BEST OF DDW 2019: IBD

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Disclosures

Abbvie/Takeda/Pfizer/Janssen/Gilead/Prometheus

-Research Support/Advisory Board/Fellowship Support/Educational Grants

416a

Vedolizumab Shows Superior Efficacy Versus Adalimumab: Results of VARSITY—The First Head-to-Head Study of Biologic Therapy for Moderate-to-Severe Ulcerative Colitis

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*Denotes equal contributions; †Note: Brihad Abhyankar was an employee of Takeda at the time of this research.

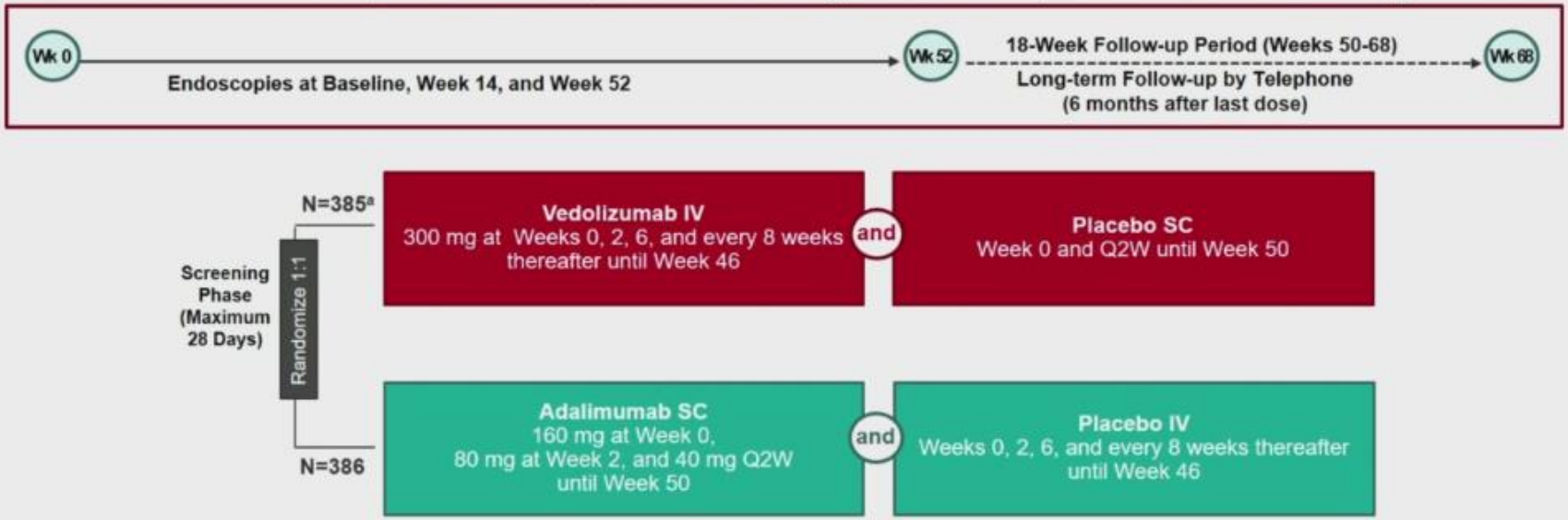
Digestive Disease Week® 2019

May 19, 2019

Slide 1

Study Design

Phase 3b randomized, double-blind, double-dummy, multicenter, active-controlled study

