Functional Bowel Disease

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NO FINANCIAL DISCLOSURES

I reference the work of the distinguished presenters at DDW 2019, San Diego
Velusetrag
Improves Gastroparesis Both in Symptoms and Gastric Emptying In Patients with Diabetic or Idiopathic Gastroparesis
a 12 week global phase 2b Study

Thomas L. Abell, Braden Kuo, Tuba Esfandyari, Daniel Canafx, Roberto Camerini, Maria Grimaldi, Giuseppe C. Viscomi, Cecilia Renzulli, Kefei Zhou, Deanna D. Nguyen, Chris N. Barnes, Richard McCallum
Velusetrag

• A potent and highly selective 5-HT\textsubscript{4} agonist with prokinetic activity throughout the GI tract

• Has no significant affinity for any other receptor types, ion channels (hERG)

• Extremely low potential for cardiac side effects. In vitro studies have not shown affect on coronary artery tone or human platelet aggregation
Study Objectives

Primary

• To evaluate the effect of velusetrag on symptoms in patients with gastroparesis

Key secondary

• To determine the effect on gastric emptying
• To assess the safety and tolerability of velusetrag in patients with gastroparesis
Study Design

12 Week, double blind, randomized, placebo controlled parallel-group

- **Baseline**
  - Day -7 to -1

- **Screening**
  - Day -35 to -1

- **Treatment Day 1 to 84**

- **Follow-up Day 98**

Assessing once daily oral Velusetrag 5, 15, or 30mg vs placebo

GCSI-24H completed daily during baseline period and throughout study

Gastric Emptying assessed at screening and day 28 using GES or GEBT
Gastroparesis Cardinal symptom Index

Each parameter scored on 0-5 scale

• Nausea
• Retching
• Vomiting
• Stomach fullness
• Not able to finish normal sized meal
• Loss of appetite
• Bloating
• Stomach or belly visibly larger

Key Patient Eligibility Criteria

### Inclusion Criteria
- Diabetic or idiopathic gastroparesis
- Gastric emptying delay
  - 99mTc GES: > 10% retention at 4H
  - GEBT: $t_{\text{max}}$ at 240min or delay at 2 of 3 time points (90, 120, or 150min)
- Gastroparesis symptoms for ≥ 3 months before screening and at baseline
- GCSI-2W composite score ≥ 2 to < 5 on nausea, bloating, feeling excessively full after meals, and not able to finish a normal-sized meal at screening
- GCSI-2W score ≥ 3 on ≥ 2 of nausea, bloating, feeling excessively full after meals, and not able to finish a normal-sized meal at screening
- GCSI-24H ≥ 2.5 points on day 1

### Exclusion Criteria
- Vomiting ≥ 2x/day for ≥ 4 days/week
- Use of opioids, linaclotide, or lubiprostone ≤ 2 weeks before screening and throughout study
  - Anticholinergics, acetylcholinesterase antagonists, or promotility medications were not allowed 24H before and during the baseline period, and 24H before GES
  - limited use of rescue medications to relieve acute exacerbations of gastroparesis was permitted at other times during the study and documented
- Symptomatic diverticulitis, predominant symptoms of IBS or IBD or other significant condition that could interfere with safety or efficacy evaluation
Randomized patients
N = 233

Patients treated with study drug
N = 232

Velusetrag 5mg
N = 59
- 49 Completed
- 10 Not completed
- 2 Adverse event
- 1 Lost to follow-up
- 7 Withdrawal by patient

Velusetrag 15mg
N = 56
- 44 Completed
- 12 Not completed
- 6 Adverse event
- 1 Physician decision
- 5 Withdrawal by patient

Velusetrag 30mg
N = 58
- 51 completed
- 7 Not completed
- 4 Adverse event
- 1 Physician decision
- 5 Withdrawal by patient
- 1 Other

