Plecanatide, a Novel Uroguanylin Analog: a 12-week, randomized, double-blind, placebo-controlled, dose-ranging trial to evaluate efficacy and safety in patients with irritable bowel syndrome with constipation (IBS-C)

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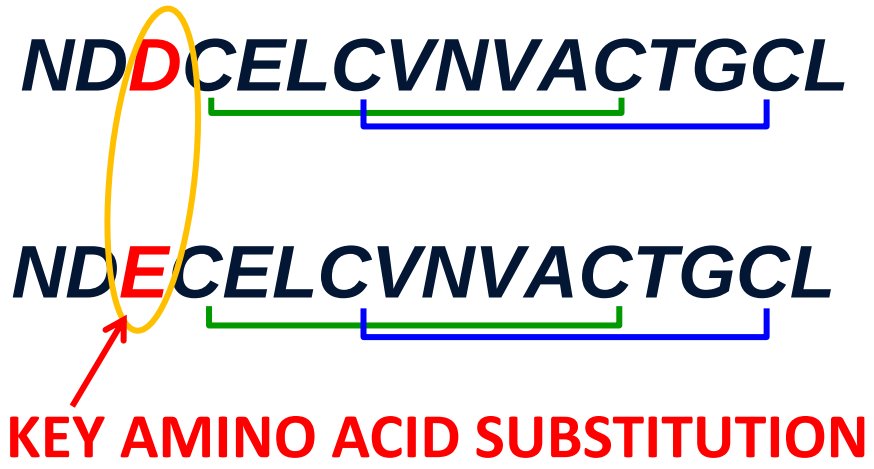
Plecanatide: a Novel Uroguanylin Analog

Uroguanylin:
Natural GC-C Ligand

Plecanatide:
Uroguanylin Analog



ST Peptide:
***E. coli* Bacteria**

Linaclotide:
Bacterial Enterotoxin

Plecanatide Phase 2b IBS-C Trial: Study Overview

Design:

- Randomized, 12-week, double blind, placebo-controlled, dose-ranging study

Population:

- Rome III Criteria for IBS-C

Treatment Groups:

- 0.3, 1.0, 3.0 and 9.0 mg plecanatide or placebo

Drug Administration:

- Once-daily oral tablet

Plecanatide Phase 2b IBS-C Trial: Patient Characteristics

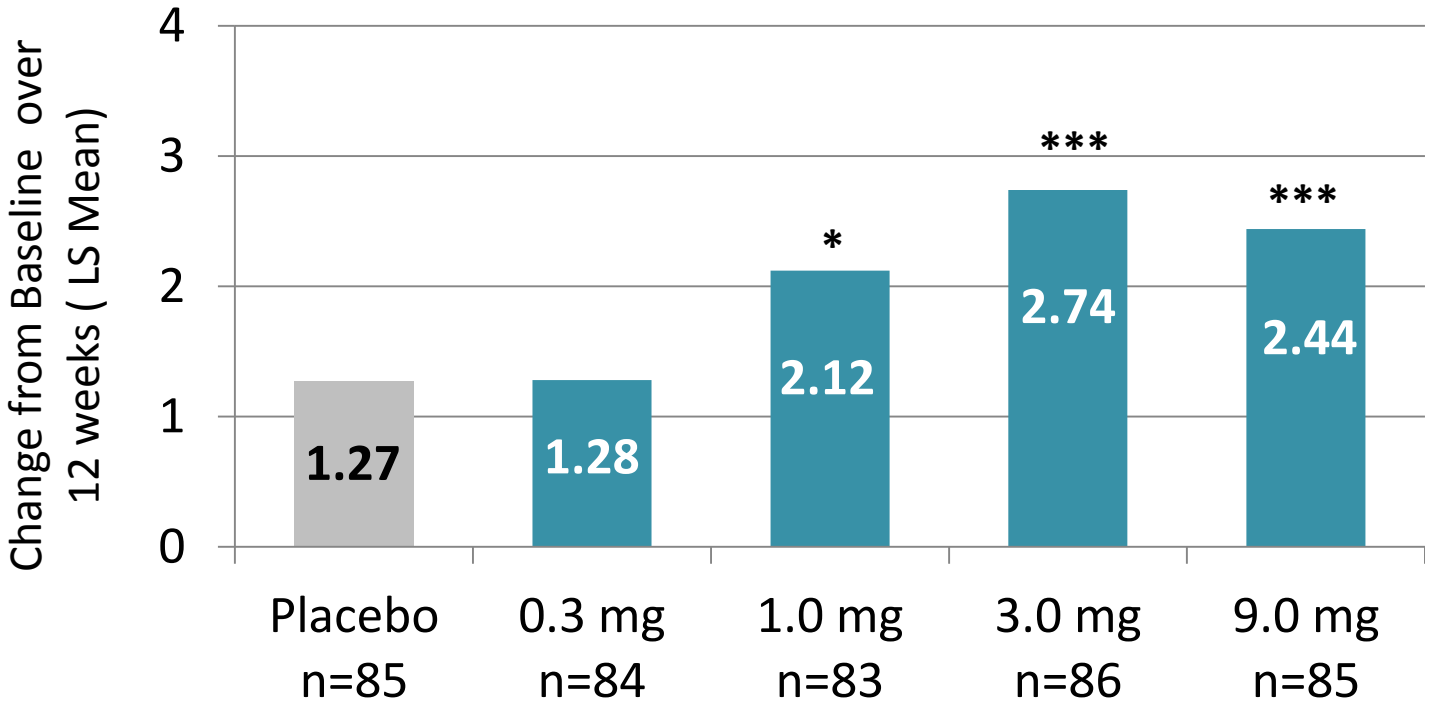
mITT Population (N= 423)

