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ROME IV

Functional Gastrointestinal Disorders
Disorders of Gut-Brain Interaction

FOURTH EDITION

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with Editors
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and the Rome IV Committees

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Functional GI Disorders:
Disorders of Gut-Brain Interaction
A Double-blind Crossover Study Using Magnetic Resonance Imaging Shows That Fructose and Inulin Mediate Symptoms in IBS Patients Through Different Mechanisms: Early Increase in Small Bowel Water versus Late Increase in Colonic Gas

Giles A. Major, Susan E. Pritchard, Kathryn Murray, Jan A. Paul, Caroline L. Hoad, Luca Marciani, Penny A. Gowland, Robin C. Spiller
Aims and Methods

Aims

• To test whether fructose or inulin ingestion would cause more symptoms than glucose in IBS patients and to determine which biomarkers could explain the origin of their symptoms

Methods

• A 3-period, 3-treatment randomized, double-blind crossover study of adults (18-65) meeting Rome III criteria for IBS and reporting bloating
  – On each day an identically appearing drink was consumed: 500ml water flavoured with lime juice containing 40 glucose (control), fructose or inulin
• Primary endpoint was a clinically important change in a composite symptom score
  – Symptoms included gas/flatulence, bloating, pain/discomfort and diarrhoea, each scored 0-3 (total max 12)
  – Increase ≥3 from baseline was defined as an important change
• Secondary endpoints included composite symptom intensity, breath hydrogen (H$_2$), SBWC, colonic volume and colonic gas
  – Measures were taken at baseline (fasted) and 0, 60, 120, 180, 240 and 300 min postprandially
  – Symptoms and H$_2$ were also measured at 30 and 90 min.
Results

- 29 patients completed 3 study days
- Symptom intensity was higher after both interventions than controls
- In those with symptoms after inulin there was a correlation between the peak rises in symptom intensity and colonic gas ($P<0.05$, $r^2 = 0.33$)
- $H_2$ was a poor predictor ($r^2 = 0.08$). After fructose the best correlate of symptoms was SBWC ($P=0.05$, $r^2 = 0.26$)

![Bar chart showing patients with increase in CSS ≥3 after ingestion of different substances.](chart.png)

* $P<0.04$

CSS, composite symptom score.
## Results

### Peak Rise from Baseline in Symptoms and Physiological Variable with Different Carbohydrate Drinks

<table>
<thead>
<tr>
<th></th>
<th>Glucose</th>
<th>Fructose</th>
<th>Inulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom intensity on VAS (mm)</td>
<td>21.8 (39.1)</td>
<td>49.3* (55.3)</td>
<td>45.5* (54.8)</td>
</tr>
<tr>
<td>SBWC/mL</td>
<td>80 (37-122)</td>
<td>182** (117-258)</td>
<td>73 (38.5-111)</td>
</tr>
<tr>
<td>Colonic volume/mL</td>
<td>56 (59)</td>
<td>142* (140)</td>
<td>265** (191)</td>
</tr>
<tr>
<td>Colonic gas/units</td>
<td>13.1 (3.3-21.5)</td>
<td>21.9* (10.1-62.0)</td>
<td>45.4** (17.2-88.7)</td>
</tr>
<tr>
<td>Breath hydrogen/ppm</td>
<td>1 (-0.5-3)</td>
<td>18** (5-50)</td>
<td>66** (31.5-125.5)</td>
</tr>
</tbody>
</table>

Mean (SD) or median (Q25-Q75).

*P<0.05; **P<0.005 vs glucose (paired t-tests).
Results

Peak Rise from Baseline in Colonic Gas in Inulin in Those With and Without a Symptom Response

- While fructose increased SBWC, inulin increased colonic gas more than either fructose or glucose, in addition to increasing total colonic volume.
- No significant differences between patients who reported a rise in symptoms and those who did not.

