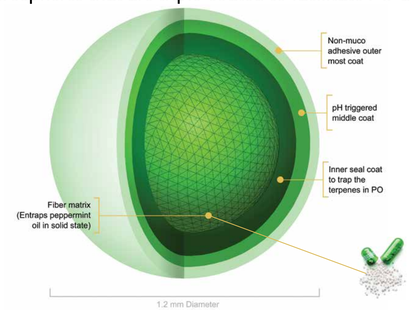
IBgard®, a novel targeted delivery system of peppermint oil, results in significant improvement in the Total IBS Symptom Score and individual IBS symptoms. Results from the US based, 4-week, randomized, placebo controlled, multi-center IBSREST™ trial.

Brooks D. Cash, MD, AGAF, FACG, FASGE[1], Michael S. Epstein, MD, AGAF, FACG[2], Syed M. Shah, PhD[3]

1. Division of Gastroenterology, University of South Alabama, Mobile, AL, United States; 2. Digestive Disorders Associates, Annapolis, MD, United States; 3. IM HealthScience LLC®, Boca Raton, FL, United States

Introduction

Peppermint oil (PO) has been shown to significantly reduce global symptoms as well as the abdominal pain of irritable bowel syndrome (IBS).[1] It is approved by the European Medicines Agency (EMEA) and used as a first line IBS therapy outside the US. However, patients receiving single-unit, enteric-coated PO may experience adverse events, such as heartburn, abdominal pain, or anal burning.[1] IBgard® is a medical food containing a novel PO formulation consisting of ultra-purified, solid-state PO microspheres that are triple-coated to facilitate PO delivery to the small intestine. The Irritable Bowel Syndrome Reduction Evaluation and Safety Trial (IBSREST) compared the efficacy and tolerability of IBgard® with placebo over a 4-week period.



IBSREST* Trial Objectives

Evaluate the effectiveness and safety of IBgard® for the management of IBS

- Confirm results of previous European clinical trials of PO in a U.S. population
- Determine if PO with Site Specific Targeting (SST®) technology results in rapid action and improved tolerability of PO in adult patients with IBS-M and IBS-D

Methods

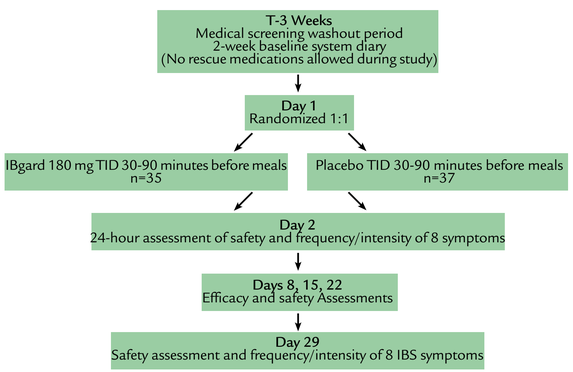
- Subjects met Rome III criteria for IBS-M or IBS-D, had average daily IBS-related abdominal pain of ≥ 4 (0-10 scale), a Total IBS Symptom Score (TISS) of ≥ 2 (0-4 scale), and were 18-60 years of age
  - Exclusion criteria: diagnosis of IBS-C or IBS-U, organic gastrointestinal disease, refusal to discontinue 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
- Primary analysis based on TISS score[2]
  - FDA guidance for patient-reported IBS outcome measures suggests the use of a total symptom score[3] in addition to abdominal pain intensity and stool consistency/frequency as primary endpoints[4]
  - Additional assessments included change from baseline in frequency and intensity of individual IBS symptoms and daily IBS-M/D symptoms
- Safety assessment included treatment-emergent adverse events (TEAE)

Total IBS Symptom Score (TISS)

- Scale used previously by Cappello et al.[2] and based on the intensity and frequency (0-4) of 8 IBS symptoms: 1) abdominal pain or discomfort, 2) bloating or distention, 3) pain at evacuation, 4) urgency, 5) constipation, 6) diarrhea, 7) mucus or gas, 8) sense of incomplete evacuation
- Means of the intensity + frequency scores for each symptom are summed and divided by 8 to obtain the TISS[2]

Intensity	
0	Absent
1	Mild
2	Moderate
3	Severe
4	Unbearable

Frequency	
0	Absent
1	Once per month
2	Once per week
3	Twice per week
4	≥ 3 times per week



