Targeted delivery of peppermint oil to the small intestine provides significant improvement in the syndrome of symptoms associated with Irritable Bowel Syndrome.

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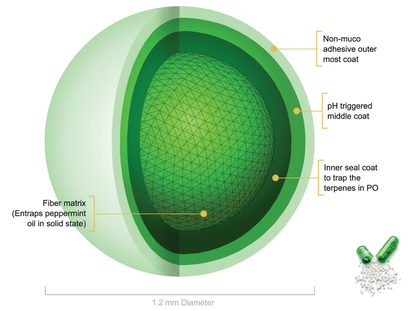
Introduction

Irritable bowel syndrome (IBS) is a chronic disorder with periodic exacerbations of 8 major symptoms, including abdominal pain or discomfort, abdominal bloating, constipation, diarrhea, incomplete evacuation, pain at evacuation, passage of gas or mucus, and urgency of bowel movement. These 8 major symptoms, have a complex relationship, which may be defined as a syndrome of symptoms. The 3 major forms of IBS are M (mixed/alternating), D (diarrhea) and C (constipation). The FDA's guidance on IBS does not specify the symptoms to be used as endpoints for IBS-M trials.[1] This guidance recommends monitoring only 2 major symptoms as provisional endpoints for IBS-D or IBS-C (abdominal pain and stool consistency/frequency). Reducing the frequency and intensity of the 8 major symptoms, rather than only 2, in a population of IBS-M plus IBS-D patients, is an unmet need. In one study, 60% of patients with IBS listed bloating as their most bothersome symptom, while 29% of patients rated abdominal pain as the symptom that bothered them most.[2] There is increasing evidence that altered motility, inflammation, altered gut/brain signaling, visceral sensi-tization, trapped gas and bacterial over-growth, in the small intestine, may lead to this syndrome of symptoms. Peppermint oil (PO) and its principal active component L-menthol may be ideally suited to help manage the syndrome of symptoms with targeted delivery to the small intestine. IBgard, a medical food, has been formulated as triple-coated controlled release microspheres of solid state purified PO for release in the small intestine.



IBSREST* Trial Objectives

Evaluate the effectiveness, safety and tolerability of IBgard for the management of IBS

- Confirm results of a more recent European clinical trial of PO in a US population[3]
- Determine if IBgard's Site Specific Targeting (SST) technology results in rapid action and amelioration of the syndrome of symptoms with improved tolerability in a population of patients with IBS-M and IBS-D

*IBSREST=Irritable Bowel Syndrome Reduction Evaluation & Safety Trial

Methods

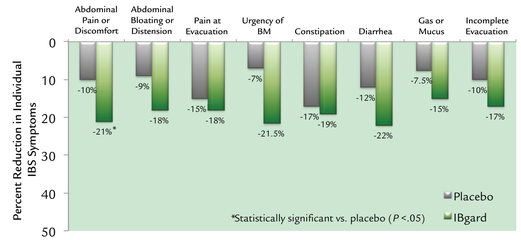
- Subjects met Rome III criteria for IBS-M or IBS-D, had average daily IBS-related abdominal pain of ≥ 4 (0-10 scale), a Total IBS Symptom Score of ≥ 2 (0-4 scale), and were 18-60 years of age
  - Exclusion criteria: diagnosis of IBS-C or IBS-U, organic gastrointestinal disease, refusal to discontinue any prohibited medications prior to study
- 3-week observation period for symptom severity assessment and prohibited medication washout
- Randomized to receive IBgard 180 mg TID or placebo for 4 weeks
  - Rescue medications were not allowed during the study
- Prior to, 24 hours, and 28 days after randomization, measurements of IBS symptom frequency and intensity (both on a scale of 0-4) were obtained
  - IBS symptoms included abdominal pain or discomfort, abdominal bloating or distention, pain at evacuation, urgency of bowel movement, constipation, diarrhea, passage of mucus or gas, and a sense of incomplete evacuation.