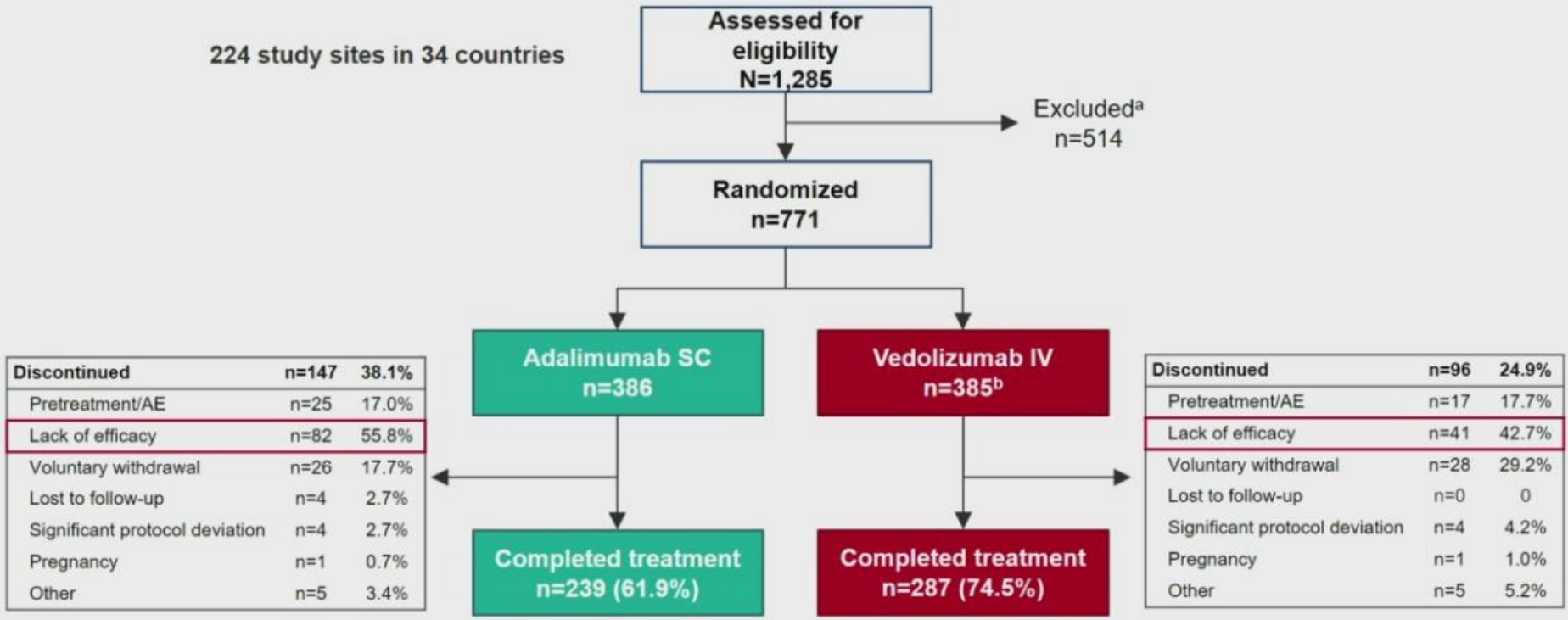


Randomization stratification factors were concomitant use of oral corticosteroids and previous exposure/failure of TNFi therapy or naïve to TNFi therapy.

IV, intravenous; Q2W, every 2 weeks; RBS, rectal bleeding score; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.
[a]Includes 2 patients who were randomized but did not receive a dose of vedolizumab.

