Peppermint Oil with Site Specific Targeting is an Effective Therapy for Irritable Bowel Syndrome with Mixed Bowel Habits

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Introduction

Irritable bowel syndrome (IBS) is a chronic functional disorder characterized by multiple symptoms including, but not limited to, abdominal pain or discomfort, constipation, diarrhea, urgency of bowel movement (BM), a sensation of incomplete evacuation, pain at evacuation, abdominal bloating, and passage of gas or mucus.[1,2] IBS typically affects persons of working age and is costly to patients and employers, with a financial burden similar to that seen with asthma, migraine headaches, hypertension, and congestive heart failure.[3] IBS can be classified into four primary subtypes: mixed IBS (IBS-M), diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), and unsubtyped IBS (IBS-U).[4] Among adult patients with IBS, a sizeable proportion suffers from IBS-M, with prevalence rates estimated to be between 44% to 66% of IBS sufferers.[5-7] IBS-M patients experience a high burden, both in terms of symptoms and diminished quality of life.[8] Because of the variability in symptoms associated with IBS-M, the broad differential encompassing both diarrhea and constipation, and the lack of effective or approved therapies, it is no surprise that clinicians face challenges in accurately diagnosing and managing this common IBS subtype.

More is being learned about the underlying causes of IBS, and there is an evolving consensus that multiple etiologies play a role in the generation of typical symptoms in patients with IBS, with inflammatory changes central to many of the putative theories regarding the causes of IBS symptoms.[9] Immune activation triggered by food sensitivity or infection may lead to mast cell infiltration, reversible low-grade inflammation, intestinal malabsorption, gut mucosal barrier dysfunction and/or disturbed intestinal transit (manifest as diarrhea or constipation, or both, depending on the up-and-down regulatory responses).[10] The same inflammatory cascade may trigger chemical signaling that results in neural excitation and smooth muscle contraction leading to heightened viscerosensory symptoms including abdominal pain. This provides a biologically plausible basis to test the efficacy of luminally acting anti-inflammatory compounds in patients with IBS.[11]

Peppermint oil (PO), which has anti-inflammatory properties,[12.,13] has been used previously to treat patients with IBS.[1,14] In addition to anti-inflammatory properties, PO and its active ingredient, l-Menthol, are kappa opioid agonists,[15] possess smooth muscle calcium channel antagonist[16] and serotonergic ($5HT_3$) antagonist properties,[17] and exert anti-infective[18] and carminative effects.[19] A recent meta-analysis of medical therapies for IBS found that PO had the lowest number needed to treat among the various options evaluated.[20]

There are no approved therapies for IBS-M and it remains an unmet clinical need. Clinical trials for patients with IBS frequently concentrate on treating only IBS-D or IBS-C and do not address IBS-M or IBS-U. IBS-M is a challenge to treat since most IBS therapies are designed to address one IBS symptom or subtype. Interventions with therapies approved for IBS-D or IBS-C may lead to symptomatic “overshoots” and decreased patient satisfaction[8]. A limited number of treatments have been evaluated for IBS-M in clinical trials, but have not been successful.[21,22] Conceptually, a candidate therapy with multiple physiologic effects such as those of PO would be an attractive option for patients with IBS-M.

The previously published IBS Reduction Evaluation and Safety Trial (IBSREST)[14] showed that PO-SST, a novel formulation of PO using solid-state microspheres to target delivery to the small intestine, was an effective IBS therapy at 24 hours, with improved efficacy at 4 weeks in a combined group of IBS-M and IBS-D patients. In view of the unmet need in IBS-M, we performed a post hoc analysis of the effects of PO-SST among only the IBS-M patients from the IBSREST trial.

Methods

Study Subjects

To be eligible for IBSREST, subjects had to meet Rome III criteria for IBS-M or IBS-D, have average daily IBS related abdominal pain of ≥ 4 on a 0-10 scale, and a Total IBS Symptom Score (TISS) of ≥ 2 on a 0-4 scale. Subjects were randomly allocated to receive PO-SST 180 mg TID or identical placebo for 4 weeks as described previously.[14] Only subjects who met the Rome III criteria for IBS-M were included in this subgroup analysis.