Change in composite symptom score ≥3 with inulin

Conclusions

• Inulin induced symptoms in more IBS patients than glucose
• Peak symptoms and colonic gas correlated with a similar time to peak
• Any effect of fructose on symptoms may be by a different mechanism, perhaps increased luminal water
• The similarity of findings between patients with and without a symptom increase suggests that the mechanism of effect may not be abnormal luminal content, but an abnormal sensory response
Candidate Genes, Mucosal mRNA and Protein Expression, Colon Transit and Large Scale Validation of a Biomarker for Diarrhea-Predominant Irritable Bowel Syndrome

Aim/Methods

Aim
• To assess blood anti-CdtB and anti-vinculin antibodies as a bimarker for D-IBS in humans for the work up of chronic diarrhea

Methods
• IBS subjects were recruited from a large multicenter clinical trial for D-IBS (TARGET 3)
  – Healthy controls, inflammatory bowel disease (IBD) subjects and celiac disease subjects were obtained for comparison
• Plasma levels of anti-CdtB and anti-vinculin antibodies were determined by ELISA and compared between groups to determine an optimal threshold that was predictive of D-IBS
• Since there is a biomarker for celiac, the primary outcome measure was to assess the effectiveness of these antibodies to differentiate IBS from Crohn’s and ulcerative colitis

Results

- Demographic characteristics similar among IBS subjects (n=2375) compared to IBD (n=142), healthy controls (n=43) and celiac disease (n=121)
  - Fewer female IBD subjects ($P<0.001$)
- Anti-CdtB and anti-vinculin antibodies were highest in IBS compared to all other groups individually or non-IBS, collectively ($P<0.00001$)
- Both tests were significant, but less specific for, differentiating D-IBS from celiac disease

<table>
<thead>
<tr>
<th>Diagnostic Accuracy for Differentiating IBS Over IBD At Ideal Cut-Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Positive</td>
</tr>
<tr>
<td>likelihood ratio</td>
</tr>
<tr>
<td>Area under the</td>
</tr>
<tr>
<td>receiver</td>
</tr>
<tr>
<td>operating curve</td>
</tr>
</tbody>
</table>

OD, optical density.

Conclusions

- This is the first large scale validation of anti-CdtB and anti-vinculin antibodies as a mechanism-based biomarker for D-IBS
- Both tests appear most important in differentiating D-IBS from IBD in subjects presenting with chronic diarrhea
Effects of Rifaximin on Urgency, Bloating, and Abdominal Pain in Patients with IBS-D: A Randomized, Controlled, Repeat Treatment Study

William D. Chey, Lin Chang, Anthony Lembo, Kavita Aggarwal, Enoch Bortey, Craig Paterson, William P. Forbes
Aim/Methods

Aim

• To examine the effect of subsequent courses of rifaximin (RFX) on core symptoms in IBS-D subjects who responded to an initial course of RFX

Methods

• Subjects with IBS-D (Rome III criteria) who presented with mean severity scores of ≥ 3 for abdominal pain (AP, scale 0-10) and bloating (scale 0-6), and ≥ 2 stools with Bristol Stool Scale (BSS) Type 6 (loose) or 7 (watery) during the 7-day baseline were enrolled

• Subjects who responded to an open-label, 2-week course of RFX 550 mg TID, and subsequently experienced a recurrence of symptoms within 18 weeks, were randomized to receive two, 2-week, double-blind (DB), repeat treatments (RFX 550 mg TID or placebo) separated by 10 weeks

• Primary endpoint, assessed after the first repeat treatment during the 4-week follow-up period, was the proportion of patients who were responders during ≥2 of 4 weeks for both AP (≥30% decrease from baseline in mean weekly pain score) and stool consistency (SC, ≥50% decrease from baseline in number of days/week with BSS Type 6 or 7)

• Secondary endpoints included proportion responders for individual symptoms: AP, SC, urgency (≥30% improvement from baseline in percentage of days with urgency), and bloating (≥1-point decrease from baseline in weekly average bloating score)
Results

