Plecanatide, A Novel Guanylate Cyclase-C Receptor Agonist, is Efficacious and Safe in Patients with Chronic Idiopathic Constipation: Results from a 951 Patient, 12 Week, Multi-Center Trial

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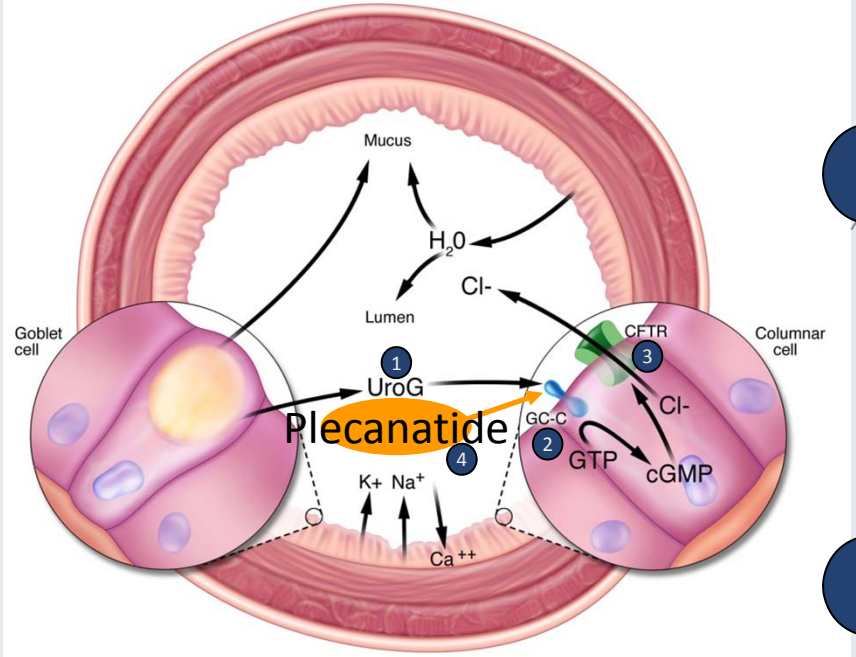
Plecanatide: Novel Approach to the Treatment of GI Disorders

- Analogue of uroguanylin- natural agonist of guanylate-cyclase C (GC-C) receptor
- Oral once-daily dosing
- Targets GC-C receptor in GI tract
- Essentially non-systemic
- Models normal physiology

Guanylate Cyclase C Receptor Agonists

Physiological mechanism

Cross section of the GI tract



1. Uroguanylin (UroG) activates guanylate cyclase-C (GC-C) receptors on the lumenal side of the gut

2. Activation of GC-C receptors stimulates synthesis of cyclic GMP, activating cystic fibrosis transmembrane conductance regulator (CFTR)

3. Activated CFTR secretes Cl-, HCO3- and fluid into the intestinal lumen. Secretion of fluid into intestine is critical for normal digestion

4. Plecanatide binds to GC-C receptors, promoting spontaneous bowel movement (SBM)

Plecanatide: A Novel Mechanism of Action to Treat Chronic Constipation and IBS-C

- 16 mer peptide with 2 disulfide bonds
- Structurally similar to uroguanylin

Uroguanylin (UroG) – Natural Hormone

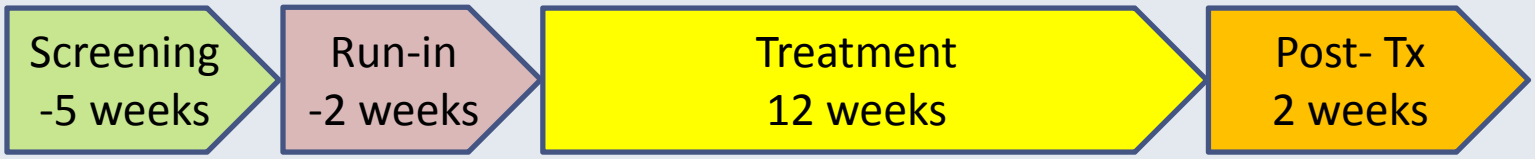
Plecanatide – Uroguanylin Analog

- Plecanatide binding constant to human GC-C receptors is 8-fold higher than uroguanylin
- No systemic absorption up to single oral doses of 48.6 mg
- Phase I and IIA Clinical Summary:
  - Results suggest Plecanatide will be useful in treating CIC and IBS-C

Protocol Design

- **Aim:** Determine safety, effectiveness and dose-response of Plecanatide in CIC patients
- Randomized, double–blind, placebo controlled, parallel group, stratified by gender, multicenter study
- Population: modified Rome III CIC criteria, including < 3 CSBMs/week
- Evaluation of Plecanatide doses: 0.3, 1.0 & 3.0 mg given QD for 12 weeks

Protocol Design:



Key Protocol Inclusion/Exclusion

- **Inclusion**
  - Modified Rome III for CIC including < 3 CSBM during each week of 2 week pre-treatment
- **Exclusion**
  - Rome III IBS-C diagnosis
  - Previous major GI surgical history
  - Recognized causes of constipation (opioids, iron supplements, hypothyroidism, etc.)