Results

Table 1. Demographic Characteristics

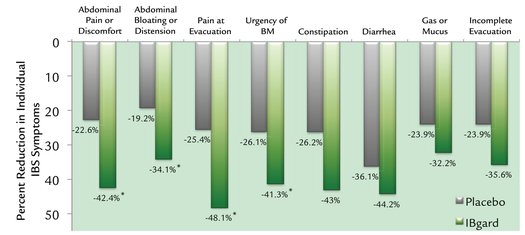
	IBgard® n (%)	Placebo n (%)
n	35	37
Mean Age (years)	40.2	41.1
Gender		
Female	28 (80.0)	26 (70.3)
Male	7 (20.0)	11 (29.7)
Race		
Caucasian	29 (82.9)	27 (73.0)
African American	6 (17.1)	8 (21.6)
Asian	0	1 (2.7)
Other	0	1 (2.7)
IBS Subtype		
IBS-M	16 (45.7)	18 (48.6)
IBS-D	19 (54.3)	19 (51.4)

Figure 1. Reduction in All Symptoms at 24 Hours



Percent reduction from baseline in individual IBS symptoms (average of frequency and intensity)

Figure 2. Reduction from Baseline in IBS Symptoms at 4 Weeks



Percent reduction from baseline in individual IBS symptoms (average of frequency and intensity)
*Statistically significant vs. placebo ($P<.05$)

Table 2. Individual IBS Syndrome of Symptoms Frequency Scores - mITT Population

Measurement	Baseline mean IBgard	Day 28 mean IBgard	P-value change from baseline*
n	35	34	
Abdominal pain or discomfort**	3.80	2.47	<0.0001
Abdominal bloating or distension	3.49	2.68	<0.0001
Constipation (<3 stools/week)	1.69	1.25	0.0594
Diarrhea (>3 defecations/day)	3.40	2.12	<0.0001
Pain at evacuation	2.63	1.50	<0.0001
Passage of gas or mucus	3.46	2.56	0.0005
Sense of incomplete evacuation	3.49	2.62	0.0038
Urgency of bowel movement**	3.60	2.29	0.0002

*P-values are from paired t-tests comparing 28 day scores to baseline
**Statistically significant vs. placebo ($P<.05$)

Table 3. Individual IBS Syndrome of Symptoms Intensity Scores - mITT Population

Measurement	Baseline mean IBgard	Day 28 mean IBgard	P-value change from baseline*
n	35	34	
Abdominal pain or discomfort	3.29	1.59	<0.0001
Abdominal bloating or distension	2.97	1.71	<0.0001
Constipation (<3 stools/week)	1.40	0.65	0.0005
Diarrhea (>3 defecations/day)	2.80	1.32	<0.0001
Pain at evacuation	2.20	0.94	<0.0001
Passage of gas or mucus	2.83	1.71	<0.0001
Sense of incomplete evacuation	2.97	1.59	<0.0001
Urgency of bowel movement	2.94	1.53	<0.0001

*P-values are from paired t-tests comparing 28 day scores to baseline

Conclusions

- IBgard was effective at reducing the syndrome of symptoms of IBS
- Improvement in all individual IBS symptom frequencies (except constipation) and intensities was significantly greater with IBgard compared to baseline
- Improvement from baseline over 4 weeks in 4 individual IBS symptoms (abdominal pain, bloating, pain at evacuation, and urgency) reached statistical significance with IBgard, versus placebo
- Improvement from baseline in frequency of abdominal pain and urgency over 4 weeks reached statistical significance with IBgard, versus placebo
- IBgard was safe and well tolerated

References

1. FDA. Guidance for Industry Irritable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment. 2012
2. Lembo et al. *Am J Gastroenterol*. 1999;94(5):1320-6.
3. Cappello et al. *Dig Liv Dis*. 2007;39:530-6.

Acknowledgements: Principal Investigators on the trial: Dennis S Riff, MD, FACG, CPI; Steven C Bowman, MD; Gigi Claire Lefebvre, MD; and Richard Krause, MD. Palm Beach CRO, LLC helped conduct the trial. SDC Biostatistics and Data Management provided power and statistical analyses. Editorial support was provided by Premier Healthcare and Precise Medical Writing, LLC. Design support was provided by Skylographic Design, LLC. The clinical study report was prepared by Hubbell Consulting, LLC.

Disclosures: Michael S. Epstein, MD, AGAF, FACG: Chief Medical Advisor, IM HealthScience®, LLC
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