• 636 patients were randomized to receive 2 repeat treatments with RFX 550 mg TID or placebo x 2 weeks
• Rifaximin led to a significantly higher proportion of composite AP and SC responders than placebo after both the first and second repeat treatments
• Significant improvements were observed for individual symptoms of urgency, bloating, AP, and SC after first repeat treatment
  – Treatment gains over PBO ranged from 8.1% – 9.2% (P<0.05 for all)
• Similar improvements observed after second repeat treatment with RFX
  – Differences relative to PBO ranged from 7.6% – 12.1% (P<0.05 for urgency and bloating)

Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>328</td>
<td>308</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>47.9</td>
<td>45.6</td>
</tr>
<tr>
<td>Female, %</td>
<td>68</td>
<td>71</td>
</tr>
<tr>
<td>Abdominal pain, mean</td>
<td>4.6</td>
<td>4.5</td>
</tr>
<tr>
<td>BSS Type 6/7</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Days per week with urgency</td>
<td>4.9</td>
<td>5.1</td>
</tr>
<tr>
<td>Daily bloating score</td>
<td>3.7</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Composite Abdominal Pain and Stool Consistency Responders

First repeat treatment (primary endpoint)
- Placebo (n=308): 25%
- Rifaximin (n=328): 33%

Second repeat treatment
- Placebo (n=308): 27%
- Rifaximin (n=328): 35%

P = 0.02 for first repeat treatment
P = 0.03 for second repeat treatment
Results

Improvement in IBS-D Symptoms
First Double-Blind Repeat Treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo (n=308)</th>
<th>Rifaximin (n=328)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>39.6</td>
<td>48.5</td>
<td>0.0251</td>
</tr>
<tr>
<td>Bloating</td>
<td>42.2</td>
<td>50.3</td>
<td>0.0345</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>39.6</td>
<td>53</td>
<td>0.0212</td>
</tr>
<tr>
<td>Stool consistency</td>
<td>37</td>
<td>45.1</td>
<td>0.0241</td>
</tr>
</tbody>
</table>

Second Double-Blind Repeat Treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Placebo (n=308)</th>
<th>Rifaximin (n=328)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency</td>
<td>38.5</td>
<td>46.8</td>
<td>0.0355</td>
</tr>
<tr>
<td>Bloating</td>
<td>35</td>
<td>47.1</td>
<td>0.0017</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>44.9</td>
<td>52.5</td>
<td>0.0549</td>
</tr>
<tr>
<td>Stool consistency</td>
<td>38.5</td>
<td>45.1</td>
<td>0.0799</td>
</tr>
</tbody>
</table>
Results/Conclusions

Results

• Most common adverse events were nausea, upper respiratory tract infection, and urinary tract infection

Conclusion

• Rifaximin produced significant improvements in core symptoms of IBS-D in patients treated with up to three, 2-week courses of therapy

<table>
<thead>
<tr>
<th>Most Common Adverse Events</th>
<th>Rifaximin (n=328)</th>
<th>Placebo (n=308)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Efficacy and Safety of ASP7147, a Bombesin-2 Receptor Antagonist, in Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D): Results of a Multicenter, Double-Blind, Placebo-Controlled Trial

Anthony Lembo, James Huber, Robert M. Schinagl, Stephen J. Waters, M. Scott Harris
Aim
• To evaluate the effectiveness and safety of ASP7147, a highly-selective oral bombesin-2 receptor (BB-2) antagonist, in patients with IBS-D

Methods
• Patients with IBS-D (Rome III) between 18-75 years of age who reported a mean worst abdominal pain (WAP) score of ≥ 3.0 out of 10 with ≥1 stool Bristol Stool Scale (BSS, 1-7) score of Type 6 or 7 ≥ 2 days per week during the screening period
• Patients randomized 1:1 to ASP7147 300 mg or placebo BID for 4 weeks followed by a 2-week treatment-free period
• Primary endpoint was change in mean WAP between groups at Week 4
• Secondary endpoints included changes in BSS and stool frequency over 4 weeks of treatment
• Statistical comparisons were made using repeated measures analysis (RMA) for overall (Weeks 1-4) and weekly comparisons and ANCOVA adjusting for baseline
Results