Patient Populations

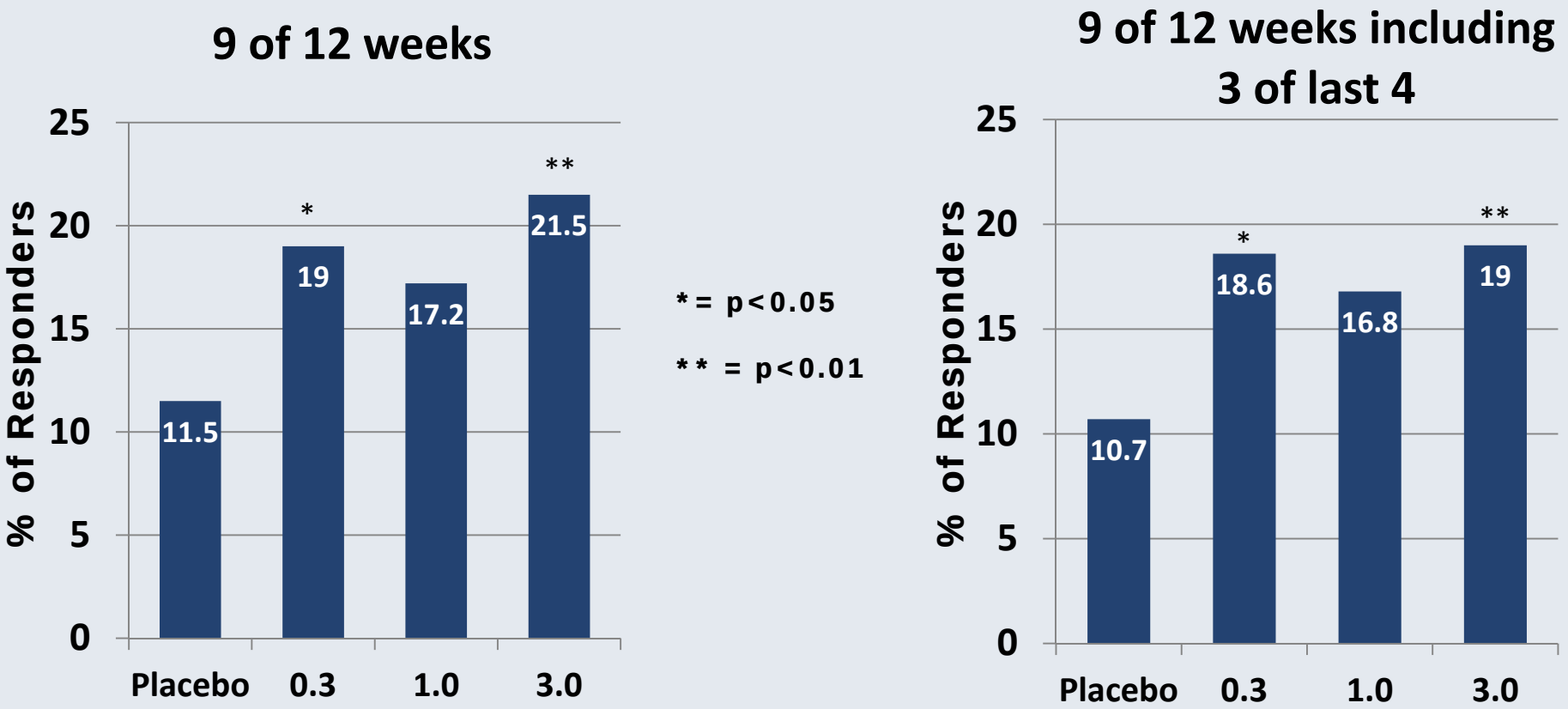
Disposition	n (%)
Screened	1722 at 113 sites in U.S.
Enrolled	951
Screen Failures:	771 (44.8)
Not willing to participate	179 (23)
IVRS noncompliance	104 (14)
≥3 CSBMs	91 (12)
Safety Population	948
mITT population	946*
Completed Treatment	738 (77.3)
Withdrawal Reason:	
Adverse event	46 (4.9)
Administrative	95 (10)
Lack of efficacy	51 (5.4)