Experimental Design

The primary analysis was based on the TISS. Additional assessments included the change from baseline in frequency and intensity of individual IBS symptoms.

Statistical Analysis

The Wilcoxon rank-sum test was used to compare results from the PO-SST and placebo groups at day 1. Day 29 *P* values were calculated from generalized linear models with the baseline score as a covariate. Additional statistical analyses for IBSREST have been described previously.[14]

Results

Patients

Seventy-two patients satisfied the inclusion criteria for IBSREST and were randomized to PO-SST (n = 35) or placebo (n = 37). Among the 72 patients, 34 met the criteria for IBS-M, while 38 met the criteria for IBS-D. The PO-SST group included 16 patients with IBS-M, and the placebo group included 18 patients with IBS-M.

Response to Treatment

As shown in Tables 1 through 8, in all cases, the baseline measures in the active and placebo arms were comparable ($P > 0.05$), thus reducing the possibility of type 1 statistical error. After 4 weeks of treatment, patients with IBS-M randomized to receive PO-SST demonstrated statistically significant reduction (improvement) of 43% in the mean TISS from baseline compared with 24% in patients randomized to receive placebo ($P = 0.0298$) (Fig. 1). Similarly, the mean reduction in the frequency of IBS symptoms of 37% (Fig. 2) was significantly greater in the PO-SST group compared with the 18% reduction observed in the placebo group ($P = 0.0349$). The 51% reduction in the mean intensity of IBS symptoms (Fig. 2) for patients receiving PO-SST was numerically superior to the 33% reduction in patients receiving placebo ($P = 0.0528$). Tables 1, 2, and 3 show the data for the TISS average of frequency and intensity, mean frequency, and mean intensity, respectively. The data compare the baseline measurement values at day 1 (visit 2) with the values after 28 days of dosing (visit 7). The last observation carried forward (LOCF) value was used for the day 29 measurement, as 1 participant did not complete the final analysis. For the average of frequency and intensity and mean frequency scores, the data demonstrated a statistically significant difference between the PO-SST treatment group and the placebo group ($P < 0.05$).

The percent change from baseline in the mean intensity and frequency of each of the 8 individual IBS symptoms comprising the TISS for PO-SST and placebo after 4 weeks are shown in Figure 3. Patients in the PO-SST group experienced a statistically significant reduction from baseline, compared with placebo, in 4 of the 8 individual IBS symptoms evaluated. Subjects randomized to PO-SST experienced a 43% reduction from baseline in abdominal pain or discomfort versus 21% with placebo ($P = 0.0426$) (Fig. 3). Tables 4 and 5 show the data for the average of frequency and intensity for the individual symptoms of IBS that comprise the TISS. These include abdominal pain or discomfort, constipation, urgency of bowel movement, sense of incomplete evacuation, abdominal bloating or distension, diarrhea, and passage of gas or mucus. The data shown compare the baseline measurement values at day 1 (visit 2) with the values after 28 days of dosing (visit 7). For abdominal pain or discomfort, constipation, urgency of bowel movement, and sense of incomplete evacuation there were statistically significant differences between the PO-SST

treatment group and the placebo group ($P < 0.05$).

Patients in the PO-SST group also had a 57% reduction from baseline in constipation compared with 22% in the placebo group ($P = 0.0085$) (Fig. 4) and there was statistically significant reduction in the frequency ($P = 0.0137$) and intensity ($P= 0.0221$) of constipation with PO-SST (Fig. 4). In addition, patients in the PO-SST group had a 44% reduction from baseline compared with 22% in the placebo group in urgency of bowel movement ($P = 0.0364$) (Fig. 3). Subjects randomized to PO-SST experienced a 38% reduction from baseline in their sense of incomplete evacuation versus 14% with placebo ($P = 0.0422$) (Fig. 3). Changes in all other individual symptom scores trended in favor of PO-SST, but did not reach statistical significance compared with placebo.

