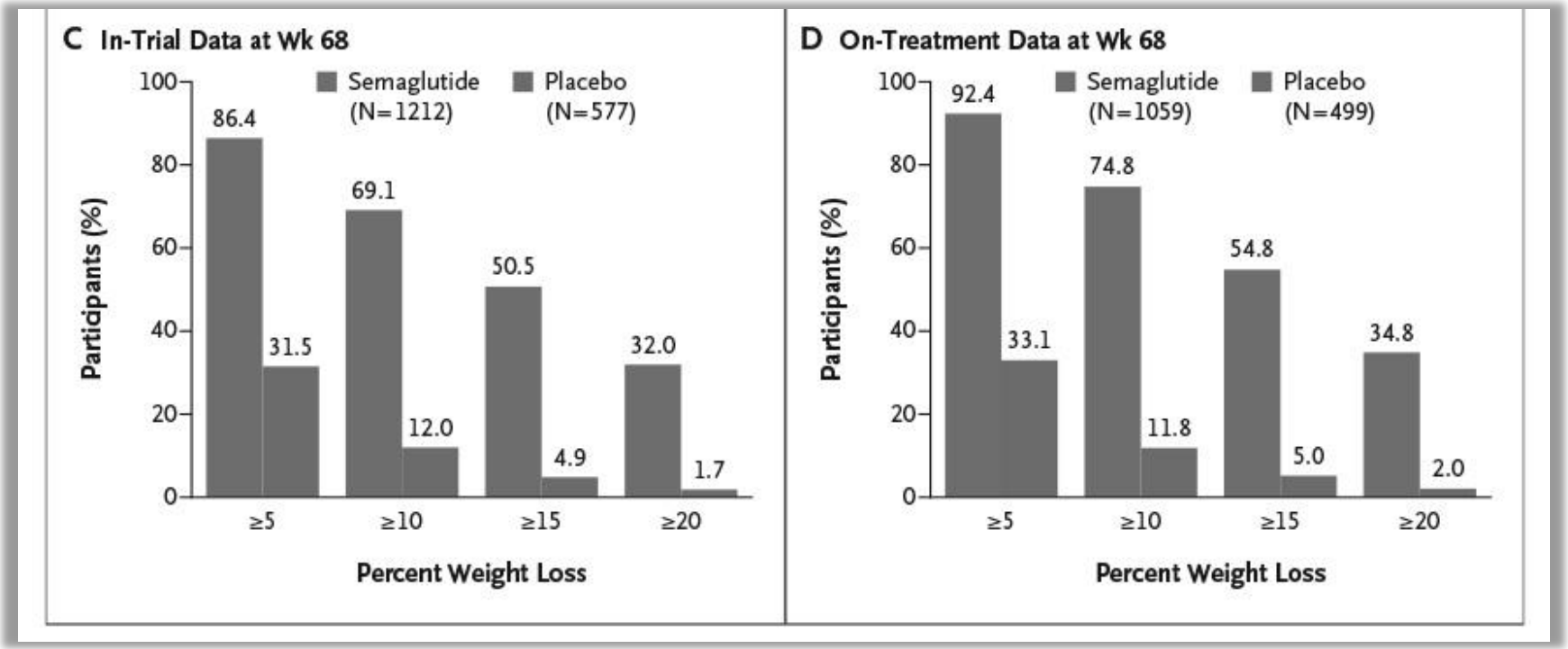

N Engl J Med 2021; 384: 989-1002

Once Weekly Semaglutide for Treatment of Overweight and Obesity

Table 3. **Adverse Events.***

Adverse Event	Semaglutide (N = 1306)			Placebo (N = 655)		
	No. of participants (%)	No. of events	Events/100 person-yr	No. of participants (%)	No. of events	Events/100 person-yr
Any adverse event	1171 (89.7)	9658	566.1	566 (86.4)	3302	398.0
Serious adverse events	128 (9.8)	164	9.6	42 (6.4)	53	6.4
Adverse events leading to discontinuation of drug or placebo	92 (7.0)	123	7.2	20 (3.1)	23	2.8
Gastrointestinal disorders	59 (4.5)	78	4.6	5 (0.8)	5	0.6
Fatal events†‡	1 (0.1)	1	0.1	1 (0.2)	3	0.3
Adverse events reported in ≥10% of participants§						
Nausea	577 (44.2)	1068	62.6	114 (17.4)	146	17.6
Diarrhea	412 (31.5)	766	44.9	104 (15.9)	138	16.6
