Functional Bowel Disease

Alexandra Guillaume, MD
Assistant Professor of Medicine
Director, Gastrointestinal Motility Center
Stony Brook University Hospital
Renaissance School of Medicine

NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019

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

NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019

Velusetrag

- A potent and highly selective 5-HT_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

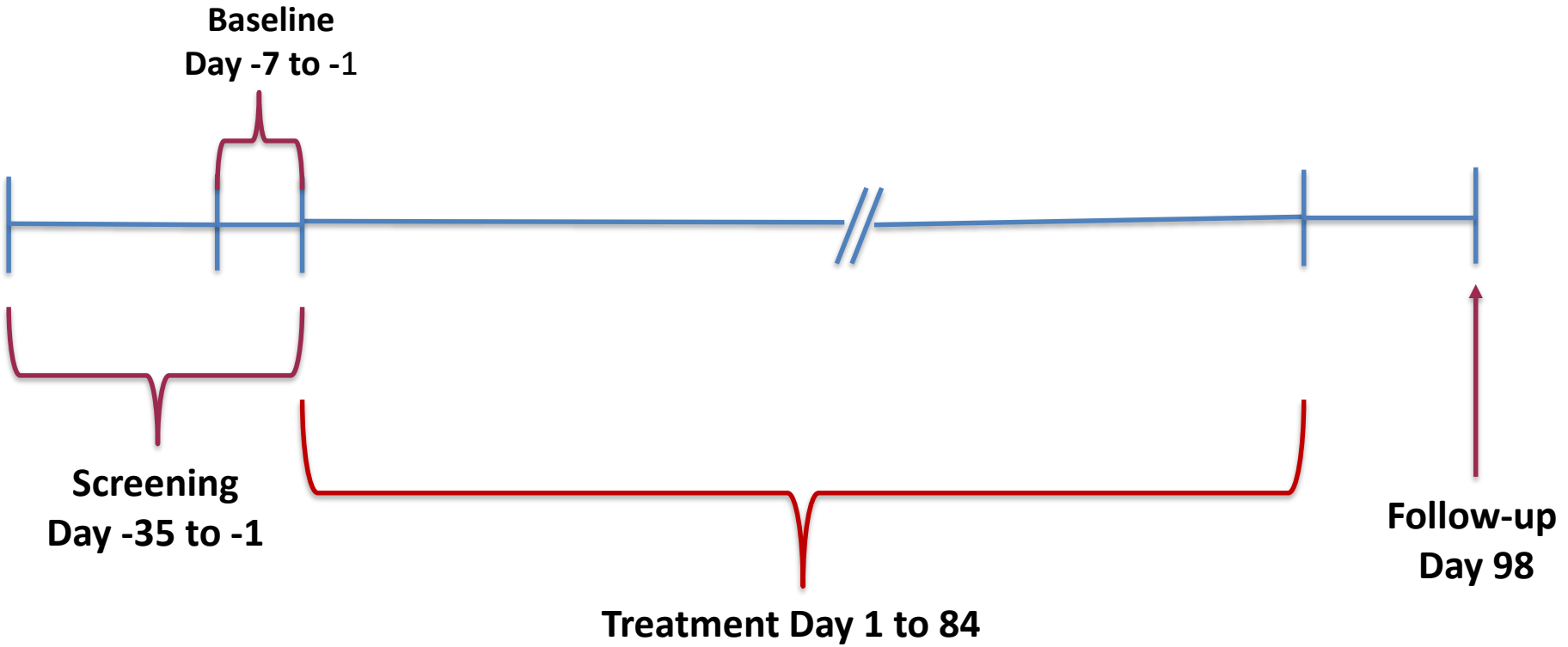
- To evaluate the effect of velusetrag on symptoms in patients with gastroparesis

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



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

NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019

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

Revicki, DA et al. *Gastroparesis Cardinal Symptom Index (GCSI): development and validation of a patient reported assessment of severity of gastroparesis symptoms*. Quality of Life Research. 2004 May;13(4):833-44.