Tables 6, 7, and 8 show the data for symptom score average of frequency and intensity, mean frequency, and mean intensity, respectively, for the individual symptom of constipation. Constipation, in this context, was defined as the patient experiencing less than 3 spontaneously passed stools per week. The data compare the baseline measurement values at day 1 (visit 2) with the values after 28 days of dosing (visit 7). In all measurements of constipation, there were statistically significant differences between the PO-SST treatment group and the placebo group ($P < 0.05$).

Discussion

Irritable bowel syndrome is among the most commonly encountered clinical conditions in primary and specialty gastroenterology care and the costs of this condition to patients and society are significant.[3] Similar to patients with IBS-C and IBS-D, patients with IBS-M experience a high burden of illness, both in terms of symptoms and diminished quality of life.[8] However, while there are effective, FDA-approved therapies available for IBS-C and IBS-D, the variability in symptoms associated with IBS-M, the broad differential encompassing both diarrhea and constipation, and the lack of effective or even approved therapies for this prevalent IBS subtype represents a significant unmet need. In this post hoc analysis of IBSREST data, subjects with moderate to severe IBS-M who received PO-SST 3 times a day for 4 weeks experienced a statistically significant decrease from baseline in mean TISS compared with placebo. This represents the first report of a pharmacotherapy that is effective for the overall symptoms of IBS-M, based on reductions in the composite TISS score and individual IBS-M symptoms.

Peppermint oil is extracted from the *mentha* plant and is a complex mixture of terpenes, which can vary with growing conditions, time of harvest, and method of distillation. L-menthol is the principal component of PO, accounting for 35% to 50% of the compound with more than 90 other minor components making up the remainder. The specifications of the PO included in the formulation used in the current trial were established to ensure a high level (47.5% ± 2.5%) of free L-menthol. The specifications for the active formulation included the level of PO (90 mg) and free L-menthol (41.5 mg) per capsule. A standard dose of two capsules contains approximately 83 mg of L-menthol, designed to release over 4 hours after exiting the stomach. A pharmacokinetic (PK) study of a single immediate-release, 100-mg dose of L-menthol in healthy adults detected only menthol glucuronide in plasma or urine, while no free menthol was detected.[23]

Other PO products are available as single-unit, liquid-filled, enteric-coated capsules originally developed in the 1970s. Treatment related adverse events reported with these formulations of PO typically reflect vagaries in their delivery systems. Single-unit, liquid-filled, enteric-coated PO capsules can rupture in the stomach and have been associated with heartburn and nausea.[24] Additionally, delayed release of L-menthol has been associated with anal

burning.[25] Such single unit, non-disintegrating dosage forms can be subject to an unpredictable risk of dose-dumping.[26] The current formulation, due to its designed disintegration in the small intestine, should be less prone to the adverse effects associated with other PO formulations. This hypothesis was borne out in the overall IBSREST study, which demonstrated excellent tolerability of PO-SST with minimal adverse effects relative to placebo.[14]

In addition to the overall improvement in IBS-M symptoms as measured by the TISS, patients receiving PO-SST also experienced a significant decrease in the mean frequency of individual IBS symptoms and the mean reduction in intensity of IBS symptoms was numerically superior with PO-SST. Of note, despite the small sample size, PO-SST demonstrated improvement versus placebo in individual IBS symptom scores for both constipation and diarrhea in this group of patients with IBS-M, suggesting that PO-SST may normalize the disordered stool form that, along with abdominal pain, defines IBS. This outcome is somewhat contrary to conventional thinking where PO is considered in the same therapeutic class as antispasmodics such as dicyclomine and hyoscyamine, neither of which has a convincing evidence base as effective therapies for IBS based on their inconsistent effects on abdominal pain and apparent lack of effect on abnormal stool form.[27] The efficacy of PO-SST observed in patients in the current analysis is encouraging evidence that this agent improves multiple symptoms of IBS-M as patients in the PO-SST group experienced a statistically significant reduction from baseline in abdominal pain and discomfort, constipation, the urgency of bowel movement, and sensation of incomplete evacuation compared with placebo.