- 64 patients (23 male, 41 female)
  - Baseline scores for BSS (6.0 for ASP7147 vs. 5.9 for placebo) and weekly stool frequency (5.4 vs. 5.6) evenly matched
  - Small but insignificant imbalance in WAP
- Significant improvements compared to baseline in WAP and BSS at Week 4, beginning at Week 1 and persisting each week through Week 4 ($P=0.039$ RMA overall for WAP, $P=0.033$ RMA overall for BSS) and the 2-week treatment-free period
- Consistent superiority of ASP7147 over placebo noted in stool frequency, bloating, urgency, and loss of control at each week
- No differences in response apparent between male and female patients
- Frequency of adverse events was similar between treatment groups
  - No constipation or use of rescue medications and no serious events attributable to active treatment

Week 4 Outcomes

<table>
<thead>
<tr>
<th>Worst abdominal pain</th>
<th>Bristol Stool Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>ASP7147</td>
</tr>
<tr>
<td>$-1.7$</td>
<td>$-2.5$</td>
</tr>
<tr>
<td>$P=0.046$ RMA</td>
<td>$P=0.077$ RMA</td>
</tr>
<tr>
<td>$P=0.095$ ANCOVA</td>
<td>$P=0.075$ ANCOVA</td>
</tr>
</tbody>
</table>
Conclusions

• ASP7147 holds promise as a safe and effective new therapy for both men and women with IBS-D, demonstrating improvement in multiple symptoms of IBS-D
• The persistence of treatment effect suggests the possibility of retained efficacy with less frequent dosing in follow-on trials
Eluxadoline Demonstrates Sustained Efficacy for the Treatment of Diarrhea-predominant Irritable Bowel Syndrome in Phase 3 Clinical Trials

William D. Chey, Scott Dove, David Andrae, J. Michael Davenport, Lisa Turner, Rocio Lopez, Paul S. Covington
Aim and Methods

Aim
• To assess the sustained efficacy of eluxadoline in two Phase 3 clinical trials

Methods
• Two, double-blind, placebo-controlled, Phase 3 clinical trials (3001 and 3002) randomized patients meeting Rome III criteria for IBS-D to twice-daily treatment with eluxadoline (75 or 100 mg) or placebo (PBO)
  – Efficacy through 26 weeks of double-blind treatment
• Efficacy assessed via composite response outcome comprised of simultaneous improvement in abdominal pain and stool consistency. Patients who met both, daily pain responder (≥30% improvement in abdominal pain) AND daily stool consistency responder criteria (Bristol Stool Score of <5) for ≥50% of days were considered study responders
• Responder analyses included monthly, 3-month and 6-month assessments of the composite endpoint
  – For the monthly or 3-month intervals, patients had to record ≥72% daily diary entries of symptoms to be assessed for response on the composite endpoint whereas for the 6-month interval they had to record ≥ 60% daily diary entries

Results

- 2428 IBS-D patients (66.1% female, mean age 45.4)
- Significantly more patients ($P \leq 0.017$) receiving eluxadoline 100mg were composite responders than patients receiving PBO over every time interval examined using the Cochran Mantel Haenszel (CMH) analysis
  - Longitudinal analyses at specific time points supported the CMH results
  - No age or gender differences were detected in the composite response rates
- Similar proportion of patients with AEs and SAEs across treatment groups
  - AEs: 75-mg (60.2%), 100-mg (58.2%), placebo (55.7%)
  - SAEs: 75-mg (4.2%), 100-mg (4.8%), placebo (3.0%)
- Most commonly reported AEs were within the GI system organ class
  - 75-mg (30.0%), 100-mg (27.7%), placebo (19.4%)

Results

Composite Response Rate at Varying Intervals

**Study 3001**

- Week 1-4: 12.9% (P=0.003), 20.6% (P<0.001), 22.5% (P=0.002)
- Week 5-8: 19.9% (P=0.023), 26.5% (P<0.001), 28.9% (P=0.002)
- Week 9-12: 21.8% (P=0.514), 23.7% (P=0.005), 30.3% (P<0.001)
- Week 13-16: 21.1% (P=0.563), 22.7% (P=0.007), 29.1% (P=0.017)
- Week 17-20: 21.8% (P=0.047), 27.6% (P=0.008), 28.9% (P=0.008)
- Week 21-24: 20.4% (P=0.016), 27.4% (P=0.008), 28.2% (P=0.008)