	Placebo (n=85)	0.3 mg (n=84)	1.0 mg (n=83)	3.0 mg (n=86)	9.0 mg (n=85)
Gender [n, (%)]					
Male	16 (18.8%)	16 (19.0%)	16 (19.3%)	16 (18.6%)	15 (17.6%)
Female	69 (81.2%)	68 (81.0%)	67 (80.7%)	70 (81.4%)	70 (82.4%)
Race [n, (%)]					
White	56 (65.9%)	57 (67.9%)	60 (72.3%)	63 (73.3%)	65 (76.5%)
Other	29 (34.1%)	27 (32.1%)	23 (27.7%)	23 (26.7%)	20 (23.5%)
Ethnicity [n, (%)]					
Hispanic or Latino	33 (38.8%)	25 (29.8%)	30 (36.1%)	37 (43.0%)	31 (36.5%)
Other	52 (61.2%)	59 (70.2%)	53 (63.9%)	49 (57.0%)	54 (63.5%)
Baseline Stool Frequency					
SBM per week	1.66	1.76	1.79	1.78	1.42
CSBM per week	0.25	0.23	0.22	0.27	0.25

Plecanatide Phase 2b IBS-C Trial: Statistical Approach to Missing Diary Data

1. **Primary Analysis of the Primary Endpoint:**
   - ***Observed Case Methodology***
     - Any missing diary entry in a week with partial data was assigned as *'no CSBM'*
     - If < 4 diary entries/week, entire week was set to zero *('no CSBM'),* assumption weekly data '*missing at random*'
2. **Sensitivity Analyses of the Primary Endpoint:**
   - Alternative missing data conventions (independent of Observed Case methodology)
     - ***Mean Replacement Approach (MRA)***
     - ***Last Observation Carried Forward (LOCF)***