Key Patient Eligibility Criteria

Inclusion Criteria

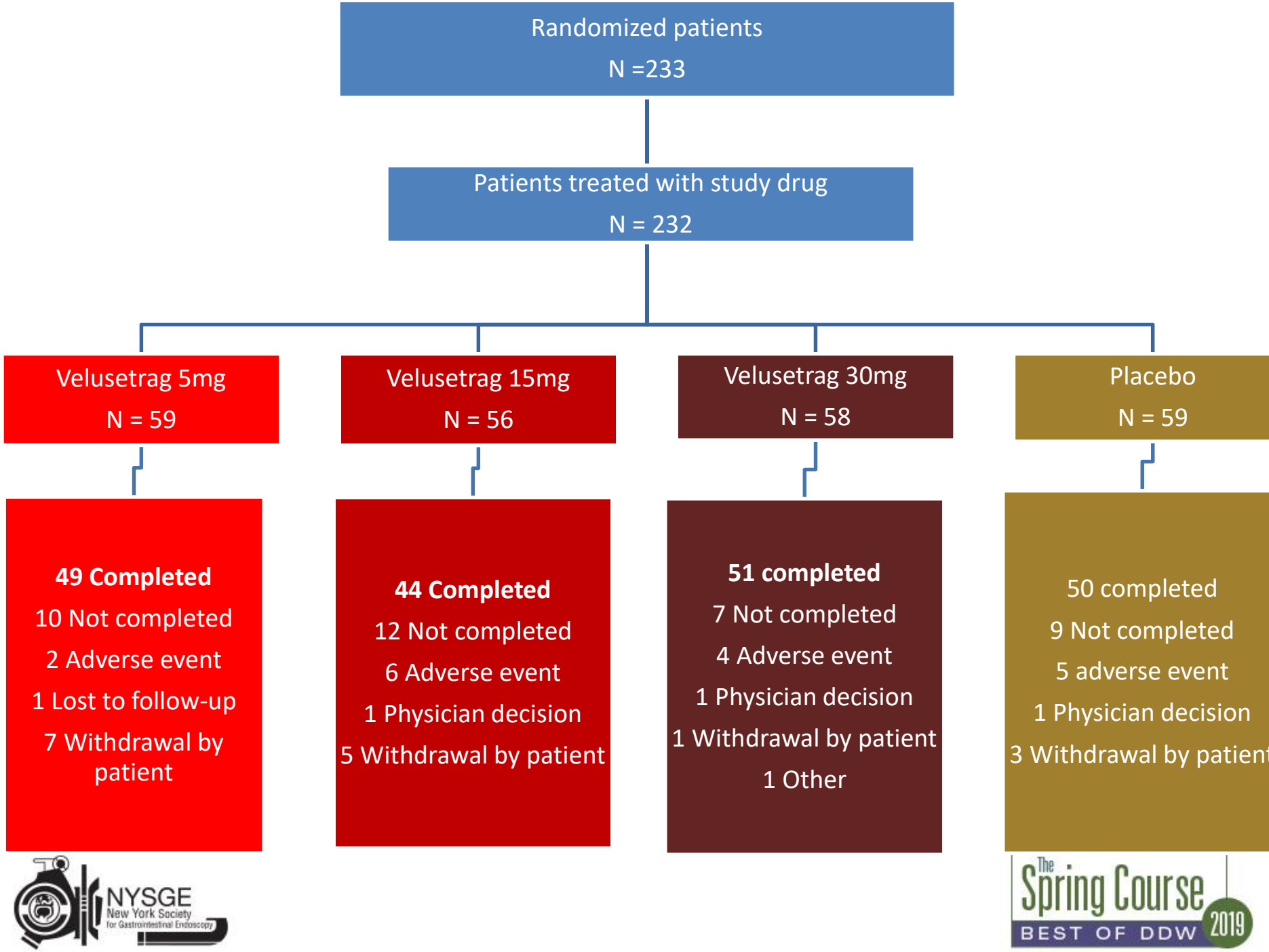
- Diabetic or idiopathic gastroparesis
- Gastric emptying delay
  - 99mTc GES: > 10% retention at 4H
  - GEBT: t_{max} at 240min or delay at 2 of 3 time points (90, 120, or 150min)
- Gastroparesis symptoms for ≥ 3 months before screening and at baseline
- GCSI-2W composite score ≥ 2 to < 5 on nausea, 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

NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019



NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019

Baseline Demographics and Clinical Characteristics (ITT analysis set)