Conclusions

Our results demonstrated that a novel formulation of PO, designed to release in the small intestine, was associated with a rapid and sustained symptomatic improvement in patients with IBS-M based on significant reductions in a global IBS symptom score and reduced frequency and/or intensity of individual IBS symptoms. In addition to its beneficial effects, PO-SST was extremely well tolerated compared to placebo. This novel formulation of PO is a promising addition to the unmet need for a rapidly acting, safe, and effective pharmacotherapy for patients with IBS-M.

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Table 1 Total IBS symptom score for the IBS-M subgroup

Visit 2 (Day 1) - Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	2.89	2.82
Standard Deviation	0.390	0.439
P value	0.7573	
Visit 7 (Day 29) - LOCF Change from Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	-1.25	-0.68
Standard Deviation	0.717	0.694
P value	0.0298*	

*$P \leq 0.05$

Table 2 IBS symptoms: mean frequency scores for the IBS-M subgroup

Visit 2 (Day 1) - Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	3.18	3.22
Standard Deviation	0.390	0.461
P value	0.7307	
Visit 7 (Day 29) - LOCF Change from Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	-1.18	-0.57
Standard Deviation	0.787	0.899
P value	0.0349*	

*$P \leq 0.05$

Table 3 IBS symptoms: mean intensity scores for the IBS-M subgroup

Visit 2 (Day 1) - Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	2.60	2.41
Standard Deviation	0.565	0.584
P value	0.4110	
Visit 7 (Day 29) - LOCF Change from Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	-1.33	-0.80
Standard Deviation	0.784	0.607
P value	0.0528	

Table 4 Individual IBS symptom scores for abdominal pain or discomfort, constipation, urgency of bowel movement, and sense of incomplete evacuation (average of frequency and intensity) in the IBS-M subgroup

	Abdominal Pain or Discomfort		Constipation		Urgency of Bowel Movement		Sense of Incomplete Evacuation	
Visit 2 (Day 1) Baseline	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo
n	16	18	16	18	16	18	16	18
Mean	3.34	3.14	2.47	2.39	2.88	2.94	3.09	2.92
Standard Deviation	0.473	0.589	1.024	0.867	0.619	0.705	0.554	0.845
P value	0.4961		0.6134		0.9573		0.7003	
Visit 7 (Day 29) - LOCF Change from Baseline	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo
n	16	18	16	18	16	18	16	18
Mean	-1.44	-0.67	-1.41	-0.53	-1.28	-0.64	-1.16	-0.42
Standard Deviation	1.014	0.822	1.200	0.831	0.983	0.854	0.908	1.033
P value	0.0426*		0.0085*		0.0364*		0.0422*	

*$P \leq 0.05$

Table 5 Individual IBS symptom scores for pain at evacuation, abdominal bloating or distension, diarrhea, and passage of gas or mucus (average of frequency and intensity) in the IBS-M subgroup

	Pain at Evacuation		Abdominal Bloating or Distension		Diarrhea		Passage of Gas or Mucus	
Visit 2 (Day 1) Baseline	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo
n	16	18	16	18	16	18	16	18
Mean	2.81	2.28	3.09	3.14	2.59	2.89	2.84	2.83
Standard Deviation	0.680	1.060	0.779	0.376	0.800	0.778	0.676	0.728
P value	0.132		0.7421		0.2922		0.9303	
Visit 7 (Day 29) - LOCF Change from Baseline	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo	PO-SST (90mg)	Placebo
n	16	18	16	18	16	18	16	18
Mean	-1.47	-0.69	-0.97	-0.67	-1.25	-1.06	-1.06	-0.81
Standard Deviation	1.008	0.877	0.763	0.569	0.966	1.187	1.167	0.807
P value	0.0720		0.1460		0.2296		0.4499	

*$P \leq 0.05$

Table 6 Average of frequency and intensity score for constipation in the IBS-M subgroup

Visit 2 (Day 1) - Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	2.47	2.39
Standard Deviation	1.024	0.867
P value	0.6134	
Visit 7 (Day 29) - LOCF Change from Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	-1.41	-0.53
Standard Deviation	1.200	0.831
P value	0.0085*	

*$P \leq 0.05$. Constipation defined as less than 3 spontaneous stools per week.