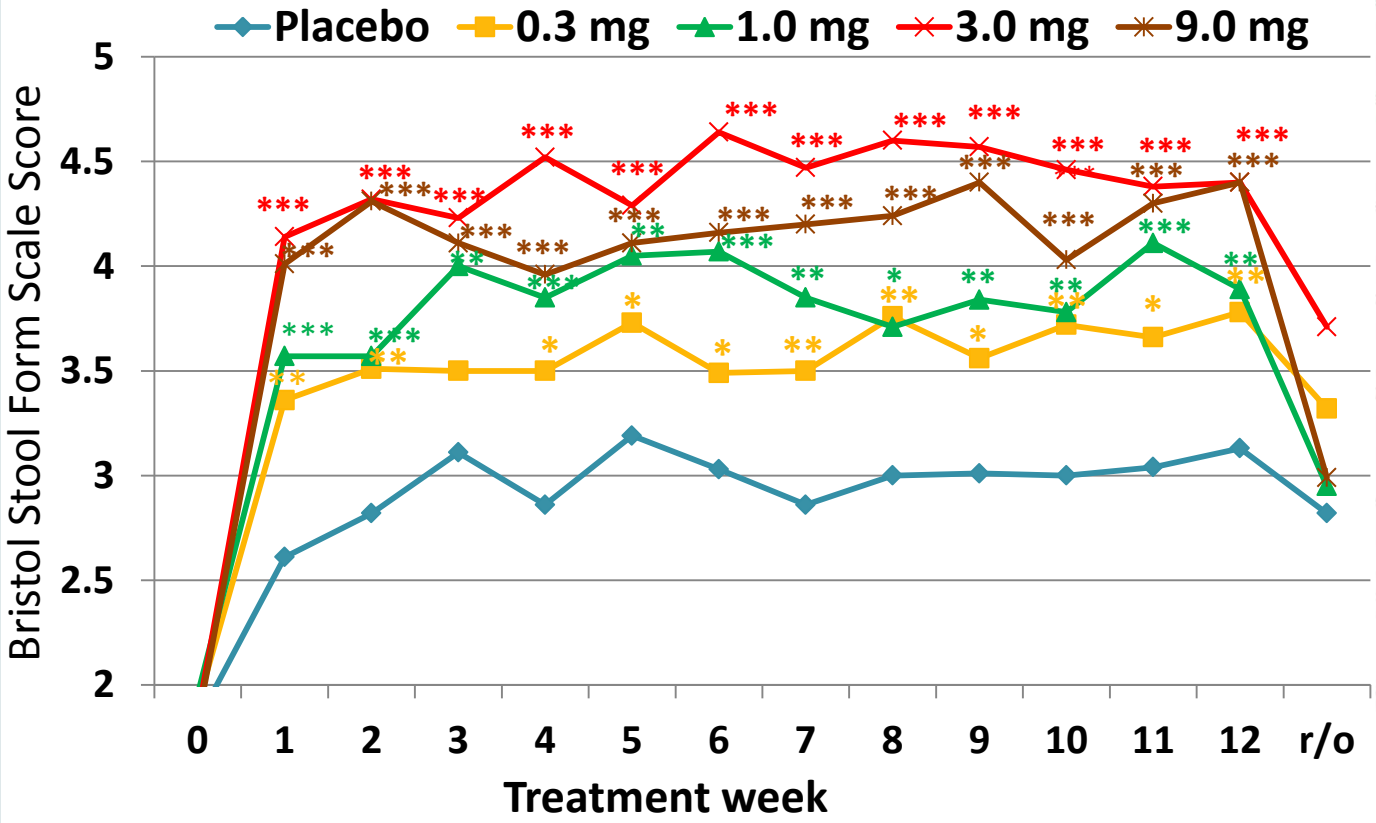
Primary Endpoint:
Mean Change from Baseline in CSBM Frequency

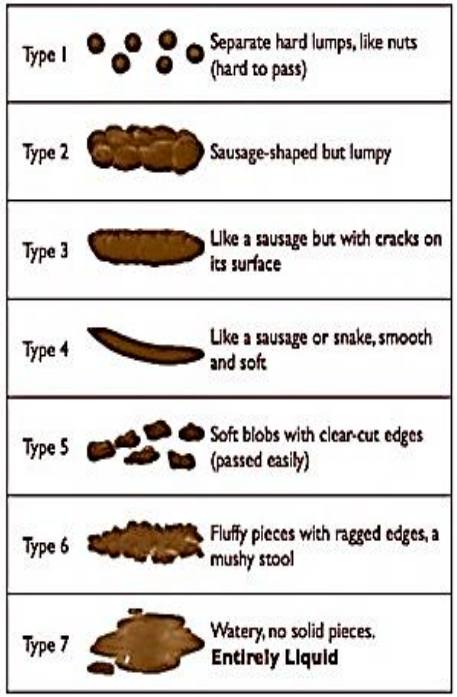


*= $p < 0.05$; ***= $p < 0.001$

Note: mITT population

Secondary Endpoint: Stool Consistency (BSFS)