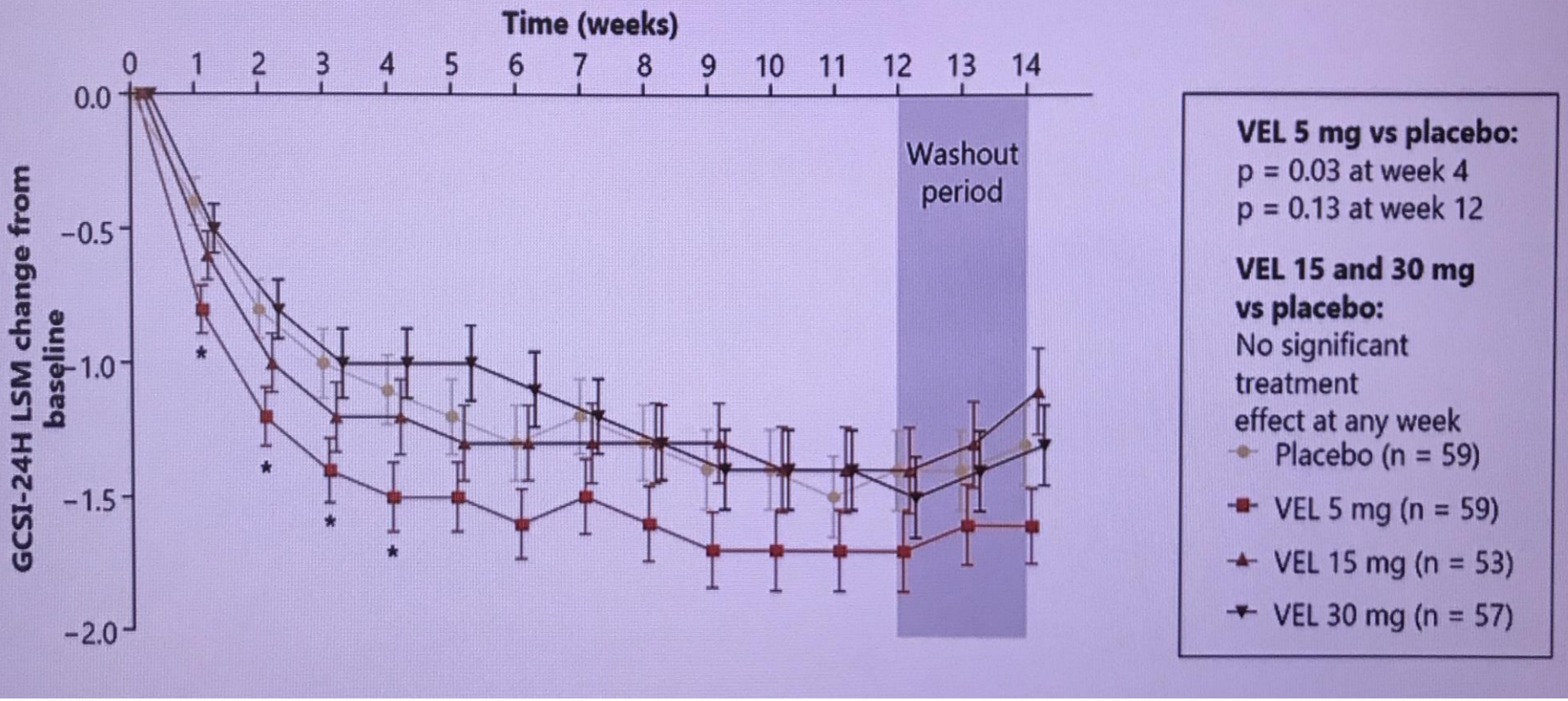
	Placebo	Velusetrag			Total
	n = 59	5 mg n = 59	15 mg n = 53	30 mg n = 57	N = 228
Age, mean (SD), years	47.0 (13.9)	51.8 (13.3)	50.2 (14.3)	52.2 (12.0)	50.3 (13.5)
Sex, n (%)					
Female	43 (72.9)	46 (78.0)	42 (79.2)	48 (84.2)	179 (78.5)
Race, n (%)					
White	53 (89.8)	52 (88.1)	44 (83.0)	52 (91.2)	201 (88.2)
Black or African American	5 (8.5)	7 (11.9)	6 (11.3)	4 (7.0)	22 (9.6)
Asian	0	0	1 (1.9)	0	1 (0.4)
Native Hawaiian or other Pacific Islander	0	0	0	1 (1.8)	1 (0.4)
American Indian or Alaska Native	1 (1.7)	0	1 (1.9)	0	2 (0.9)
BMI, median (range), kg/m²	28.8 (18.8–41.3)	29.7 (20.1–41.9)	29.6 (18.1–41.1)	28.3 (18.0, 41.3)	29.3 (18.0, 41.9)
HbA1c, median (range), %	7.3 (5.0–11.0)	6.7 (4.7–9.3)	7.6 (5.1–10.6)	6.9 (5.2–10.1)	7.1 (4.7–11.0)
Gastroparesis Type, n (%)					
Idiopathic	27 (45.8)	29 (49.2)	24 (45.3)	31 (54.4)	111 (48.7)
Diabetic	32 (54.2)	30 (50.8)	29 (54.7)	26 (45.6)	117 (51.3)
GCSI-24H, mean (SD)	3.0 (0.4)	3.1 (0.5)	3.1 (0.5)	3.3 (0.6)	3.1 (0.5)

