IBgard®, a novel small intestine targeted delivery system of peppermint oil, results in significant improvement in severe and unbearable IBS symptom intensity. Results from the US based, 4-week, randomized, placebo-controlled, multi-center IBSREST™ trial.

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Introduction

Approximately 25% of patients with irritable bowel syndrome (IBS) describe their symptoms as severe.[1] Multiple items (mean 7 items) have been identified as contributing to IBS severity.[2] The level of severity seems related to the number and intensity of these contributing factors.[2] High severity is reflected by higher intensity and higher frequency of individual symptoms. The IBS patients with severe symptoms have lower quality of life, are out of work from IBS most often, and see their physicians on average more than once a month.[1] Although IBS is not life threatening, one survey found that its symptoms can be so distressing that some patients would be willing to give up 25% of their remaining life (average 15 years) and 14% would risk a 1/1,000 chance of death to receive a treatment that would make them symptom free.[2] The 3 primary sub-types of IBS are M (mixed/alternating), D (diarrhea), and C (constipation). While there are prescription options for IBS-C, there are no approved products for IBS-M and limited options for IBS-D. The Irritable Bowel Syndrome Reduction Evaluation and Safety Trial (IBSREST™), comparing IBgard® with placebo in a group of patients with IBS-M and IBS-D, preferentially recruited patients with a high Total IBS Symptom Score and high average daily IBS-related abdominal pain. This trial was designed to recruit patients with moderate to severe IBS since these patients seek more medical care and represent an area of unmet need. IBgard® is a medical food containing a novel formulation consisting of ultra-purified, solid-state peppermint oil (PO) microspheres that are triple-coated to facilitate PO delivery to the small intestine. This targeted delivery of PO to the site of disturbance in IBS (small intestine) was expected to help address this unmet need.

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[3]
- Determine if PO with Site Specific Targeting (SST®) technology is tolerable and results in rapid action in a population of adult patients with IBS-M and IBS-D with moderate or severe symptoms

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
- The inclusion criteria specified abdominal pain of ≥ 4 instead of ≥ 3 (recommended in FDA guidances) and a TISS score of ≥ 2 (instead of no criteria in Cappello et al.[3]) in order to recruit patients with higher frequency and higher intensity of symptoms
- 3-week observation period for symptom severity assessment and washout of prohibited medicines
- Randomized to receive IBgard 180 mg TID or placebo for 4 weeks
- Efficacy variables: change from baseline in intensity of IBS symptoms rated as severe/unbearable (≥ 3 on 1-4 scale) by subjects
  - For frequency, 3= symptom felt twice per week and 4= symptom felt ≥ three times a week
  - For intensity, 3=symptom that is felt as severe and 4=symptom felt as unbearable
- Safety assessment included treatment-emergent adverse events (TEAE)

Intensity and Frequency Scale

- Scale was the same as used previously by Cappello et al.[3] 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 were summed and divided by 2 to obtain the average for that symptom[3]
- Symptoms that had an average score of ≥ 3 were considered Severe or Unbearable

Intensity	
0	Absent
1	Mild
2	Moderate
3	Severe
4	Unbearable

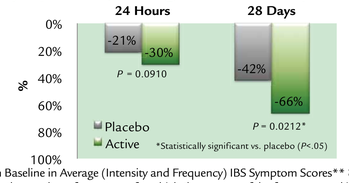
Frequency	
0	Absent
1	Once per month
2	Once per week
3	Twice per week
4	≥ 3 times per week

Results

Table 1. Subject Characteristics

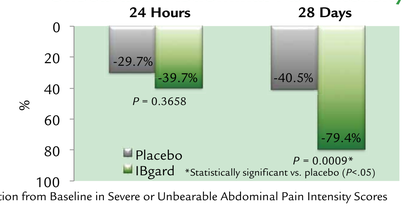
	IBgard® n (%)	Placebo n (%)
n	35	37
Mean Age (years)	40.2	41.1
IBS Subtype		
IBS-M	16 (45.7)	18 (48.6)
IBS-D	19 (54.3)	19 (51.4)
Gender		
Female	28 (80.0)	26 (70.3)
Male	7 (20.0)	11 (29.7)
Race		
Caucasian	29 (82.9)	27 (73.0)
African American	6 (17.1)	8 (21.6)
Asian	0	1 (2.7)
Other	0	1 (2.7)
Subject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

Figure 1. Reduction in Number of Severe and Unbearable Symptoms (Average of Frequency and Intensity ≥3)



Reduction from Baseline in Average (Intensity and Frequency) IBS Symptom Scores** ≥ 3
**Calculated as the number of symptoms for which the average of the frequency and intensity is ≥ 3 for each of the 8 IBS symptoms (abdominal pain or discomfort, bloating or distention, pain at evacuation, urgency, constipation, diarrhea, mucus or gas, sense of incomplete evacuation)

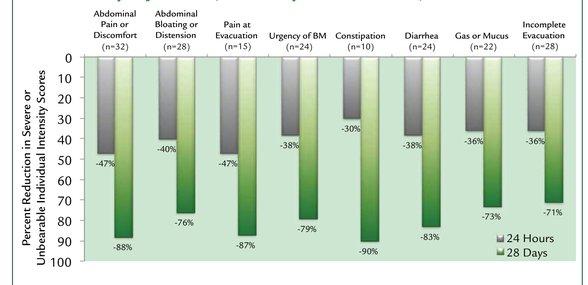
Figure 2. Reduction in Patient Reported Severe or Unbearable Abdominal Pain Intensity



Reduction from Baseline in Severe or Unbearable Abdominal Pain Intensity Scores

Baselines in Table 1, Figure 1 and Figure 2 were not significantly different between IBgard and placebo ($P > 0.05$).

Figure 3. Favorable Trend Across All 8 Severe/Unbearable Symptoms (Intensity vs. Baseline)



Percent Reduction from Baseline in Severe or Unbearable Individual Intensity Scores

Conclusions

- Reduction in the number of severe or unbearable IBS symptoms (average of intensity and frequency ≥ 3) over 4 weeks reached statistical significance with IBgard, versus placebo
- Reduction in severe or unbearable abdominal pain intensity at 4 weeks reached statistical significance with IBgard, versus placebo
- IBgard showed a favorable trend for improvement from baseline in all 8 severe or unbearable symptom intensity scores at 24 hours and 28 days
- IBgard was safe and well tolerated

References

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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: 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

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