Table 7 Frequency score for constipation in the IBS-M subgroup

Visit 2 (Day 1) - Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	2.69	2.61
Standard Deviation	1.014	1.092
P value	0.7286	
Visit 7 (Day 29) - LOCF Change from Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	-1.38	-0.33
Standard Deviation	1.258	1.283
P value	0.0137*	

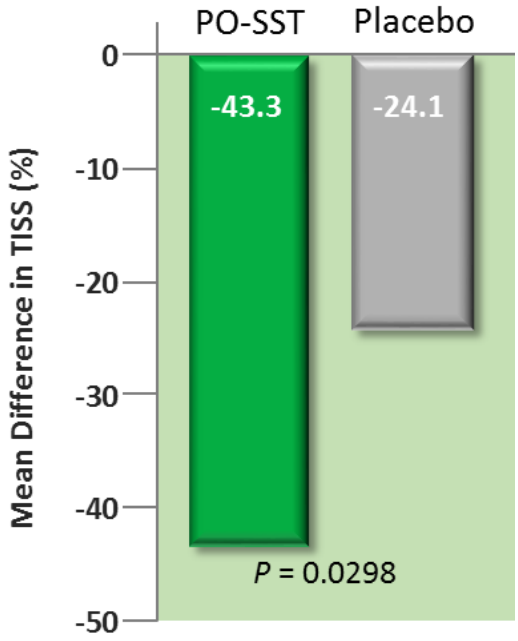
*$P \leq 0.05$. Constipation defined as less than 3 spontaneous stools per week.

Table 8 Intensity score for constipation in the IBS-M subgroup

Visit 2 (Day 1) - Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	2.25	2.17
Standard Deviation	1.291	0.924
P value	0.8314	
Visit 7 (Day 29) - LOCF Change from Baseline	**PO-SST (90mg)**	**Placebo**
n	16	18
Mean	-1.44	-0.72
Standard Deviation	1.365	0.575
P value	0.0221*	

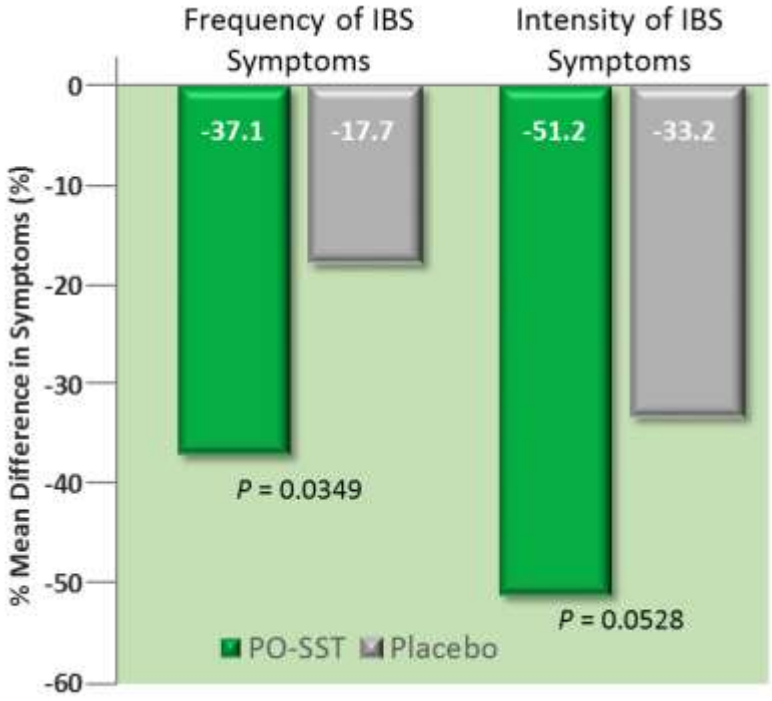
*$P \leq 0.05$. Constipation defined as less than 3 spontaneous stools per week.