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

NYSGE New York Society for Gastrointestinal Endoscopy

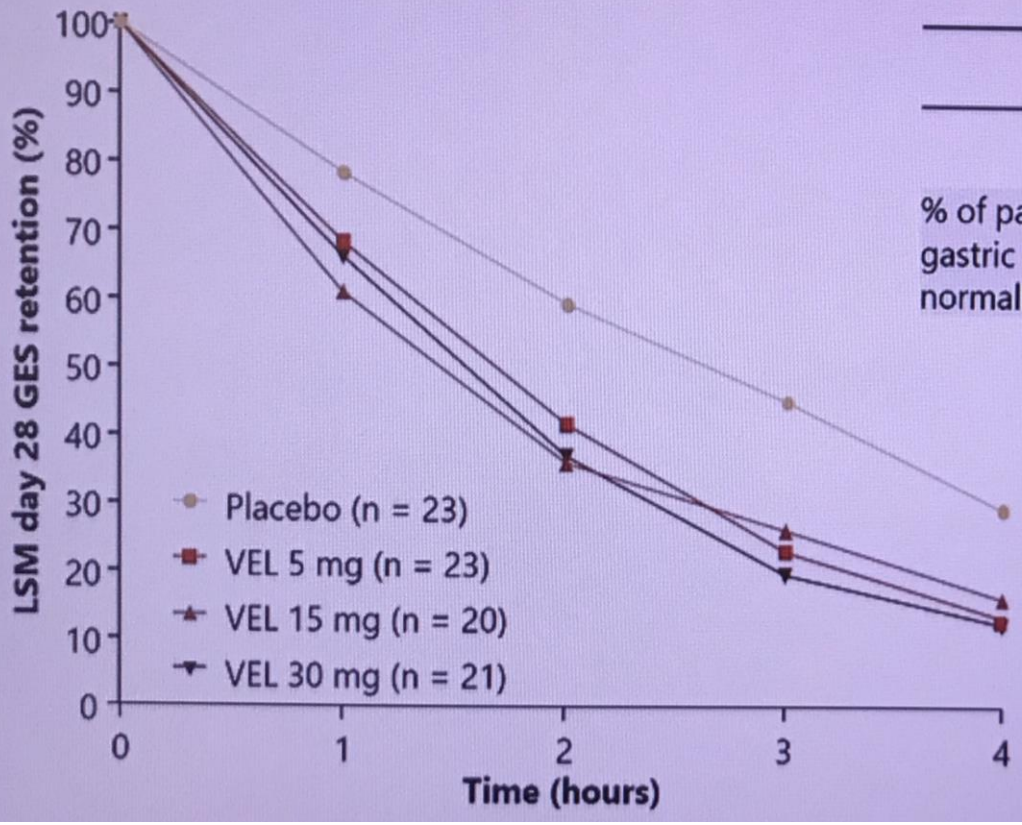
The Spring Course BEST OF DDW 2019

Individual Subscale Score Change from Baseline

	Least squares mean (standard error)		
	Placebo (n = 59)	Velusetrag 5 mg (n = 59)	p value for difference
GCSI-24H Nausea/Vomiting			
Week 4	−0.9 (0.11)	−1.1 (0.11)	0.3388
GCSI-24H Postprandial Fullness/Early Satiety			
Week 4	−1.2 (0.16)	−1.8 (0.15)	**0.0116**
GCSI-24H Bloating			
Week 4	−1.2 (0.16)	−1.6 (0.16)	**0.0406**
GRS Abdominal Pain			
Week 4	−1.0 (0.16)	−1.5 (0.16)	**0.0230**
Week 12	−1.4 (0.18)	−1.9 (0.18)	0.0664

GRS = Gastroparesis Rating Scale

Velusetrag Improves Gastric Emptying



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

GES = gastric emptying scintigraphy
LSM = least squares mean

Adverse Events in >5% of Patients in a Group

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

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

Prashant Singh, Judy Nee, Johanna Iturrino, Wing Fei Wong, Shrish Budree, Zain Kassam, Vivian Cheng, John Kelley, William Hirsch, Anthony Lembo