Vomiting	324 (24.8)	636	37.3	43 (6.6)	52	6.3
Constipation	306 (23.4)	390	22.9	62 (9.5)	73	8.8
Nasopharyngitis	281 (21.5)	480	28.1	133 (20.3)	216	26.0
Headache	198 (15.2)	387	22.7	80 (12.2)	104	12.5
Dyspepsia	135 (10.3)	179	10.5	23 (3.5)	30	3.6
Abdominal pain	130 (10.0)	175	10.3	36 (5.5)	41	4.9
Upper respiratory tract infection	114 (8.7)	158	9.3	80 (12.2)	116	14.0
Safety focus areas¶						
Gastrointestinal disorders‖	969 (74.2)	4309	252.6	314 (47.9)	739	89.1

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Once Weekly Semaglutide for Treatment of Overweight and Obesity

Discontinuation due to GI adverse events: 4.5% vs 0.8%

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GI ReConnect


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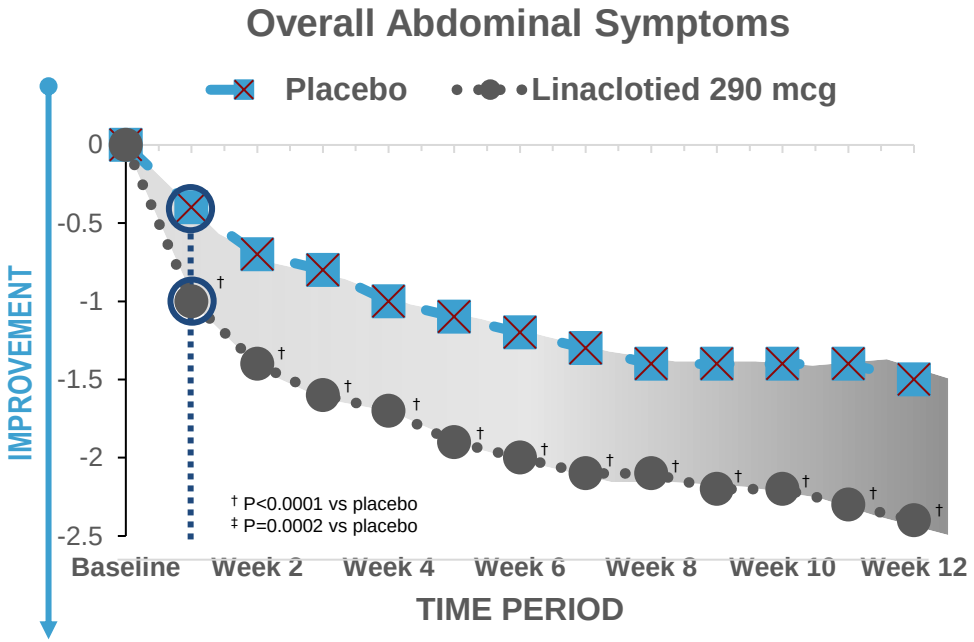
7.
BRISTOL STOOL CHART
Happy Birthday
Daddy