*mITT population for all efficacy analyses

Patient Demographics By Treatment Group

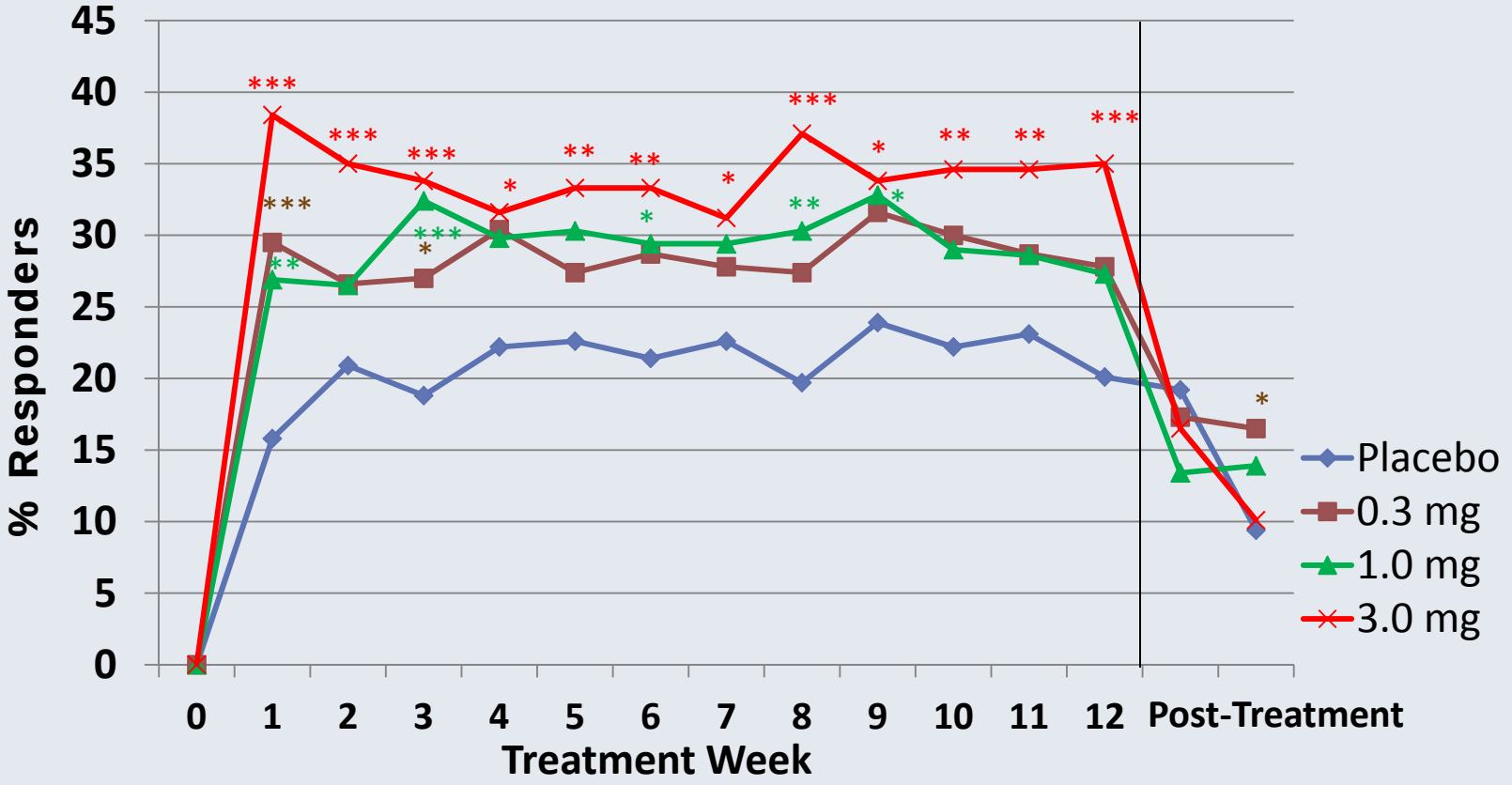
Category	Placebo	Plecanatide		
n (%)	Placebo N =234	0.3 mg N =237	1.0 mg N =238	3.0 mg N =237
Female Gender	209 (88.6)	203 (85.7)	202 (84.9)	205 (86.5)
Mean Age (yr) (Min, Max)	46.2 (19, 75)	47.8 (20, 75)	47.1 (18, 75)	47.1 (18, 75)
Race- White	171 (72.5)	171 (72.2)	170 (71.4)	175 (73.8)
Race- Other	65 (27.6)	66 (27.8)	68 (28.6)	62 (26.2)
Mean BMI (SD) (kg/m^2)	26.9 (4.5)	27.6 (4.3)	27.2 (4.0)	27.3 (4.1)

Primary Endpoint
Percent CSBM Responders



Plecanatide CIC Study

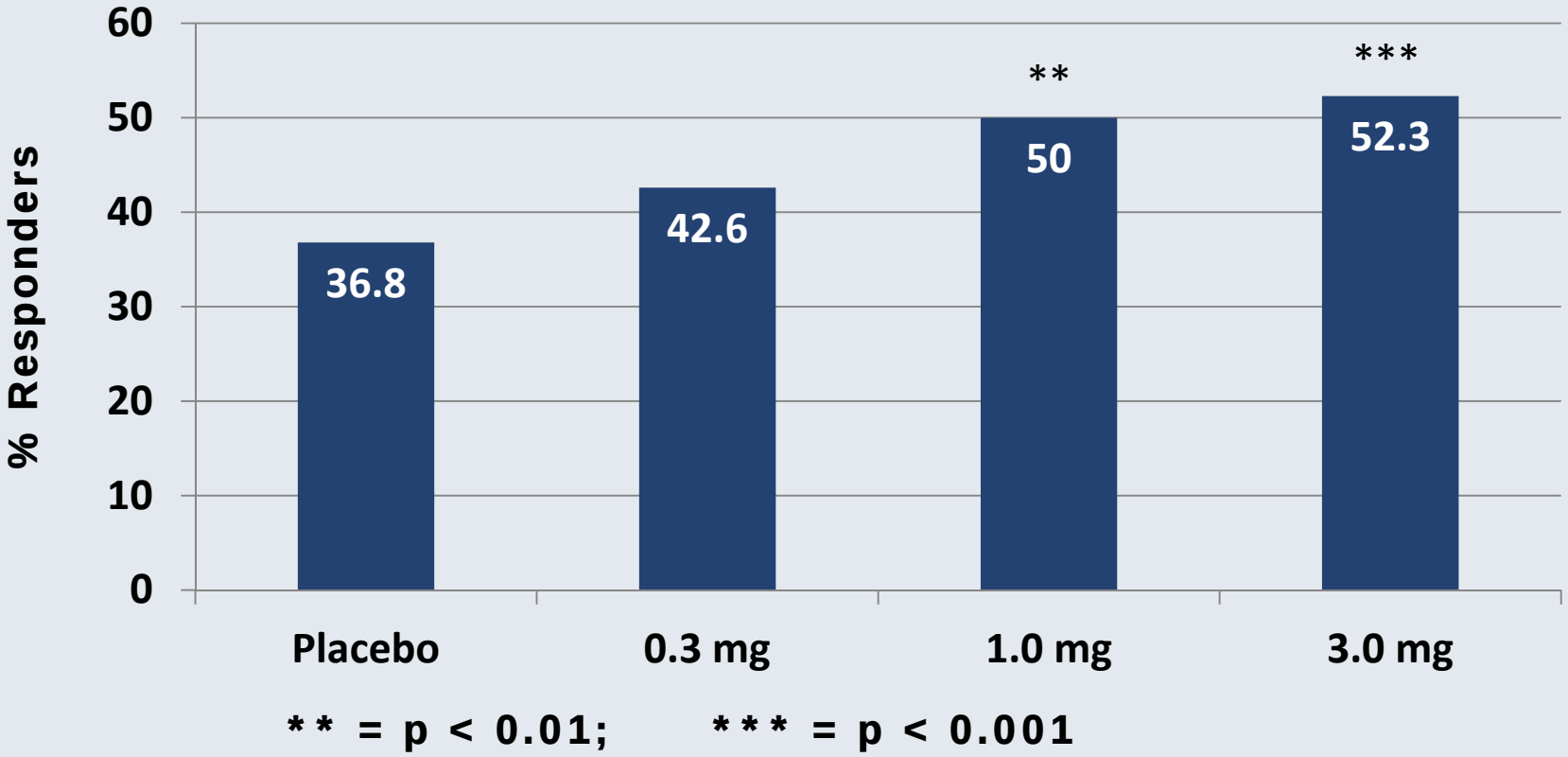
Weekly Responder Rates
≥3 CSBMs/wk with an increase of ≥ 1 CSBM/wk