Placebo
N = 59
- 50 completed
- 9 Not completed
- 5 adverse event
- 1 Physician decision
- 3 Withdrawal by patient
### Baseline Demographics and Clinical Characteristics (ITT analysis set)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Velusetrag</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 59</td>
<td>n = 59</td>
<td>N = 228</td>
</tr>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>47.0 (13.9)</td>
<td>51.8 (13.3)</td>
<td>50.3 (13.5)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>43 (72.9)</td>
<td>46 (78.0)</td>
<td>179 (78.5)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>53 (89.8)</td>
<td>52 (88.1)</td>
<td>201 (88.2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>5 (8.5)</td>
<td>7 (11.9)</td>
<td>22 (9.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (1.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>1 (1.7)</td>
<td>0</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td><strong>BMI, median (range), kg/m²</strong></td>
<td>28.8 (18.8–41.3)</td>
<td>29.7 (20.1–41.9)</td>
<td>29.3 (18.0, 41.9)</td>
</tr>
<tr>
<td><strong>HbA1c, median (range), %</strong></td>
<td>7.3 (5.0–11.0)</td>
<td>6.7 (4.7–9.3)</td>
<td>7.1 (4.7–11.0)</td>
</tr>
<tr>
<td><strong>Gastroparesis Type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>27 (45.8)</td>
<td>29 (49.2)</td>
<td>111 (48.7)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>32 (54.2)</td>
<td>30 (50.8)</td>
<td>117 (51.3)</td>
</tr>
<tr>
<td><strong>GCSI-24H, mean (SD)</strong></td>
<td>3.0 (0.4)</td>
<td>3.1 (0.5)</td>
<td>3.1 (0.5)</td>
</tr>
</tbody>
</table>

**ITT = intent to treat**

**GCSI-24H = Gastroparesis Cardinal Symptoms Index 24-hour version**

**HbA1c = glycosylated hemoglobin**
Velusetrag Improves Gastroparesis Symptoms

Error bars represent standard error of the LSM
- Nominal p vs placebo < 0.05
- LSM = least squares mean
- VEL = velusetrag
<table>
<thead>
<tr>
<th>Subscale</th>
<th>Placebo (n = 59)</th>
<th>Velusetrag 5 mg (n = 59)</th>
<th>p value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCSI-24H Nausea/Vomiting</td>
<td>−0.9 (0.11)</td>
<td>−1.1 (0.11)</td>
<td>0.3388</td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSI-24H Postprandial Fullness/Early Satiety</td>
<td>−1.2 (0.16)</td>
<td>−1.8 (0.15)</td>
<td>0.0116</td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCSI-24H Bloating</td>
<td>−1.2 (0.16)</td>
<td>−1.6 (0.16)</td>
<td>0.0406</td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRS Abdominal Pain</td>
<td>−1.0 (0.16)</td>
<td>−1.5 (0.16)</td>
<td>0.0230</td>
</tr>
<tr>
<td>Week 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>−1.4 (0.18)</td>
<td>−1.9 (0.18)</td>
<td>0.0664</td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GRS = Gastroparesis Rating Scale
Velusetrag Improves Gastric Emptying

GES = gastric emptying scintigraphy
LSM = least squares mean

% of patients with gastric emptying normalization:
- Placebo: 0%
- VEL 5 mg: 44%
- VEL 15 mg: 65%
- VEL 30 mg: 71%

Mean retention significantly lower vs placebo for VEL 15 and 30 mg at hour 1 and VEL all doses at hours 2, 3, and 4.
# Adverse Events in >5% of Patients in a Group

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 59)</th>
<th>5 mg (n = 59)</th>
<th>15 mg (n = 56)</th>
<th>30 mg (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>38 (64.4)</td>
<td>35 (59.3)</td>
<td>38 (67.9)</td>
<td>29 (50.0)</td>
</tr>
<tr>
<td>SAE</td>
<td>3 (5.1)</td>
<td>4 (6.8)</td>
<td>2 (3.6)</td>
<td>3 (5.2)</td>
</tr>
<tr>
<td>AE leading to study discontinuation</td>
<td>5 (8.5)</td>
<td>2 (3.4)</td>
<td>6 (10.7)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td><strong>AEs by preferred term</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (6.8)</td>
<td>7 (11.9)</td>
<td>17 (30.4)</td>
<td>11 (19.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3.4)</td>
<td>4 (6.8)</td>
<td>4 (7.1)</td>
<td>8 (13.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (13.6)</td>
<td>0</td>
<td>5 (8.9)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (5.1)</td>
<td>6 (10.2)</td>
<td>1 (1.8)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3 (5.1)</td>
<td>2 (3.4)</td>
<td>2 (3.6)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>URTI</td>
<td>5 (8.5)</td>
<td>3 (5.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>2 (3.4)</td>
<td>3 (5.1)</td>
<td>0</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 (5.1)</td>
<td>1 (1.7)</td>
<td>1 (1.8)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
<td>2 (3.6)</td>
<td>4 (6.9)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0</td>
<td>1 (1.7)</td>
<td>3 (5.4)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0</td>
<td>1 (1.7)</td>
<td>0</td>
<td>3 (5.2)</td>
</tr>
</tbody>
</table>