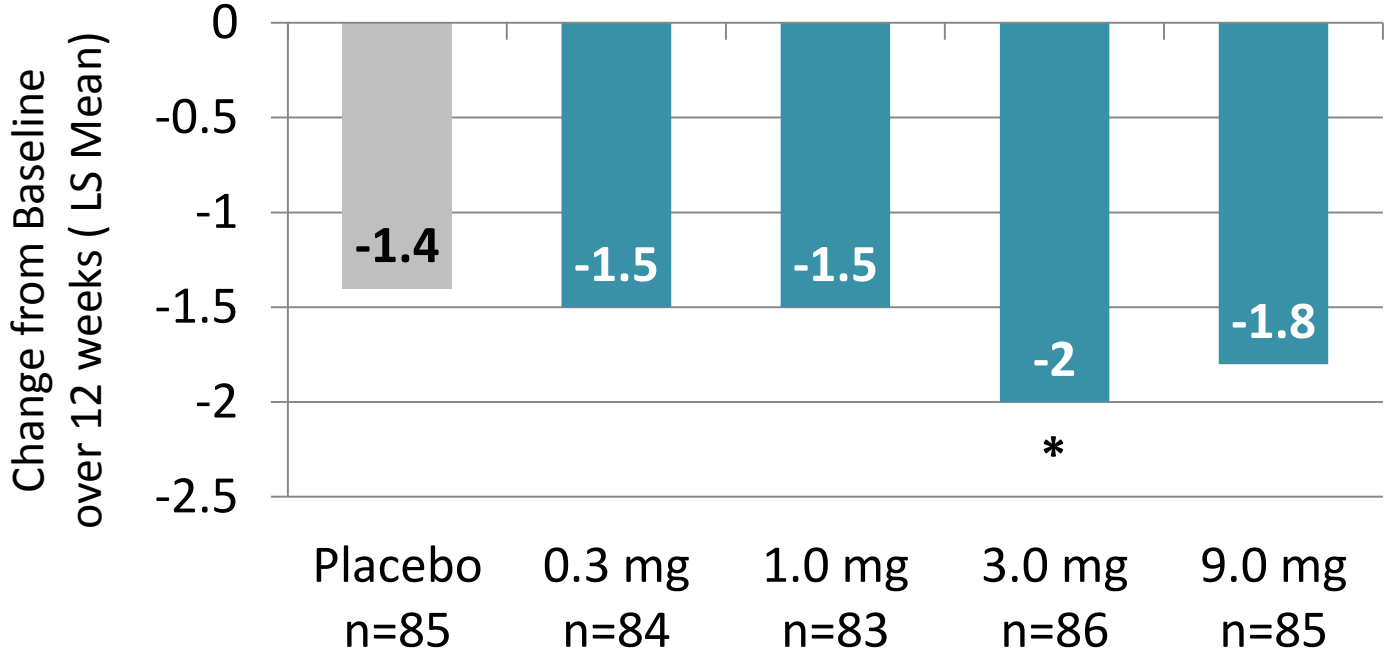


* = p<0.05; ** = p < 0.01; *** = p < 0.001

Note: mITT population

Secondary Endpoint: Abdominal Pain Intensity

"For today, rate your abdominal pain at its worst on a scale of 0 to 10"