Beth Israel Deaconess Medical Center

Harvard Medical School

NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019

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

Jeffery, et al Gut 2012
Liu HN, et al, DLD 2017

IBS treatments
Alter gut microbiome

- Antibiotics – Rifaximin
- Probiotics
- Diet – Low FODMAP

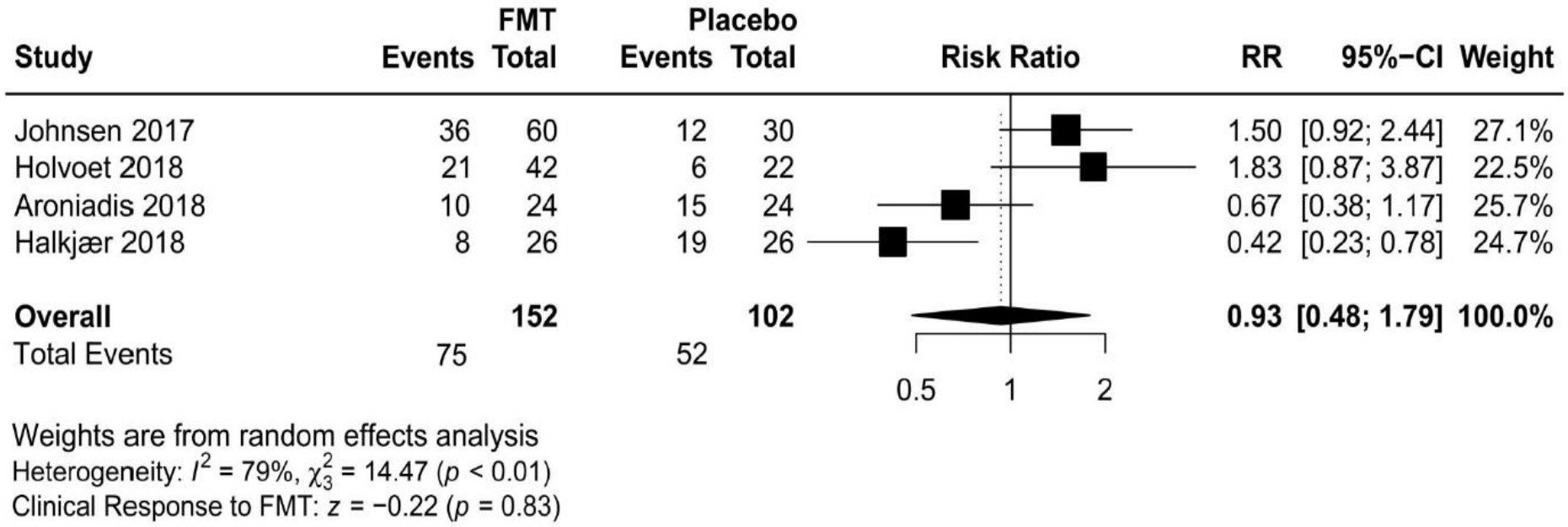


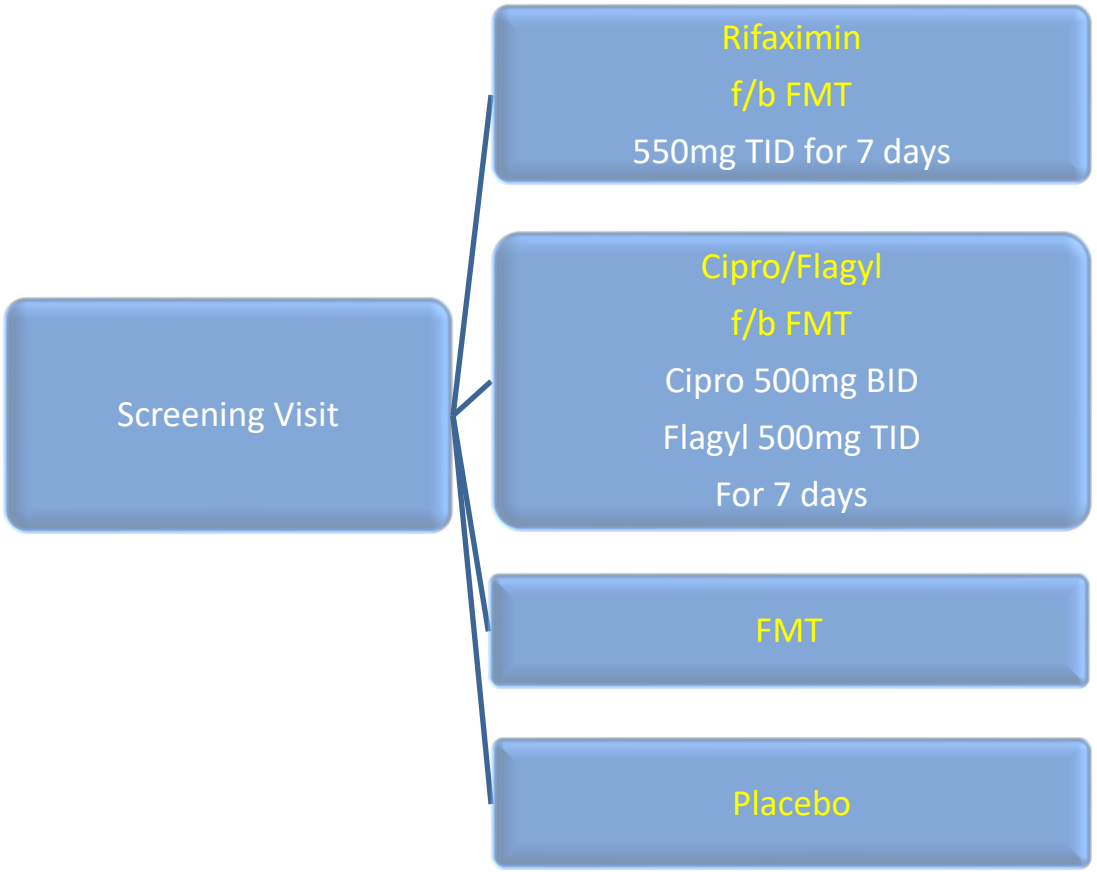
Figure 2 Forest plot of all studies for efficacy of FMT vs placebo on global improvement of IBS symptoms. CI, confidence interval; FMT, fecal microbiota transplantation; IBS, irritable bowel syndrome; RR, risk ratio.