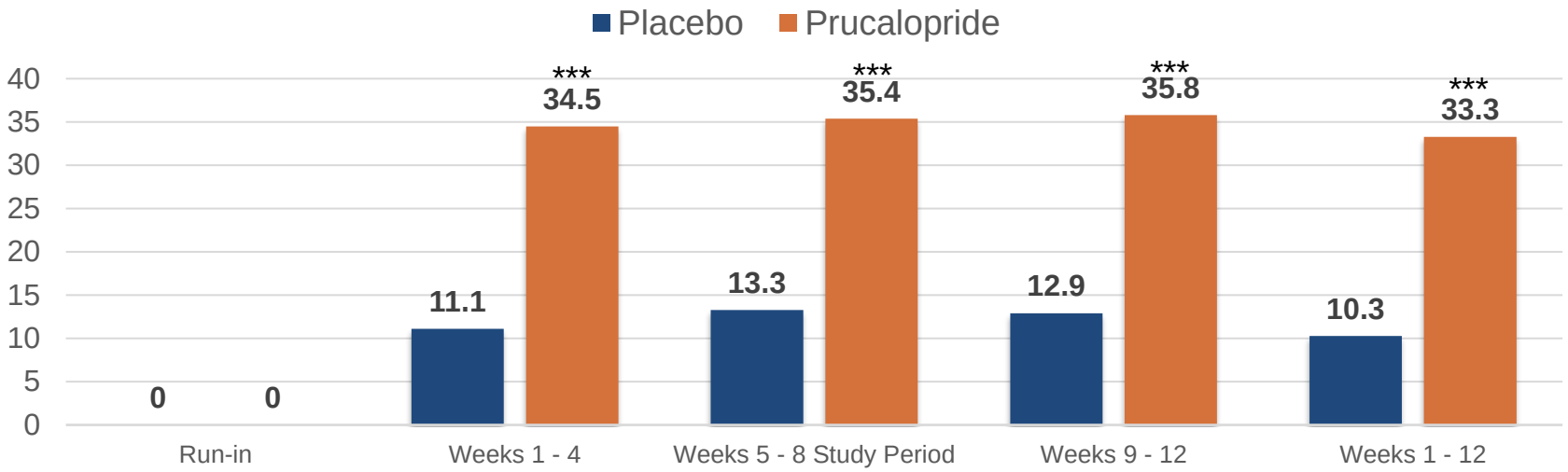
Linaclotide Decreases Overall Abdominal Symptoms (Bloating, Pain, Discomfort) in IBS-C

- Phase IIIB RCT of IBS-C patients
- Proportion of abdominal symptom responders approximately double in linaclotide group (34% vs 18.5%)



Linzess Prescribing Information September 2020.