Figure 1



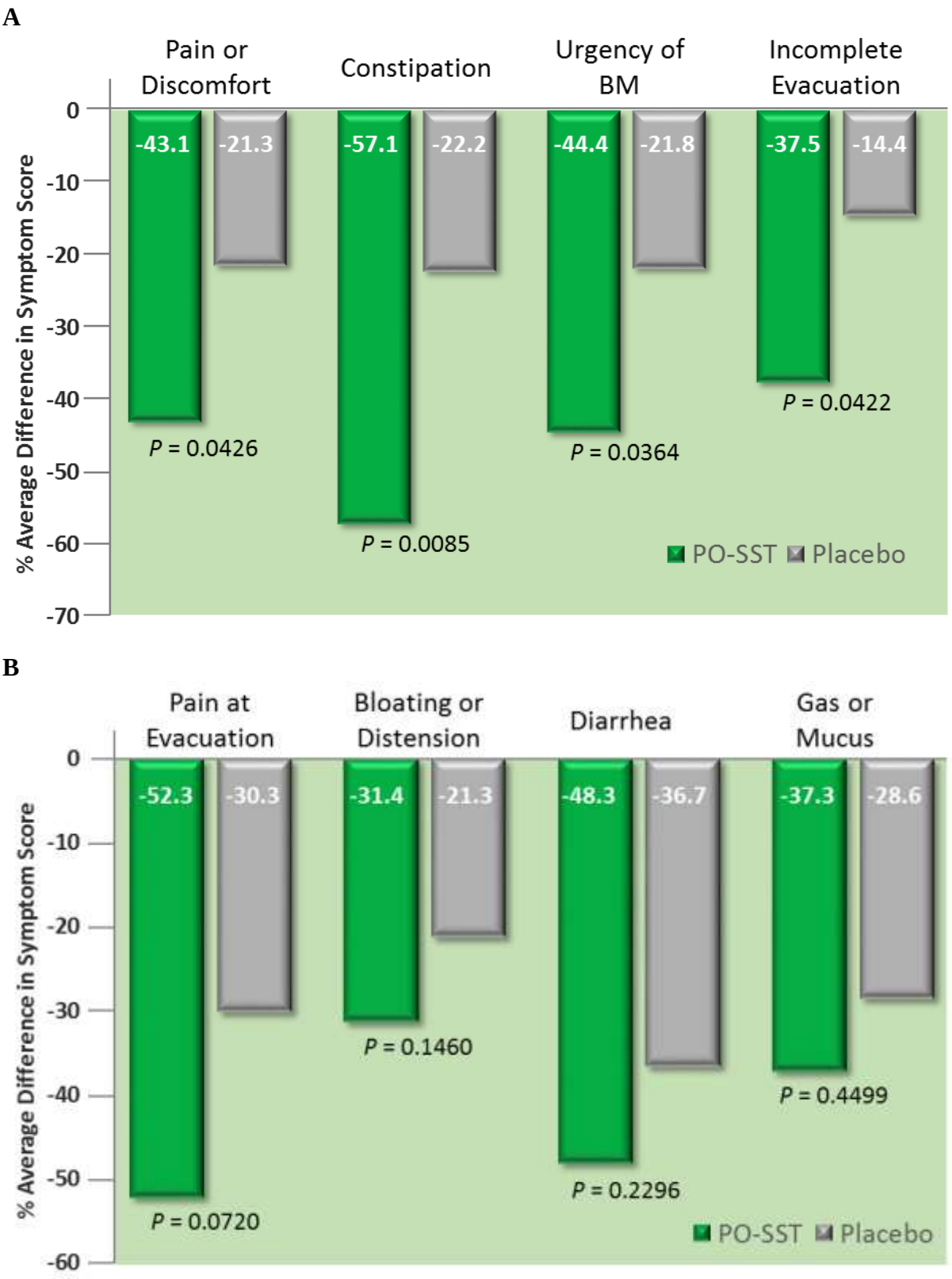
Total IBS Symptom Score (TISS) for Patients with IBS-M after 4 Weeks. TISS = mean intensity and frequency score for each of the 8 IBS symptoms (abdominal pain or discomfort, bloating or distension, pain at evacuation, urgency of BM, constipation, diarrhea, mucus or gas, sense of incomplete evacuation) summed and divided by 8. The mean percent reduction from baseline in TISS is shown. *P* value was calculated from a generalized linear model with the baseline score as a covariate.