Slide 4

Patient Disposition

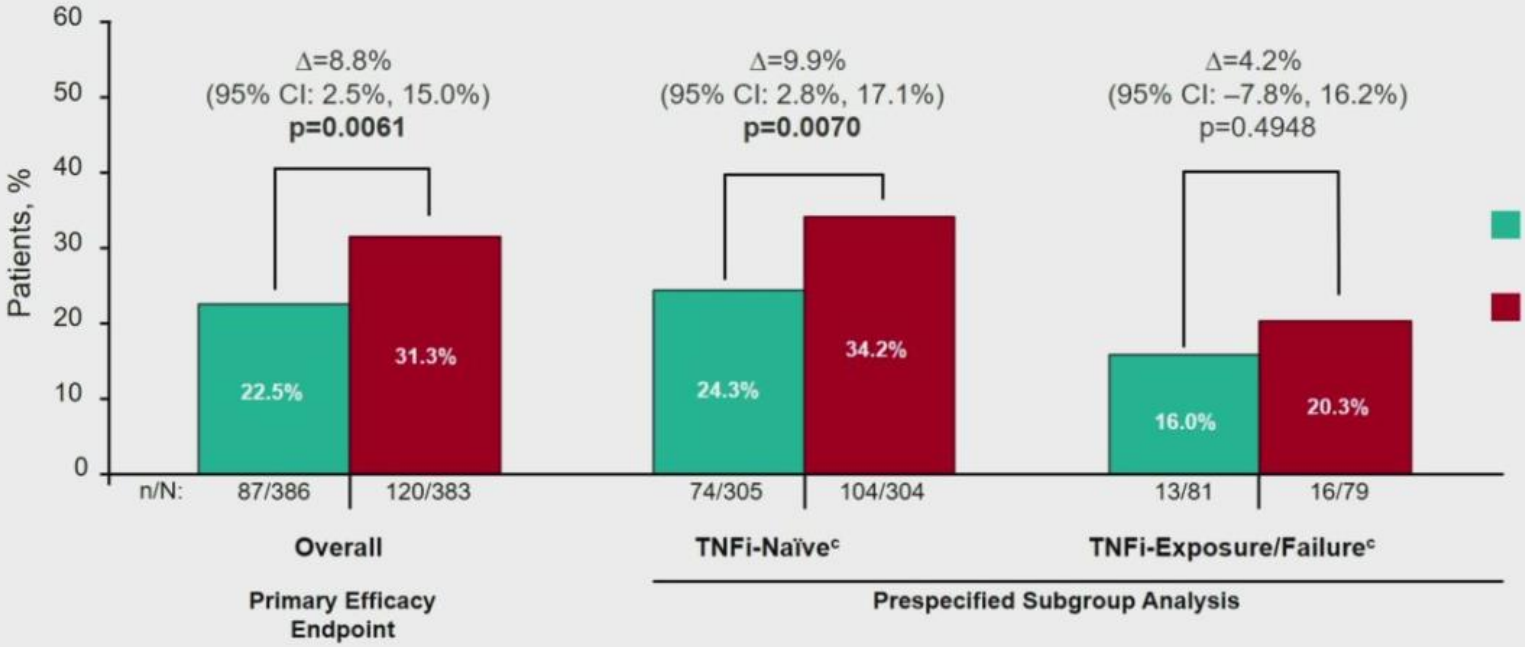


Discontinued	n=147	38.1%
Pretreatment/AE	n=25	17.0%
Lack of efficacy	n=82	55.8%
Voluntary withdrawal	n=26	17.7%
Lost to follow-up	n=4	2.7%
Significant protocol deviation	n=4	2.7%
Pregnancy	n=1	0.7%
Other	n=5	3.4%

Discontinued	n=96	24.9%
Pretreatment/AE	n=17	17.7%
Lack of efficacy	n=41	42.7%
Voluntary withdrawal	n=28	29.2%
Lost to follow-up	n=0	0
Significant protocol deviation	n=4	4.2%
Pregnancy	n=1	1.0%
Other	n=5	5.2%

AE, adverse event; IV, intravenous; SC, subcutaneous.
[a]Most common reasons for exclusion were not meeting entrance criteria (81.3%), voluntary withdrawal (6.8%), and pretreatment/AE (3.7%).
[b]Includes 2 patients who were randomized but did not receive a dose of vedolizumab.