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



Week 1 Follow-up

Week 10 Follow-up

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

NYSGE New York Society for Gastrointestinal Endoscopy

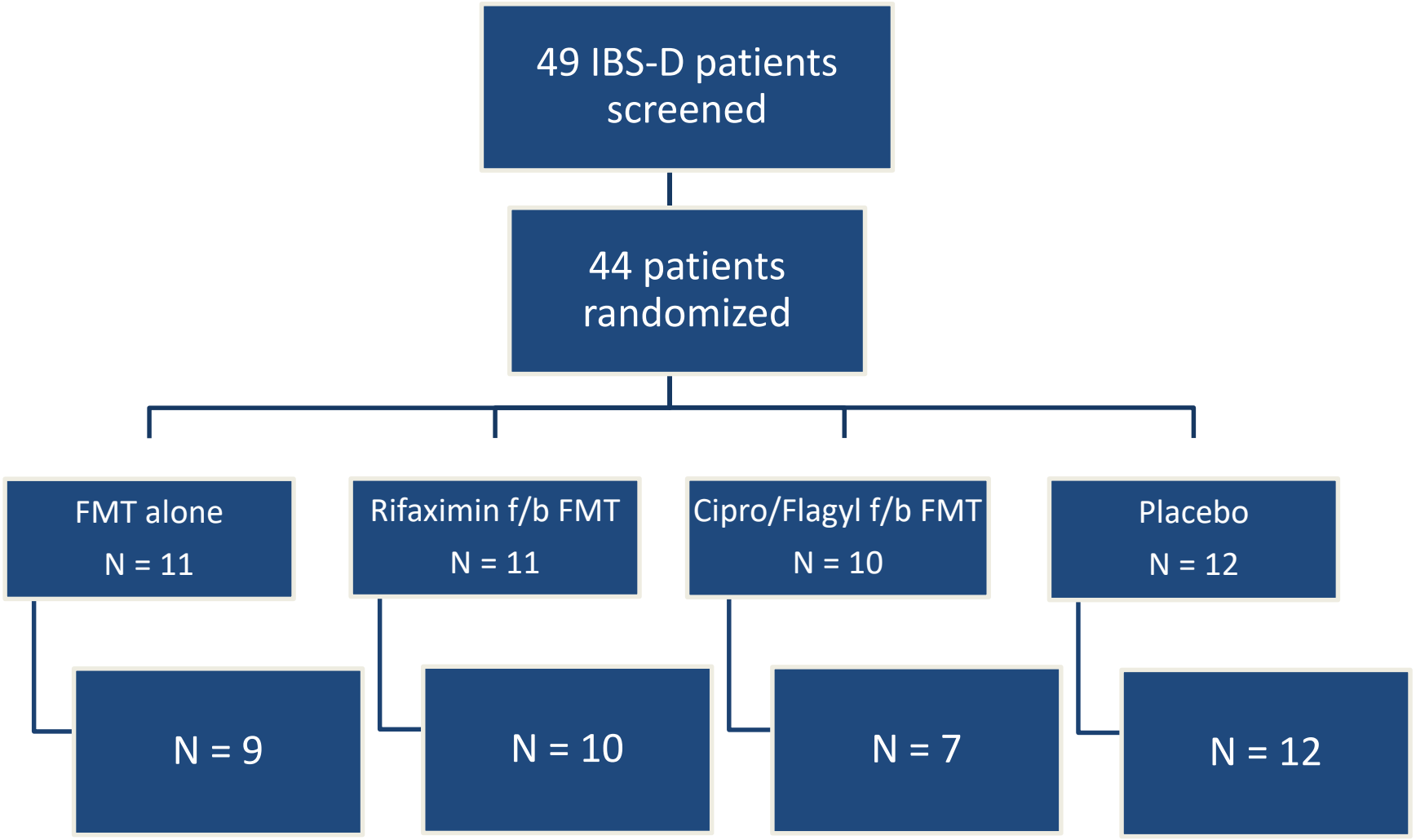
The Spring Course BEST OF DDW 2019

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



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

Parameters	FMT N = 11	Rifaximin f/b FMT N = 10	Cipro/Metro f/b FMT N = 7	Placebo N = 12	P value
IBS-SSS	**347.5**	277.8	339.1	282.3	0.03
Severe IBS	**9 (81.8)**	4 (36.4)	7 (70)	4 (33.3)	0.052

Clinical Outcomes at Week 10

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

No statistically significant difference in clinical parameters between all 4 groups

Responder Outcomes at Week 10

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

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 Patcharatrakul, MD, Rachel Parr, MS, Satish SC Rao, MD, PhD