**Study 3002**

- Week 1-4: 12% (P<0.001), 25.2% (P<0.001), 26.7% (P<0.001)
- Week 5-8: 19.9% (P=0.001), 31.5% (P<0.001), 33.5% (P<0.001)
- Week 9-12: 22% (P=0.001), 32.3% (P<0.001), 31.9% (P=0.002)
- Week 13-16: 20.9% (P=0.007), 30.7% (P=0.002), 33.8% (P<0.001)
- Week 17-20: 22.5% (P=0.007), 31.2% (P=0.004), 31.2% (P=0.004)
- Week 21-24: 19.9% (P=0.004), 28.9% (P<0.001), 32.5% (P<0.001)
Results

Proportion of Patients Achieving Daily Composite Response Criteria Versus Time

Conclusions

• Results from two Phase 3 clinical trials demonstrated that eluxadoline was an effective treatment for IBS-D and exhibited rapid onset of action along with sustained efficacy over the 6 months studied.

Low-FODMAP Diet In Irritable Bowel Syndrome Patients Offers More Benefit Than A Low-FODMAP Gluten-free Diet in the Medium- and Long-term Results From A Double-blind Randomized Controlled Clinical Study and Follow-up

Daria Piacentino, Sara Rossi, Valeria Alvino, Rosanna Di Nunno, Luca Piretta, Danilo Badiali, Nadia Pallotta, Enrico Corazziari
Aim and Methods

Aim

- To compare low FODMAP and gluten-free (FOD-GF), low FODMAP and normal gluten (FOD-NG) and normal-gluten diets with respect to effectiveness on abdominal bloating and pain, satisfactory relief, compliance, and follow-up

Methods

- Rome III IBS consecutive outpatients were recruited
  - Patients completed the SCL-90-R, a VAS to rate the intensity of bloating, and a 2-week diary card registering diet and frequency of abdominal bloating/pain
- Patients were blindly assigned to one of three 4-week diets (FOD-GF, FOD-NG, or normal-gluten)
  - During the last 2 weeks, patients completed a 2nd diary card and rated the intensity of bloating and compliance (VAS), plus satisfactory relief
- Patients were reassessed after a mean follow-up of 16 months
- Data analyzed by independent t-test, X² test, one-way ANOVA with Tukey post-hoc test, and Pearson’s r
Results

• 75 patients (51 female, age range=21-68 years)
  – Baseline characteristics similar among 3 groups

• FOD-GF and FOD-NG groups showed improved intensity of abdominal bloating and frequency of abdominal bloating/pain after the diets ($P$-values 0.001-0.008 in FOD-GF and 0.000 in FOD-NG), vs slight improvement in controls
  – Intensity of bloating and frequency of abdominal bloating/pain were comparable in the 3 groups pre-diet, but differed post-diet ($P$=0.000)
## Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS symptom improvement</td>
<td>• Greater improvement of IBS symptoms in the 2 test diet groups vs. the control group, and a trend favoring the FOD-NG group vs. the FOD-GF group were found</td>
</tr>
<tr>
<td>Satisfactory relief</td>
<td>• No difference between groups when assessed with a “yes/no” question</td>
</tr>
<tr>
<td></td>
<td>• Significantly higher in the FOD-NG than the FOD-GF group when evaluated by VAS ($P=0.044$)</td>
</tr>
<tr>
<td>Compliance</td>
<td>• Lower with FOD-GF than FOD-NG group ($P=0.041$)</td>
</tr>
<tr>
<td></td>
<td>• No correlation found between objective benefits, satisfactory relief, compliance, and SCL-90-R scores</td>
</tr>
<tr>
<td>Follow-up</td>
<td>• 72% FOD-NG continued diet with benefit, the remainder found it too monotonous</td>
</tr>
<tr>
<td></td>
<td>• 52% FOD-GF continued diet, the remainder considered it too restrictive or had only partial benefit</td>
</tr>
<tr>
<td></td>
<td>• 40% controls continued the diet, the remainder found no significant benefit ($P=0.051$, FOD-NG vs. FOD-GF vs. controls)</td>
</tr>
</tbody>
</table>