Figure 2



Change in Frequency and Intensity of Symptoms for Patients with IBS-M after 4 Weeks. The mean percent reduction from baseline in frequency and intensity of symptoms are shown. *P* values were calculated from generalized linear models with the baseline score as a covariate.

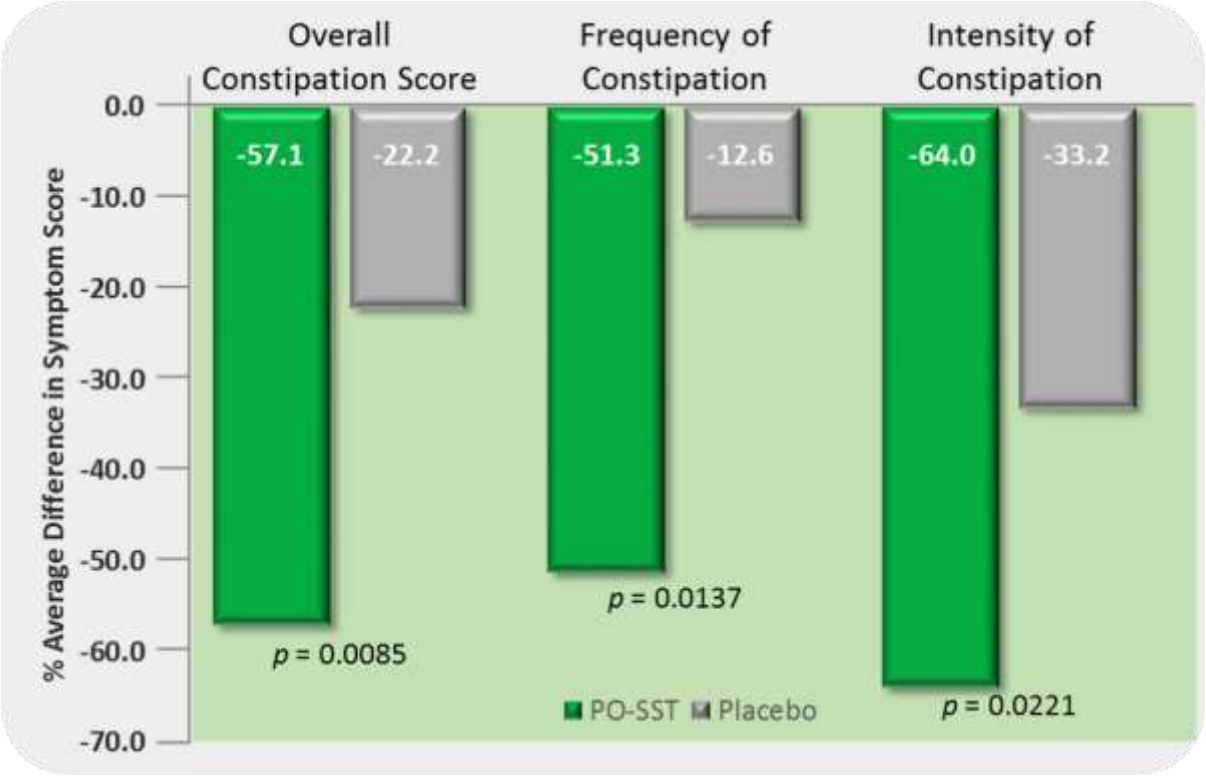
Figure 3



Analysis of Individual IBS Symptom Scores for Patients with IBS-M after 4 Weeks. Percent reduction from baseline in individual IBS symptoms (average of frequency and intensity) are shown. *P* values were calculated from generalized linear models with the baseline score as a covariate. **A** Pain or discomfort, constipation, urgency of BM (bowel movement), and

sensation of incomplete evacuation. **B** Pain at evacuation, bloating or distension, diarrhea, and gas or mucus.

Figure 4. Analysis of Overall Constipation and its Intensity and Frequency



Analysis of Overall Constipation and Intensity and Frequency of Constipation. The mean percent reduction from baseline in overall constipation score, frequency, and intensity of constipation are shown. *P* values were calculated from generalized linear models with the baseline score as a covariate.

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