All data are n (%)  
AE = adverse event  
SAE = serious AE
Velusetrag

- 12 weeks treatment demonstrated a prokinetic effect and reduced gastroparesis symptoms compared with placebo
- Generally well tolerated
- Phase 3 studies assessing efficacy with a focus on optimal dosing appear promising
Fecal Microbiota Transplantation (with or without antibiotic pretreatment) in IBS-D: A double-blind, randomized, placebo-controlled trial


Beth Israel Deaconess Medical Center

Harvard Medical School
IBS and Gut dysbiosis

• IBS patients have lower microbial diversity compared to healthy controls

• A meta-analysis of stool qPCR studies identified lower levels of *Lactobacillus, Bifidobacterium*, and *Faecalibacterium* in IBS

• Stool transfer from IBS-D patients to animals induces innate immune-activation and increased intestinal permeability, and visceral hypersensitivity

Liu HN, et al, DLD 2017
IBS treatments

Alter gut microbiome

• Antibiotics – Rifaximin

• Probiotics

• Diet – Low FODMAP
### Meta-Analysis of FMT for IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>FMT Events</th>
<th>FMT Total</th>
<th>Placebo Events</th>
<th>Placebo Total</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%–CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnsen 2017</td>
<td>36</td>
<td>60</td>
<td>12</td>
<td>30</td>
<td>1.50 [0.92; 2.44]</td>
<td>1.50</td>
<td>[0.92; 2.44]</td>
<td>27.1%</td>
</tr>
<tr>
<td>Holvoet 2018</td>
<td>21</td>
<td>42</td>
<td>6</td>
<td>22</td>
<td>1.83 [0.87; 3.87]</td>
<td>1.83</td>
<td>[0.87; 3.87]</td>
<td>22.5%</td>
</tr>
<tr>
<td>Aroniadis 2018</td>
<td>10</td>
<td>24</td>
<td>15</td>
<td>24</td>
<td>0.67 [0.38; 1.17]</td>
<td>0.67</td>
<td>[0.38; 1.17]</td>
<td>25.7%</td>
</tr>
<tr>
<td>Halkjær 2018</td>
<td>8</td>
<td>26</td>
<td>19</td>
<td>26</td>
<td>0.42 [0.23; 0.78]</td>
<td>0.42</td>
<td>[0.23; 0.78]</td>
<td>24.7%</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>152</strong></td>
<td><strong>75</strong></td>
<td><strong>102</strong></td>
<td><strong>52</strong></td>
<td><strong>0.93 [0.48; 1.79]</strong></td>
<td>0.93</td>
<td>[0.48; 1.79]</td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

Weights are from random effects analysis

Heterogeneity: $I^2 = 79\%$, $x_3^2 = 14.47$ ($p < 0.01$)

Clinical Response to FMT: $z = -0.22$ ($p = 0.83$)

**Figure 2** Forest plot of all studies for efficacy of FMT vs placebo on global improvement of IBS symptoms. CI, confidence interval; FMT, fecal microbiota transplantation; IBS, irritable bowel syndrome; RR, risk ratio.