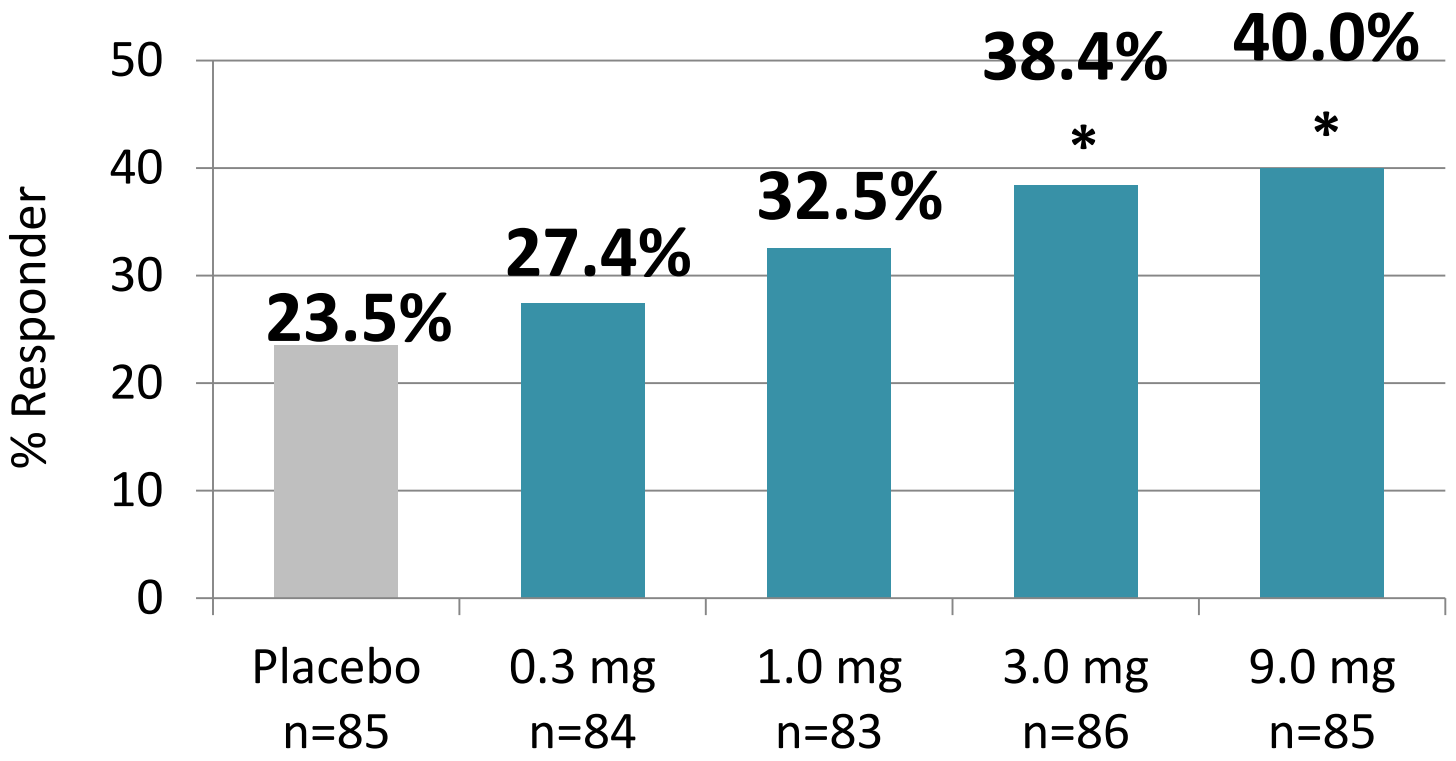


* = $p < 0.05$

Note: mITT population

Secondary Endpoint: Abdominal Pain Responder

Abdominal Pain Responder= ≥ 30% reduction in pain in 9 out of 12 treatment weeks (75%)