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

Plecanatide CIC Study

Patients Reporting an Increase of ≥ 1 CSBM / week



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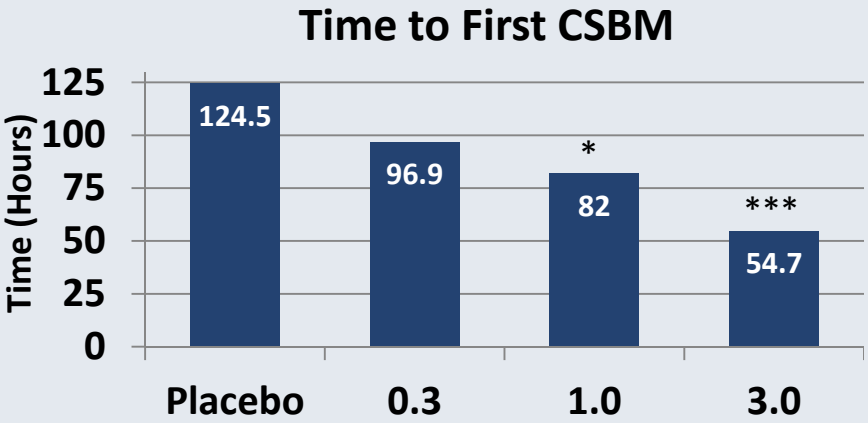
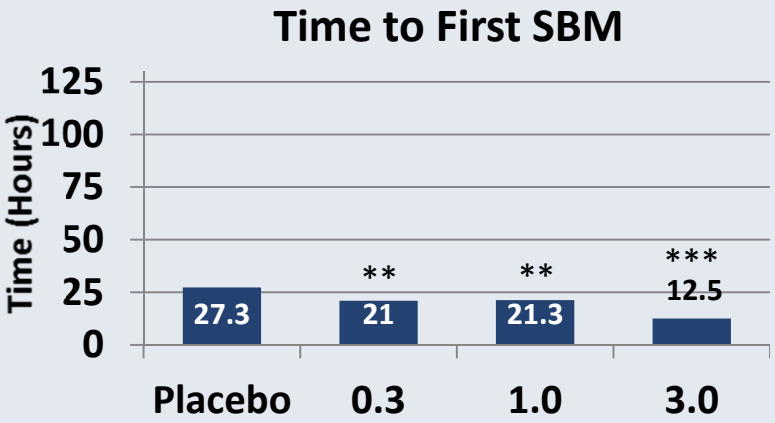
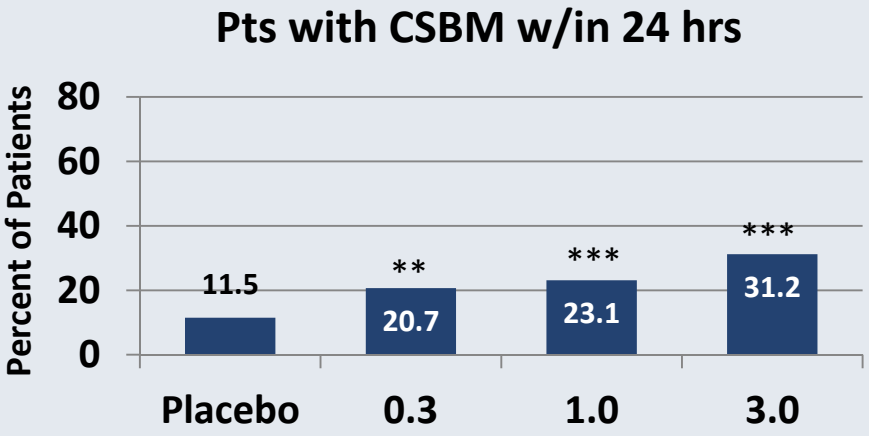
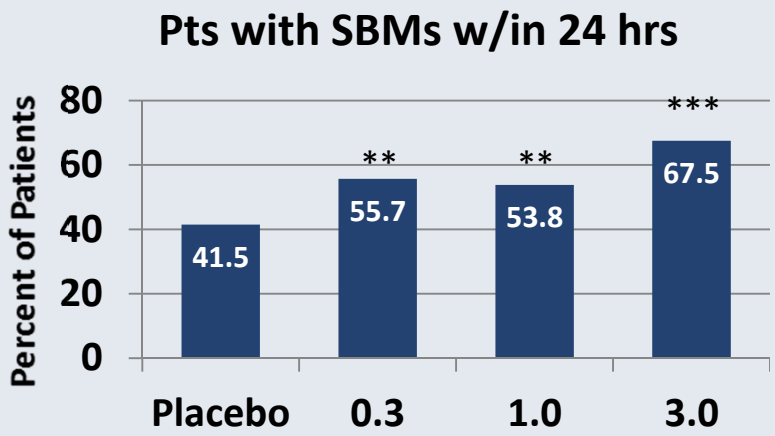
Plecanatide CIC Study