Results

Table 1. Subject Characteristics

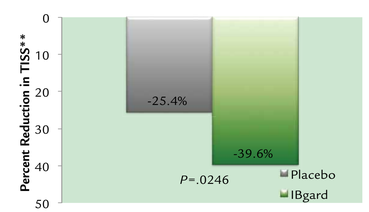
	IBgard® n (%)	Placebo n (%)
n	35	37
Mean Age (years)	40.2	41.1
IBS Subtype		
IBS-M	16 (45.7)	18 (48.6)
IBS-D	19 (54.3)	19 (51.4)
Gender		
Female	28 (80.0)	26 (70.3)
Male	7 (20.0)	11 (29.7)
Race		
Caucasian	29 (82.9)	27 (73.0)
African American	6 (17.1)	8 (21.6)
Asian	0	1 (2.7)
Other	0	1 (2.7)
Subject Completion		
Completed	34 (97.1)	36 (97.3)
Withdrawn	1 (2.9)	1 (2.7)

Table 2. TISS and Individual IBS Symptom Scores at Baseline (mITT Population)

Measurement	Baseline IBgard ®	Baseline placebo	P-value*
Number in group	35	37	
Total IBS Symptom Score	2.93	2.76	n.s.
Individual Symptoms (average of frequency and intensity)**			
Abdominal pain or discomfort	3.54	3.28	n.s.
Abdominal bloating or distension	3.23	3.08	n.s.
Constipation (< 3 stools/week)	1.54	1.45	n.s.
Diarrhea (≥ 3 defecations/day)	3.10	3.16	n.s.
Pain at evacuation	2.41	2.09	n.s.
Passage of gas or mucus	3.14	2.93	n.s.
Sense of incomplete evacuation	3.23	2.85	n.s.
Urgency of bowel movement	3.27	3.22	n.s.

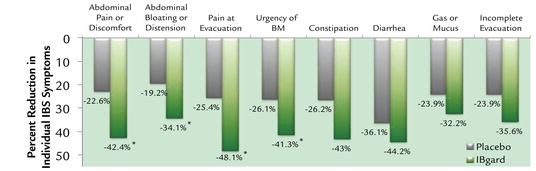
*Wilcoxon rank sum test ($P \leq 0.05$ considered statistically significant)
**Intensity and frequency were both measured on a scale of 0 to 4.
n.s.=not significant

Figure 1. Reduction in Total IBS Symptom Score at 4 Weeks*



*Percent reduction from baseline
**TISS=mean intensity and frequency score for each IBS symptom summed and divided by 8

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 3. Treatment Emergent Adverse Events

	IBgard (n=35) n (%)	Placebo (n=37) n (%)	All subjects (n=72) n (%)
Total TEAEs	2 (5.7%)	4 (10.8%)	6 (8.3%)
Dyspepsia	1 (2.9%)	0	1 (1.4%)
Flatulence	0	1 (2.7%)	1 (1.4%)
Gastroesophageal Reflux Disease	0	1 (2.7%)	1 (1.4%)
Gastroenteritis viral	0	1 (2.7%)	1 (1.4%)
Upper Respiratory Tract Infection	1 (2.9%)	0	1 (1.4%)
Back Pain	0	1 (2.7%)	1 (1.4%)
TEAEs >Grade 1	0	1 (2.7%)	1 (2.7%)
Serious TEAEs and Deaths	0	0	0
TEAEs that led to discontinuation	0	0	0

TEAE=treatment emergent adverse events
Grade 1=Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Conclusions

- IBgard was effective at improving the composite IBS symptom score (TISS) and all 8 individual IBS symptoms (average of frequency and intensity) over 4 weeks
- Improvement from baseline in TISS and 4 individual IBS symptoms (abdominal pain, bloating, pain at evacuation, and urgency) was significantly greater with IBgard than placebo
- IBgard was well tolerated and safe

References

1. Khanna R, et al. *J Clin Gastroenterol*. 2014;48:505-12.
2. Cappello et al. *Dig Liv Dis.* 2007;39:530-6.
3. FDA. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.
4. FDA. Guidance for Industry Imitable Bowel Syndrome — Clinical Evaluation of Drugs for Treatment . 2012

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: Brooks D. Cash, MD: Consultant, IM HealthScience®, LLC; Michael S. Epstein, MD: Chief Medical Advisor, IM HealthScience®, LLC; Syed M. Shah, PhD: CIO, IM HealthScience®, LLC