Xu Dabo, et al. Am J Gastroenterology 2019; Published Ahead of Print
AIM

To compare the efficacy of FMT with or without pretreatment of antibiotics in improving clinical symptoms in IBS-D patients
Study Design

Screening Visit

Rifaximin
f/b FMT
550mg TID for 7 days

Cipro/Flagyl
f/b FMT
Cipro 500mg BID
Flagyl 500mg TID
For 7 days

FMT

Placebo

All groups received colonoscopy prep prior to treatment

FMT; single dose; oral; 19 capsules frozen fecal material
Total grams of stool per dose = 18.75g

Week 1 Follow-up
Week 10 Follow-up
Inclusion Criteria

• Fulfill Rome III criteria for IBS-D
• Moderate to severe IBS (IBS-SSS >175)
• Normal colonoscopy (following onset of IBS symptoms and within the last five years or since the onset of alarm features)
• Stable IBS meds
• No plans to change lifestyle or diet during the study period

Exclusion Criteria

• Hx of IBD
• Hx of major abdominal surgery except cholecystectomy, appendectomy etc
• Recent hx of cholecystitis, diverticulitis, pancreatitis
• Recent use of antibiotics
• Allergy to antibiotics being used in the study
• Hx of malignancy in 5 years of screening
• Hx of HIV/AIDS or other immunodeficiencies
• Pregnant or breastfeeding
• History of dysphagia or pill esophagitis
49 IBS-D patients screened

44 patients randomized

- FMT alone: N = 11
  - N = 9

- Rifaximin f/b FMT: N = 11
  - N = 10

- Cipro/Flagyl f/b FMT: N = 10
  - N = 7

- Placebo: N = 12
  - N = 12
Endpoints Assessed at Week 1 and 10

- Change in mean IBS–SSS
  - Eval of Sx (pain, distension, BMs) over last 10 days
  - Range of 0-500
  - Responder if decrease of 50 points on IBS-SSS

- Change in mean IBS-QOL score
  - 34 item disease-specific QoL assessment
  - Range of 0-100
  - Responder if increase of 12 points

- Adequate relief

- Global improvement
Baseline Characteristics

- Mean age 35 – 40 years (P = 0.71)
- Predominantly female (P = 0.80)
- IBS-QoL comparable in all 4 (P = 0.09)
- IBS-SSS higher in FMT group; 80% of pts had severe IBS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FMT N = 11</th>
<th>Rifaximin f/b FMT N = 10</th>
<th>Cipro/Metro f/b FMT N = 7</th>
<th>Placebo N = 12</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-SSS 9</td>
<td>347.5 (81.8)</td>
<td>277.8 (43.6)</td>
<td>339.1 (70)</td>
<td>282.3 (33.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>Severe IBS</td>
<td>9 (81.8)</td>
<td>4 (36.4)</td>
<td>7 (70)</td>
<td>4 (33.3)</td>
<td>0.052</td>
</tr>
</tbody>
</table>
Clinical Outcomes at Week 10

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FMT alone (N=9)</th>
<th>Rifaximin f/b FMT (N=10)</th>
<th>Cipro/Metro f/b FMT (N=7)</th>
<th>Placebo (N=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in IBS-SSS</td>
<td>-45.9</td>
<td>-74.8</td>
<td>-114</td>
<td>-93.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Mean change in IBS-QoL</td>
<td>14.7</td>
<td>6.8</td>
<td>20.9</td>
<td>10.3</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean Global Improvement score</td>
<td>4.9</td>
<td>4.5</td>
<td>4.7</td>
<td>4.2</td>
<td>0.80</td>
</tr>
<tr>
<td>Adequate relief</td>
<td>33.3%</td>
<td>40%</td>
<td>57.1%</td>
<td>33.3%</td>
<td>0.74</td>
</tr>
</tbody>
</table>

No statistically significant difference in clinical parameters between all 4 groups
## Responder Outcomes at Week 10

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FMT alone (N=9)</th>
<th>Rifaximin f/b FMT (N=10)</th>
<th>Cipro/Metro f/b FMT (N=7)</th>
<th>Placebo (N=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS-SSS responder</td>
<td>3 (33.3)</td>
<td>6 (60)</td>
<td>5 (71.4)</td>
<td>8 (66.7)</td>
<td>0.43</td>
</tr>
<tr>
<td>IBS-QoL responder</td>
<td>4 (44.4)</td>
<td>2 (20)</td>
<td>5 (71.4)</td>
<td>5 (41.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>Global Improvement responder</td>
<td>3 (33.3)</td>
<td>4 (40)</td>
<td>3 (42.9)</td>
<td>2 (16.7)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