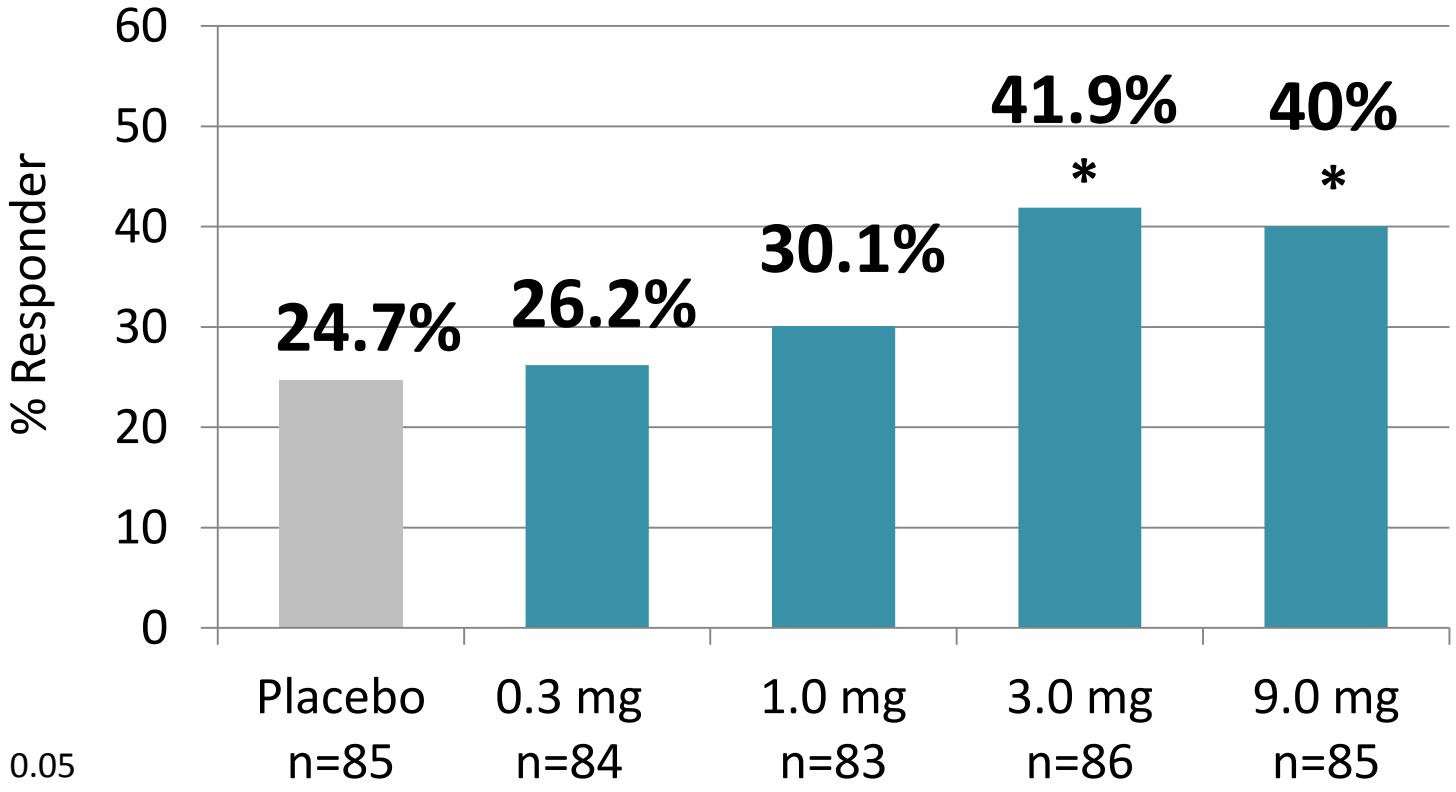


*p < 0.05

Note: mITT population

Secondary Endpoint: Overall Responder (FDA Endpoint)

Overall Responder= fulfills both ≥ 30% reduction in worst abdominal pain *and* Increase of ≥ 1 CSBMs from baseline in the same week for at least 50% of the weeks (6/12 weeks)



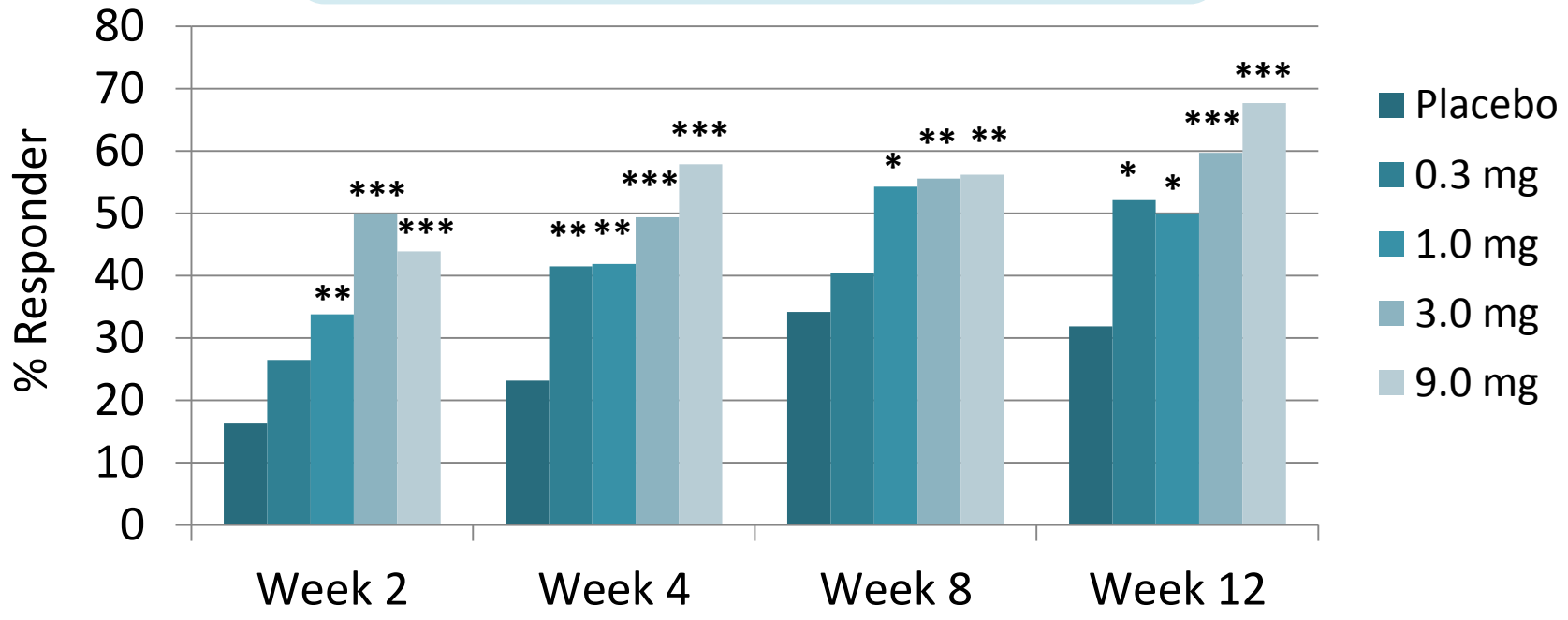
* $p < 0.05$

Note: mITT population

Secondary Endpoint: Ability to Relieve IBS-C Symptoms

"How would you rate the ability of your study drug treatment to provide relief from your IBS-C symptoms?"