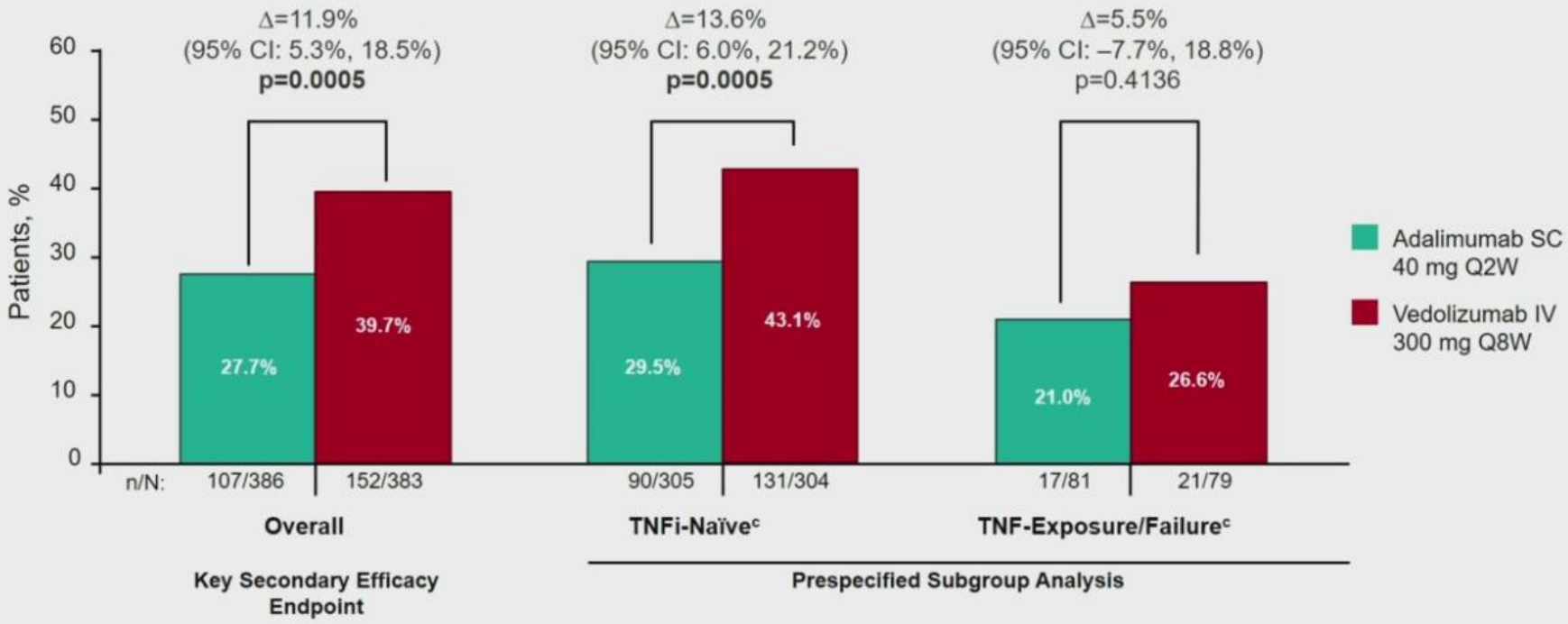
Primary Efficacy Endpoint: Overall Clinical Remission[a] at Week 52[b]



CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.
[a]Clinical remission was defined as a complete Mayo score of ≤2 points and no individual subscore >1 point.
[b]Full analysis set includes all randomized patients who received at least 1 dose of study drug.
[c]TNFi subgroup analysis was prespecified and produced nominal p values.

Slide 11

Key Secondary Efficacy Endpoint: Overall Endoscopic Improvement (Mucosal Healing)[a] at Week 52[b]

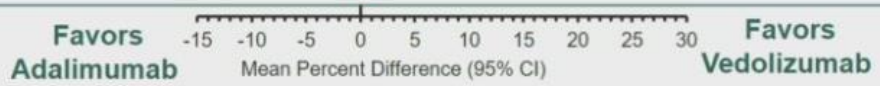


CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor.
[a]Endoscopic improvement was defined as a Mayo endoscopic subscore of ≤1 point.
[b]Full analysis set includes all randomized patients who received at least 1 dose of study drug.
[c]TNFi subgroup analysis was prespecified and produced nominal p values.