Augusta University Medial Center

NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019

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

NYSGE New York Society for Gastrointestinal Endoscopy

The Spring Course BEST OF DDW 2019

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

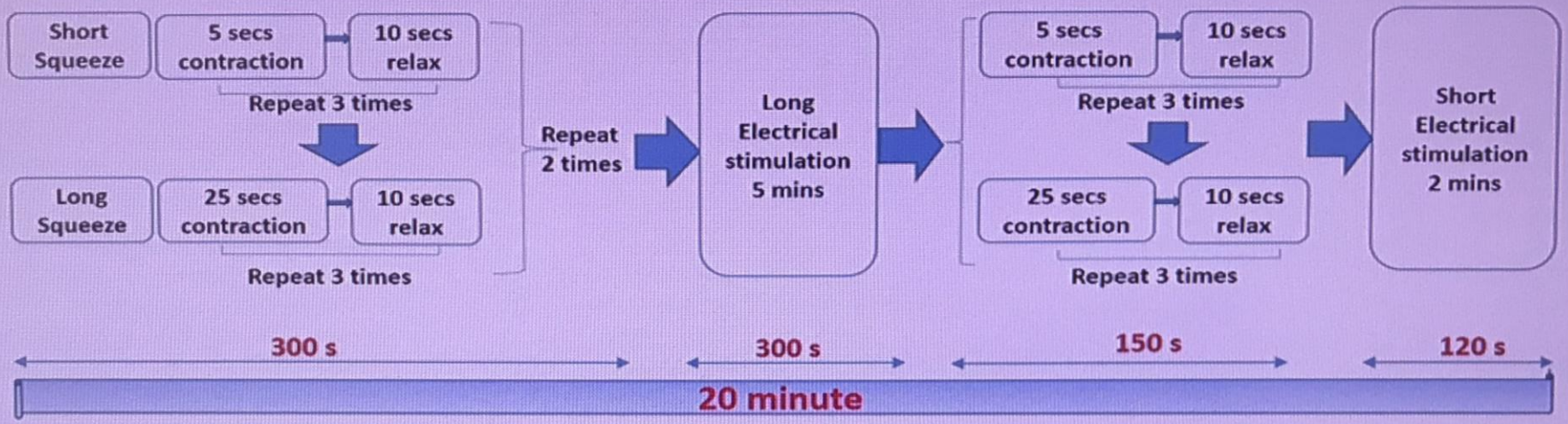
Inclusion Criteria:

1) Recurrent episodes of FI for 6 months
2) No mucosal disease (colonoscopy within 10 years)
3) Ona 2-week stool diary patients reported at least one episode of solid or liquid FI/week

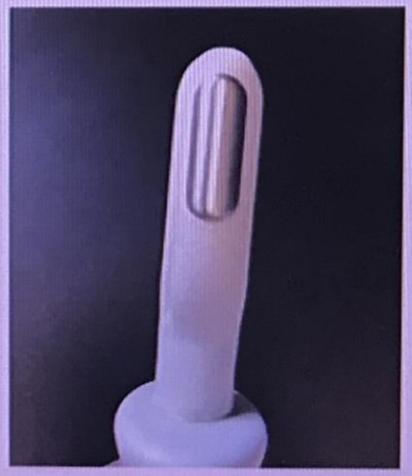
Exclusion Criteria:

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



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

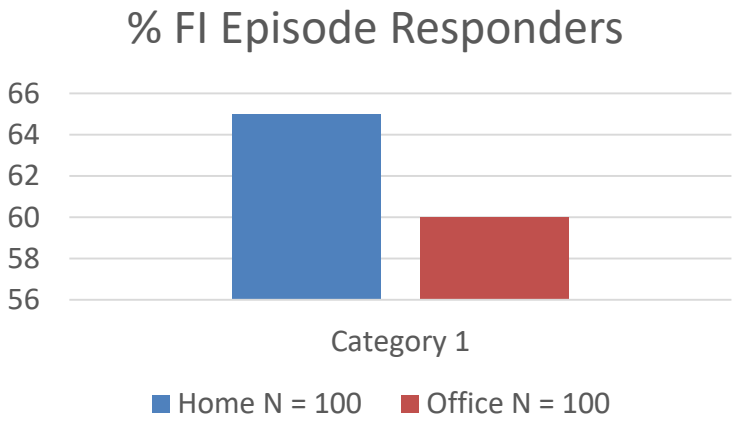
23 Home Group – 20 completed

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

NYSGE
New York Society
for Gastrointestinal Endoscopy

The Spring Course
BEST OF DDW 2019

NYSGE
New York Society
for Gastrointestinal Endoscopy

The Spring Course
BEST OF DDW 2019