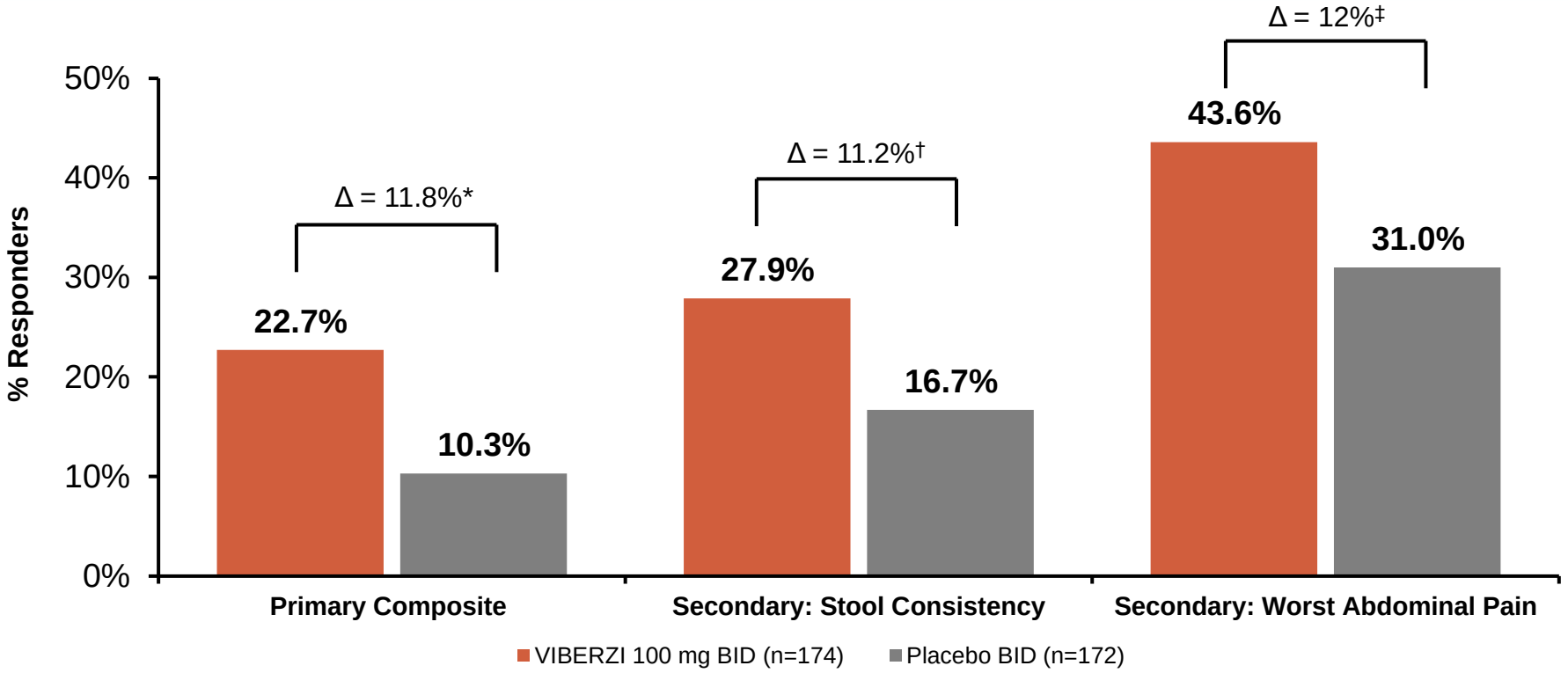
Prucalopride (Motegrity®) vs Placebo in CIC- Results of Double-blind RCT



- Endpoint: Percentage of patients with > 3 complete spontaneous bowel movements per week.
- At baseline, study patients have zero complete spontaneous bowel movements per week.

Ke M, et al. *Neurogastroenterol Motil* 2012; 24: 999.

RELIEF Trial: Eluxadoline in Loperamide Failures



Am J Gastroenterol 2019; 114: 1502-11

Treatment of IBS-C*

Class	Agent	Recommendation	Quality of Evidence
Soluble fiber**	Psyllium (Metamucil®)	Strong	Moderate
Chloride channel activator	Lubiprostone (Amitiza®)	Strong	Moderate
Secretagogues	Linaclotide (Linzess®) Plecanatide (Trulance®)	Strong Strong	High High

Recommends against use of PEG products (MiraLax®) for IBS-C and recommends against anti-spasmodic agents, including dicyclomine (Bentyl®), for global IBS.

*Strength of recommendations and quality of evidence determined using GRADE (Grading of Recommendations Assessment Development and Evaluation).
**For global IBS symptom improvement in any type of IBS
1. Lacy B et al. Am J Gastroenterol. 2021;116:17-44; 2. Guyatt et al. J Clin Epidemiol. 2011;64:383-94.

Treatment of IBS-D*

Class	Agent	Recommendation	Quality of Evidence
Antibiotic	Rifaximin (Xifaxan®)	Strong	Moderate
Mixed peripheral opiod-receptor	Eluxadoline (Viberzi®)	Conditional	Moderate
Tri-cyclic antidepressants	Consider Nortriptyline (Pamelor®)	Strong	Moderate
Peppermint Oil**	Various forms	Conditional	Low

Recommends against using probiotics for global IBS.

*Strength of recommendations and quality of evidence determined using GRADE (Grading of Recommendations Assessment Development and Evaluation).
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