Conclusions

• The majority of IBS patients have medium- and long-term benefit with low-FODMAP diet
• Gluten avoidance does not seem to offer any additional benefit and has a negative impact on compliance
• A VAS, rather than a satisfactory relief binary response question, can better discriminate treatment outcome
• FOD-NG diet was continued by patients to maintain the benefit, showing better performance at follow-up
• Psychopathology does not influence clinical improvement, satisfactory relief, or compliance during the diets
A Randomized, Controlled Trial Comparing A Diet Low in FODMAPs With Traditional Dietary Advice in Patients With IBS

Lena Böhn, Stine Störsrud, Therese M. Liljebo, Perjohan Lindfors, Hans Törnblom, Magnus Simren
Aim and Methods

Aim
• To compare the effects on IBS symptoms of a low-FODMAP diet and traditional dietary advice in patients with IBS

Methods
• 75 patients with IBS randomized to receive dietary advice from a dietitian about a low FODMAP diet (n=38) or traditional IBS dietary advice, based on dietary recommendations from NICE and the British Dietary Association (n=37)
  – Patients followed diets for 4 weeks and completed 4-day food diary before and during intervention
  – Patients blinded to identity of the dietary advice
• IBS Severity Scoring System (IBS-SSS) used to assess symptom severity
  – Responders defined as those reporting a reduction in IBS-SSS by ≥ 50 at end of treatment relative to baseline
• Potential factors predicating a positive treatment response were evaluated
  – Baseline dietary intake, demographics, anxiety and depression (HAD), GI-specific anxiety (VSI), and symptom pattern (PHQ-15, IBS-SSS, Rome III subgroup)

Results

- 67 patients completed dietary intervention
- IBS symptom severity (IBS-SSS) improved in both groups during the intervention, with no difference between groups ($P=0.62$)
- 56% patients in the low FODMAP group were responders to treatment at end of study vs 46% receiving the traditional IBS diet ($P=0.72$)
- Food diaries demonstrated that patients in the low FODMAPs group had lower intake of carbohydrates ($P=0.007$), dietary fiber ($P=0.001$) and FODMAPs ($P<0.0001$) than in the traditional IBS diet group during the intervention period
- Calorie intake during the intervention period reduced in both groups ($P<0.0001$)
- Lower FODMAP intake at baseline predicted a positive response to a low FODMAP diet
- Responders to the low FODMAP diet were older and almost exclusively female
- IBS subtype influenced the likelihood of being a responder to the traditional IBS diet (IBS-C less likely to respond favorably)
Results

Improvement in IBS-SSS

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Baseline Score</th>
<th>After Treatment Score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional IBS diet</td>
<td>324</td>
<td>246</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low FODMAP diet</td>
<td>302</td>
<td>236</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Proportion of Responders at End of Treatment

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Responders (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional IBS diet</td>
<td>46</td>
<td>0.72</td>
</tr>
<tr>
<td>Low FODMAP diet</td>
<td>56</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• Dietary advice is efficient in reducing the gastrointestinal symptoms of IBS without any clear difference noted when comparing a low FODMAPs diet with traditional IBS dietary advice
• Combining elements from these two strategies in future dietary advice for IBS should be tested

Efficacy and Safety of Tenapanor in Patients with Constipation Predominant Irritable Bowel Syndrome: A 12-Week, Double-Blind, Placebo-Controlled, Randomized Phase 2b Trial

William D. Chey, Anthony Lembo, James A. Phillips, David P. Rosenbaum
Aim and Methods

Aim
• To evaluate the efficacy and safety of tenapanor in patients for the treatment of IBS-C