Responder= Patient's response is considerable or completely improved

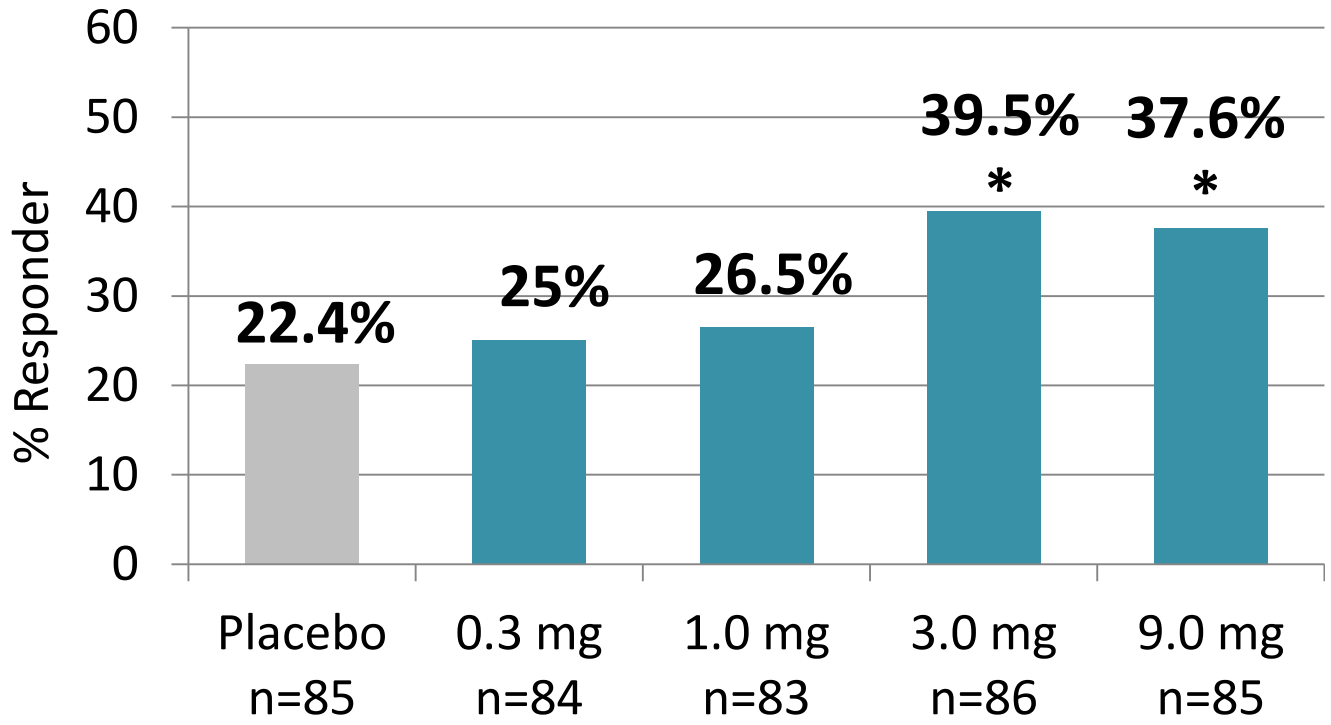


* p< 0.05 ** p≤0.01 *** p≤ 0.001

Note: mITT Population

Post Hoc Analysis:
Sustained Responder Rate

Sustained Responder= ≥ 30% decrease in worst abdominal pain + an increase = 1 CSBM/wk for at least 50% of the weeks (6/12)
+ at least two weeks of response in month 3



*p < 0.05

Note: mITT population

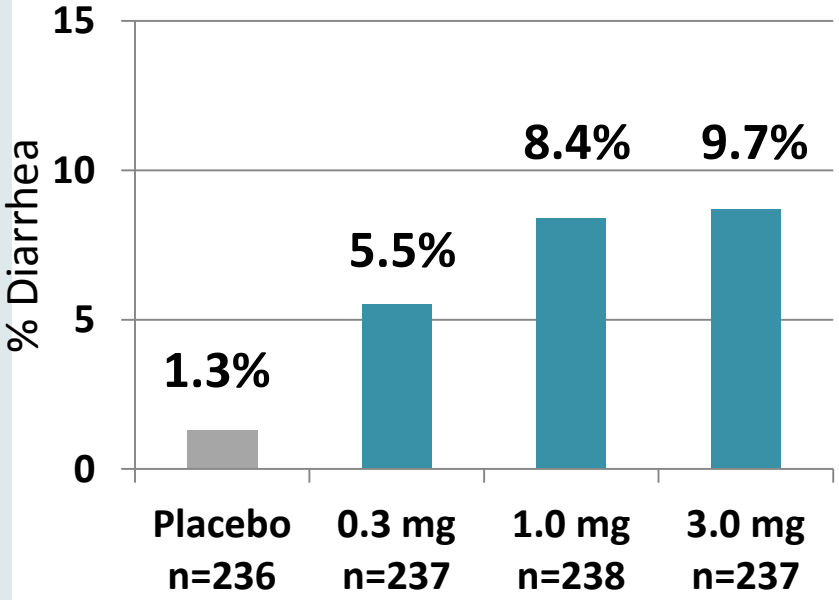
Plecanatide Phase 2b IBS-C Trial: Summary of Adverse Events (AEs)