Time to First SBM & CSBM









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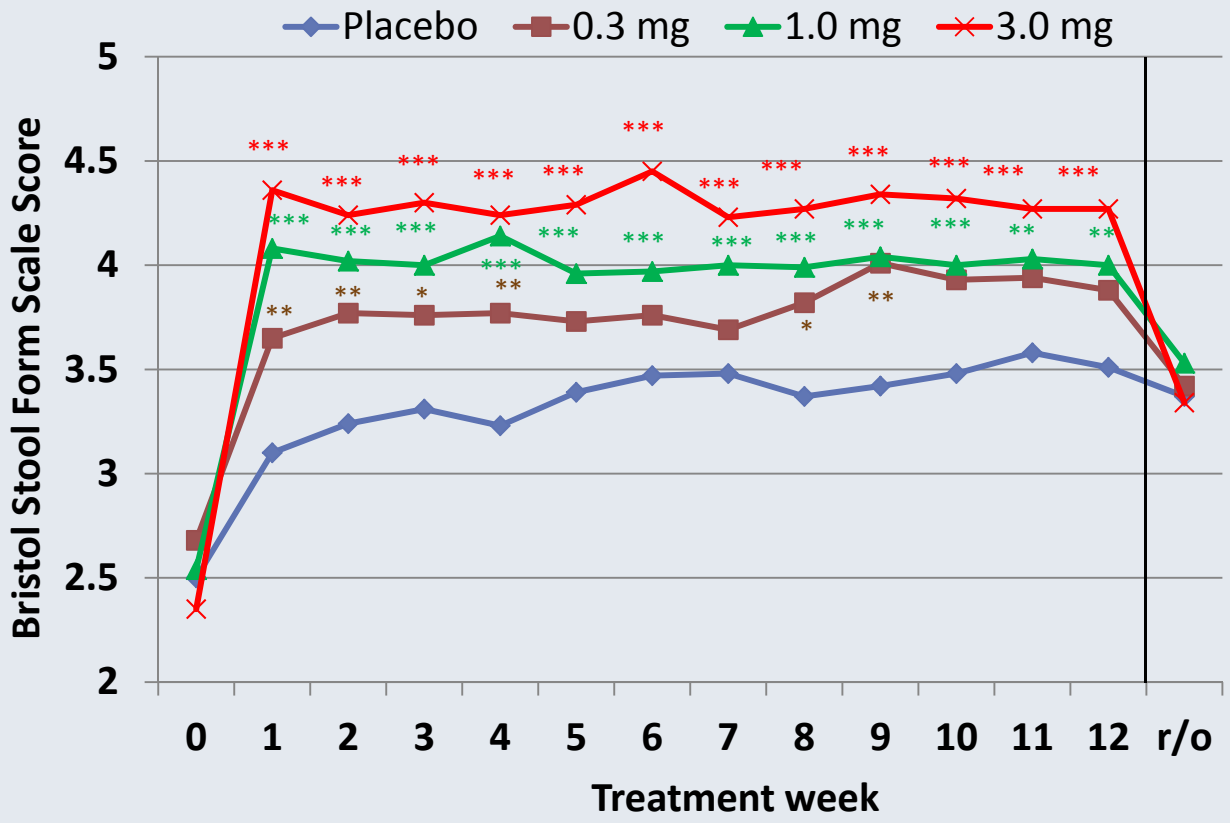
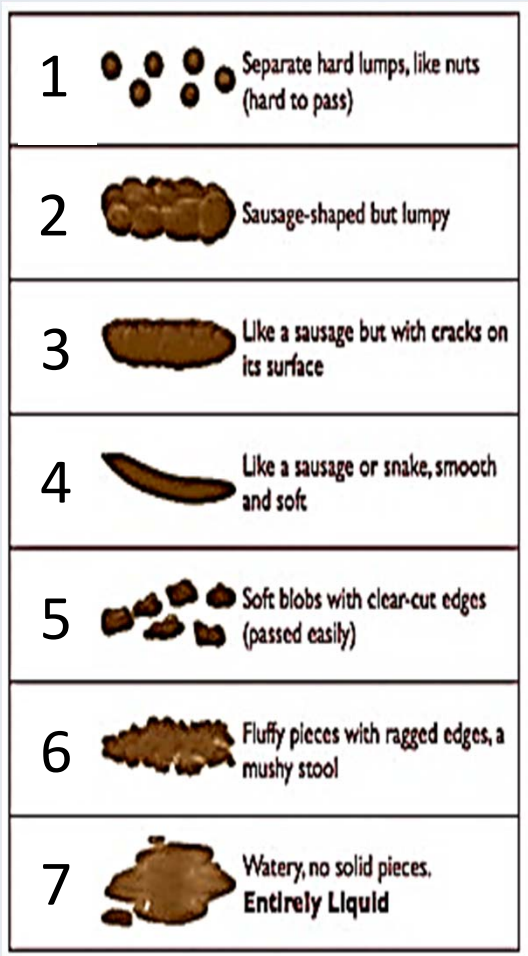
Plecanatide CIC Study