Methods
• Randomized, double-blind, placebo-controlled trial
• Patients had IBS-C (per modified Rome III criteria) with an average of <3 complete spontaneous bowel movements (CSBM)/week, <5 SBM/week, and abdominal pain ≥3 (0-10 rating scale) during a 2-week baseline period
• Patients received oral tenapanor 5, 20 or 50 mg or placebo BID over a 12-week treatment period
• Responder analysis and secondary endpoints were analyzed over 12 weeks using the Cochran-Mantel-Haenszel (CMH) test (responder analysis) and Analysis of Covariance (ANCOVA, change-from-baseline)
Results

• N=356 (ITT population)
  – Mean age 45.7 years, 87% female (~90/group)

• Baseline characteristics similar between groups
  – CSBMs = 0.2/week, SBMs = 2/week, Bristol Stool Form Scale (BSFS) score = 1.8, and abdominal pain score = 6.1 from the 2-week screening period for all pooled groups

• Dose-related effects of tenapanor were observed on most endpoints
  – However, tenapanor 5 and 20 mg BID were not significant for primary and most secondary outcome measures

• Compared to placebo, significantly more subjects taking 50 mg tenapanor BID daily met the primary endpoint and demonstrated statistically significant improvement on 9 secondary endpoints over the 12 week study

• Diarrhea was the most common adverse event during the treatment period
  – 0%, placebo; 8%, 5 mg bid; 12.4%, 20 mg bid; 11.2%, 50 mg bid
  – Caused discontinuation in 3.3% of patients who received tenapanor
Results

**Primary Endpoint**

- ≥1 CSBM increase: Placebo (33.7%) vs. Tenapanor 50 mg BID (60.7%).
- ≥30% abdominal pain reduction: Placebo (48.3%) vs. Tenapanor 50 mg BID (65.5%).

**Secondary Endpoints**

- ≥30% abdominal pain reduction and ≥1 CSBM increase in the same week: Placebo (23.6%) vs. Tenapanor 50 mg BID (50%).
## Results

### LS Mean Change from Baseline to Week 12

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Tenapanor 50 mg BID</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain (0–10)</td>
<td>-2.3</td>
<td>-3.1</td>
<td>0.014</td>
</tr>
<tr>
<td>Abdominal discomfort (0–10)</td>
<td>-2.0</td>
<td>-3.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Abdominal bloating (0–10)</td>
<td>-1.6</td>
<td>-2.6</td>
<td>0.023</td>
</tr>
<tr>
<td>Straining (0–5)</td>
<td>-0.7</td>
<td>-1.2</td>
<td>0.006</td>
</tr>
<tr>
<td>Stool consistency BSFS (1=hard, 7=watery)</td>
<td>1.0</td>
<td>2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSBM/week</td>
<td>0.9</td>
<td>2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBM/week</td>
<td>1.6</td>
<td>3.4</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*ANCOVA*
Conclusions

- In patients with IBS-C, 50 mg of tenapanor administered twice daily produced statistically significant improvements in the primary endpoint (CSBM responder) and secondary endpoints including abdominal pain, stool frequency and composite endpoints.
- Tenapanor also improved multiple secondary endpoints addressing a wide range of symptoms in patients with IBS-C.
- Improvements occurred rapidly and were sustained throughout the treatment period.

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### Visiting Professorship
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  - Medical and gastroenterology grand rounds
  - Clinical case conferences with faculty and trainees
  - Individual advisory meetings with young aspiring faculty seeking careers in FGIDs
  - Workshops or other training programs as requested

### Visiting Lectureship
- One day visit to a medical center, large clinical practice, GI club or community oriented educational venue
  - Grand rounds to an academic program
  - Round table discussion, case conference or lecture
Year One

• Completed

Year Two

• March 1 – December 31, 2015  Call for Year Two applications
• December 1– December 31, 2015  Grant review, speaker and site selection
• January 1 – December 31, 2016  Grant award period – year two

Selection Committee

William D. Chey, MD  USA  (co-chair)  Jan Tack, MD PhD  Belgium  (co-chair)
Douglas A. Drossman MD  USA  Magnus Simren, MD, PhD  Sweden

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