No statistically significant difference in clinical parameters between all 4 groups
Adverse Events

- Genital HSV1 2 weeks after FMT with cipro/flagyl; N = 1
- UTI after FMT alone; N = 1
- Strep infection (placebo); N = 1
- Severe headache requiring ED visit after FMT with Cipro/flagyl; N = 1
Conclusion

- FMT administered orally did not improve symptoms in patients with IBD-D

- Pre-treatment with antibiotics before FMT did not have significant impact on clinical outcomes in IBS-D patients
Limitations

• Small sample size
• 13.6% did not fill out follow-up questionnaires
• 56% with severe IBS symptoms
• Did not adjust for lifestyle
• The study period occurred similar in time to studies listed in Xu meta-analysis
Home Biofeedback Therapy with Novel Device versus Office Biofeedback Therapy for FI
Randomized Controlled Study

Amol Sharma, MD, Xuelian Xiang, MD, Yun Yan, MD, Tanisa Patchcharatrakul, MD, Rachel Parr, MS, Satish SC Rao, MD, PhD

Augusta University Medical Center
Background

Office Biofeedback Therapy

• Requires multiple office visits (4-8)
• Labor intensive
• Results in loss of work-related productivity
• Does not provide a durable response

Aim:
To assess the feasibility, efficacy, and safety of a new Home BT device compared to Office BT in a RCT
Protocol

• Screen (H&P, anorectal manometry and questionnaires)
• Randomized 2:1 Home:Office
• 6 week treatment plus stool diary
• FI severity and QoL questionnaires completed at end of study
• Anorectal manometry repeated
Inclusion Criteria:
1) Recurrent episodes of FI for 6 months
2) No mucosal disease (colonoscopy within 10 years)
3) On a 2-week stool diary patients reported at least one episode of solid or liquid FI/week

Exclusion Criteria:
1) Severe diarrhea (>6 liquid stools/day, Bristol scale >6)
2) Opioid, tricyclics (except on stable doses > 3 months)
3) Active depression
4) Comorbid illnesses, severe cardiac disease, chronic renal failure
5) Impaired cognizance and/or legally blind
6) Pacemaker or implanted defibrillator
7) Previous pelvic surgery, bladder repair, radical hysterectomy
8) UC and Crohn colitis
9) Rectal prolapse, anal fissure, or inflamed hemorrhoids
10) Pregnant women and nursing mothers
Home Biofeedback Protocol

- Short Squeeze: 5 secs contraction, 10 secs relax, Repeat 3 times
- Long Squeeze: 25 secs contraction, 10 secs relax, Repeat 3 times
- Long Electrical stimulation: 5 mins
- Short Electrical stimulation: 2 mins

300 s
300 s
150 s
120 s

20 minute

Inflatable probe
Metal electrode
Primary Outcome Measures

**Responder:** > 50% decrease in the weekly FI episode in the final week compared with baseline period

Secondary Outcome Measures
Pts evaluation of QoL, severity questionnaires, and electrophysiology testing

42 patients consented

33 Eligible patients

23 Home Group – 20 completed

10 Office Group – 10 completed

Total Completed 30
Results

• All patients had an overall decrease in total number of FI episodes (statistically significant = SS)

• Primary Outcome – not SS

• Resting and maximal squeeze pressure improved in both arms (+SS)
  Sustained squeeze only showed improvement in the Home arm

• Subject’s Global Assessment
  Significant improvement in the home arm not achieved in the office arm
  (considerable or completely relieved)
Conclusions

• Home BT is as effective as Office BT
• Home BT improves resting and squeeze anal sphincter pressures
• Home BT improves rectal compliance and QoL

Home BT is more efficient, potentially more cost effective, more durable, and possibly improves patient compliance; these observations require validation in larger sham controlled RCT
THANK YOU