	Placebo n= 86	0.3 mg n= 85	1.0 mg n= 85	3.0 mg n= 86	9.0 mg n= 85
Treatment-emergent adverse events (TEAEs)	30 (34.9%)	37 (43.5%)	41 (48.2%)	37 (43.0%)	40 (47.1%)
Serious AEs	0	1 (1.2%)	0	1 (1.2%)	2 (2.4%)
Mild Diarrhea	0	0	5 (5.9%)	3 (3.5%)	2 (2.4%)
Moderate Diarrhea	0	1 (1.2%)	2 (2.4%)	5 (5.8%)	5 (5.9%)
Severe Diarrhea	0	2 (2.4%)	1(1.2%)	0	3 (3.5%)
All Diarrhea TEAEs	0	3 (3.5%)	8 (9.4%)	8 (9.3%)	10 (11.8%)
Discontinued due to any TEAE	1 (1.2%)	1 (1.2%)	5 (5.9%)	7 (8.1%)	6(7.1%)
Discontinued due to Diarrhea	0	0	1 (1.2%)	5 (5.8%)	3 (3.5%)

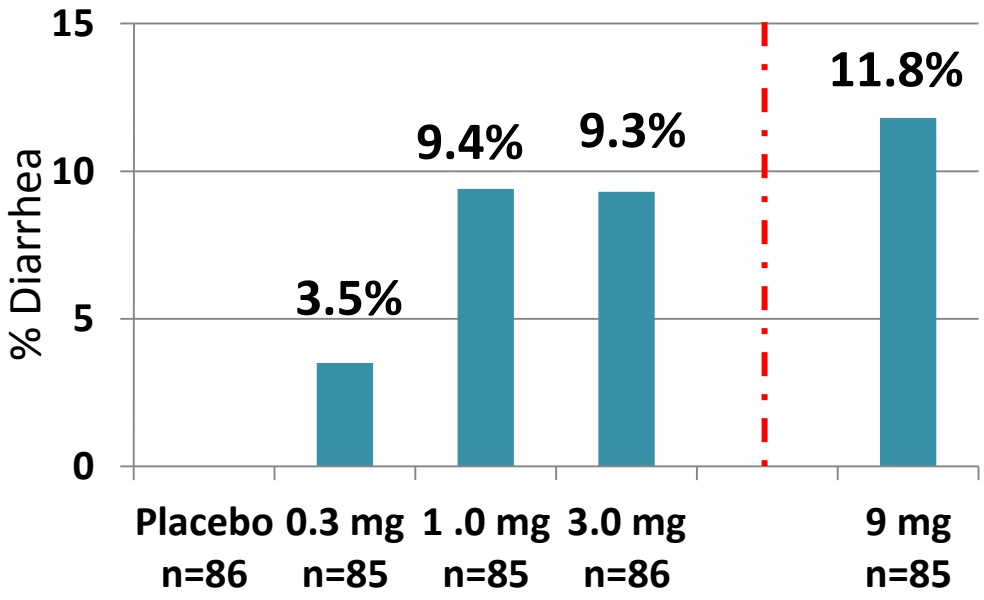
No signals in vital signs, hematology, serum chemistries, urinalysis or ECG

Plecanatide:
Consistent Tolerability Profile for CIC & IBS-C

CIC Phase 2b Trial



IBS-C Phase 2b Trial



Note: This is a cross trial comparison.
Plecanatide phase 2b CIC trial did not include 9.0 mg dose.

Plecanatide Phase 2b IBS-C Trial: Data Confirm Efficacy, Safety & Unique Profile

- Plecanatide was safe, well tolerated and efficacious for treatment of IBS-C patients
- Trial confirms dose-response pharmacology
- Predictable treatment response: efficacy and safety observed in same dose range as CIC trials
- 3.0 and 6.0 mg doses selected for phase 3 IBS-C development (consistent with CIC)