Stool Consistency





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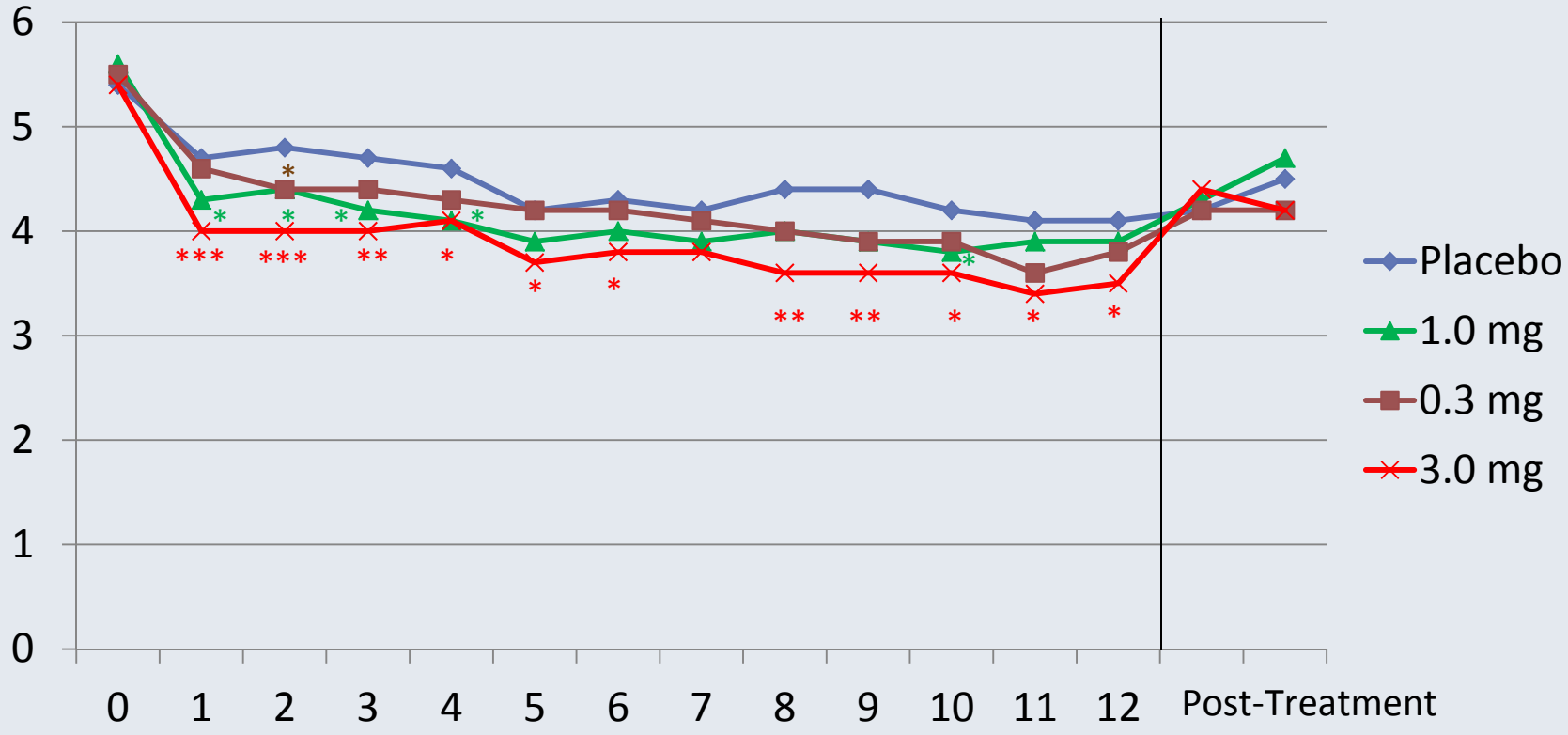
Plecanatide CIC Study

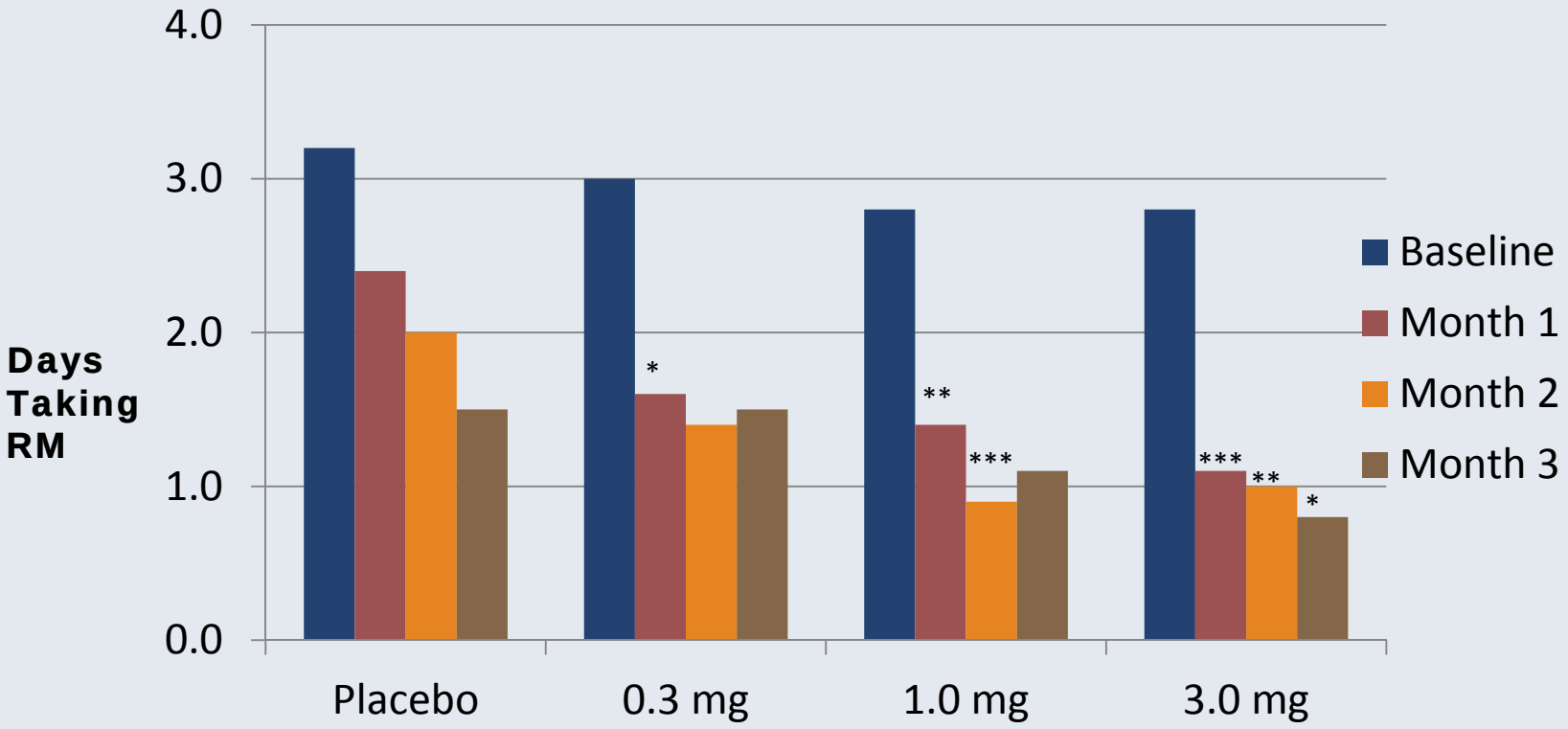
Weekly Straining Scores



Straining score based on 11-point score (0-10 rating)
*** = p<0.05; ** = p < 0.01; *** = p < 0.001**

Plecanatide CIC Study

Cumulative Days of Rescue Medication Use Per Month



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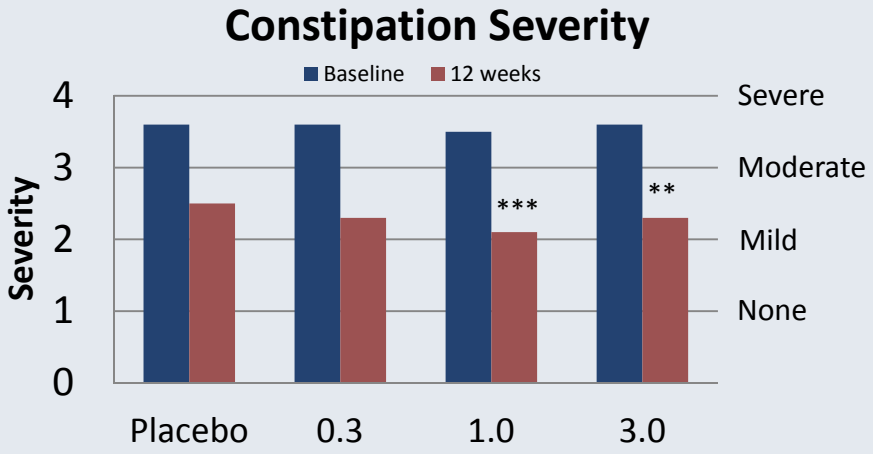
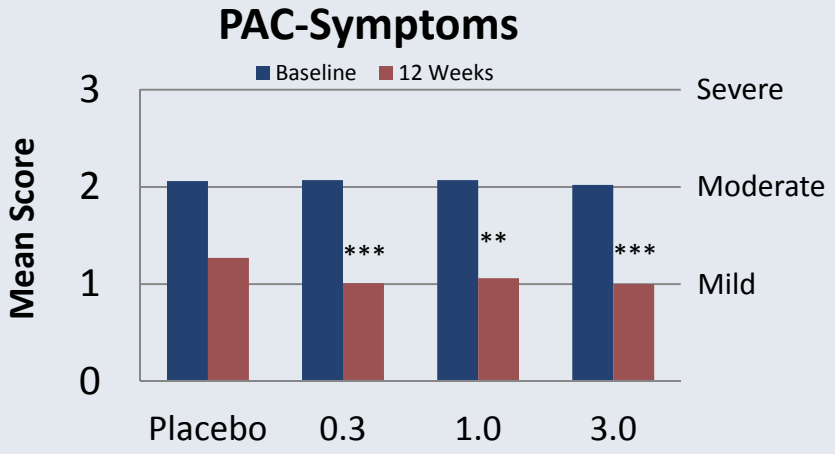
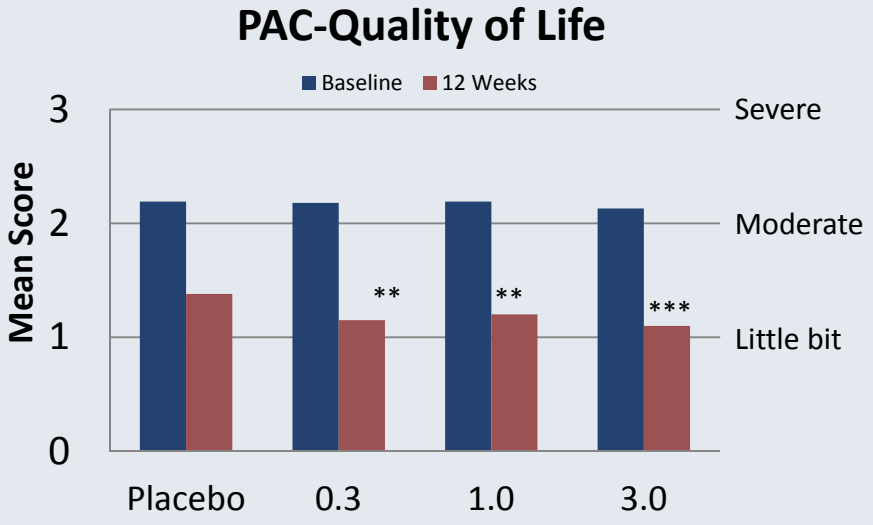
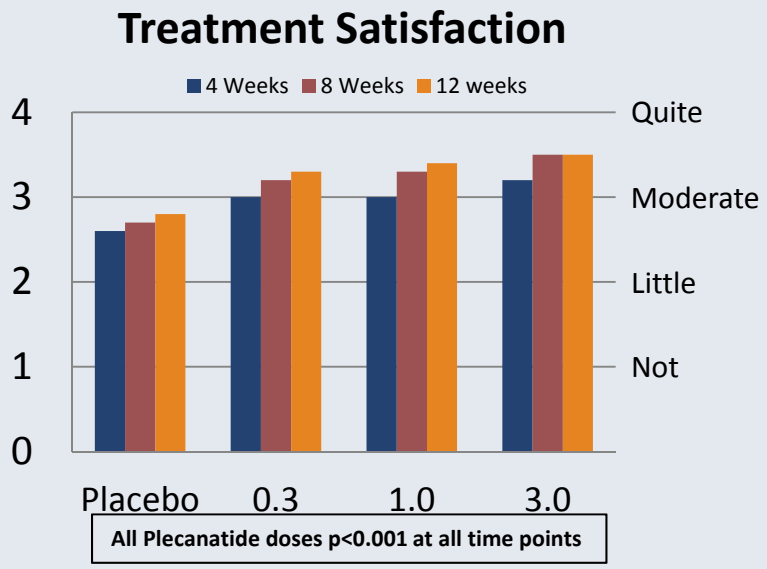
Plecanatide CIC Study

Global Assessments, Symptoms and QOL









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Plecanatide CIC Study

Treatment Emergent Adverse Events >2%

Event	Placebo	Plecanatide		
Adverse Event n (%)	**Placebo N=236**	**0.3 mg N=327**	**1.0 mg N=238**	**3.0 mg N=237**
Any event	96 (40.7)	99 (41.8)	103 (43.3)	106 (44.7)
Diarrhea	3 (1.3)	13 (5.5)	20 (8.4)	23 (9.7)
Flatulence	5 (2.1)	5 (2.1)	3 (1.3)	14 (5.9)
Abdominal Pain	11 (4.7)	6 (2.5)	9 (3.8)	12 (5.1)
Abdominal Distension	5 (2.1)	5 (2.1)	10 (4.2)	9 (3.8)
Nausea	5 (2.1)	5 (2.1)	12 (5.0)	8 (3.4)
URI	5 (2.1)	6 (2.5)	5 (2.1)	9 (3.8)
Nasopharyngitis	5 (2.1)	5 (2.1)	3 (1.3)	4 (1.7)
UTI	6 (2.5)	5 (2.1)	9 (3.8)	8 (3.4)
Headache	5 (2.1)	10 (4.2)	11 (4.6)	9 (3.8)

Summary of AEs and Diarrhea AEs

Event	Placebo	Plecanatide		
n (%)	Placebo N=236	0.3 mg N=237	1.0 mg N=238	3.0 mg N=237
Serious AEs	5 (2.1)	1 (0.4)	1 (0.4)	2 (0.8)
Treatment-emergent (TE) AEs	96 (40.7)	99 (41.8)	103 (43.3)	106 (44.7)
AEs leading to withdrawal	8 (3.4)	9 (3.8)	16 (6.7)	13 (5.5)
All Diarrhea TEAEs	3 (1.3)	13 (5.5)	20 (8.4)	23 (9.7)
Severe Diarrhea TEAEs	0	0	4 (1.7)	1 (0.4)
WD due to Diarrhea	**1 (0.4)**	**2 (0.8)**	**8 (3.4)**	**7 (3.0)**

Serious Adverse Events (SAEs)

Placebo	Plecanatide		
Placebo n=5	0.3 mg n=1	1.0 mg n=1	3.0 mg n=2
Hypertension exacerbation	Non-cardiac chest pain	Endometriosis	Acute cholecystitis
Gastroenteritis			Hypoaesthesia with weakness
Spontaneous abortion			
Atypical chest pain			
Asthma exacerbation			

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

Summary

- Plecanatide 3.0 mg produced a statistically significant improvement in all primary and key secondary endpoints
- Clear dose-response with doses below 3 mg achieving statistical significance in some primary and key secondary endpoints
- Safe and well tolerated with a diarrhea rate at the highest dose below 10%

Conclusion

- This study demonstrates Plecanatide 3.0 mg dose appears to be safe and effective at this phase in development.