Slide 12

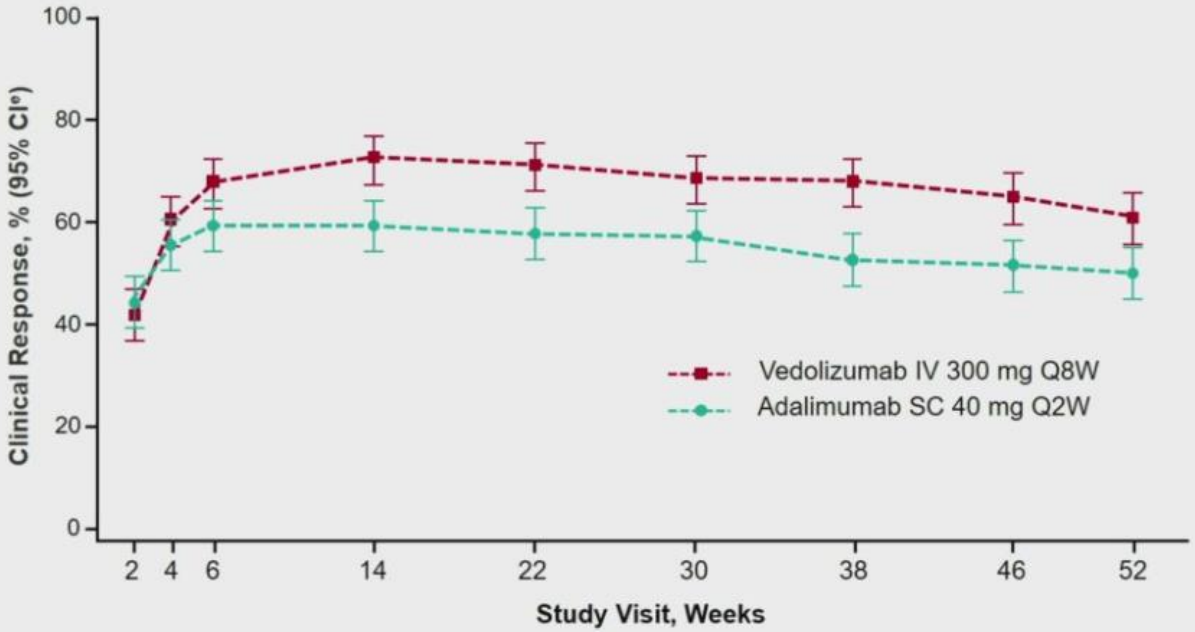
Efficacy Outcomes at Week 52 by Baseline Use of Corticosteroids or Immunomodulators

Subgroup	Adalimumab SC n/N (%)	Vedolizumab IV n/N (%)	Δ	95% CI
Without **baseline[a] corticosteroid use***				
Clinical remission[b]	50/246 (20.3)	83/245 (33.9)	13.6	(5.8, 21.3)
Endoscopic improvement[c]	62/246 (25.2)	104/245 (42.4)	17.2	(9.0, 25.5)
Without **baseline[a] immunomodulator use***				
Clinical remission[b]	61/286 (21.3)	96/282 (34.0)	12.7	(5.4, 20.0)
Endoscopic improvement[c]	75/286 (26.2)	119/282 (42.2)	16.0	(8.3, 23.7)
With baseline[a] corticosteroid use				
Clinical remission[b]	37/140 (26.4)	37/138 (26.8)	0.4	(–10.0, 10.8)
Endoscopic improvement[c]	45/140 (32.1)	48/138 (34.8)	2.6	(–8.5, 13.7)
With baseline[a] immunomodulator use				
Clinical remission[b]	26/100 (26.0)	24/101 (23.8)	–2.2	(–14.2, 9.7)
Endoscopic improvement[c]	32/100 (32.0)	33/101 (32.7)	0.7	(–12.3, 13.6)



*Post hoc analyses.
CI, confidence interval; IV, intravenous; SC, subcutaneous.
[a]Baseline corticosteroids recorded by interactive web response system, and baseline immunomodulators by electronic case report forms.
[b]Complete Mayo score of ≤2 points and no individual subscore >1 point.
[c]Mayo score endoscopic subscore of ≤1 point.

Clinical Response[a,b] by Visit Based on Change in Partial Mayo Score From Baseline[c,d]



CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; RBS, rectal bleeding score; SC, subcutaneous.

[a]Clinical response based on partial Mayo score is defined as a reduction in partial Mayo score of ≥2 points and ≥25% from Baseline, with an accompanying decrease in RBS of ≥1 point or absolute RBS of ≤1 point.

[b]Patients with missing clinical response status were considered nonresponders.

[c]Full analysis set includes all randomized patients who received at least 1 dose of study drug.

[d]Prespecified analysis.

[e]The 95% CI of the percentage is based on the Clopper-Pearson method.

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Conclusions

- Vedolizumab showed superior clinical and endoscopic efficacy over adalimumab in the treatment of moderately to severely active UC
- Treatment effects were most pronounced in the TNFi–naïve subpopulation (subgroup analysis)
- Corticosteroid-free remission rates were numerically higher with adalimumab than with vedolizumab (p=NS)
- Regardless of concomitant CS or immunomodulator use at Baseline, vedolizumab demonstrated a consistent advantage over adalimumab; the two drugs seemed to perform equally well in the presence of these concomitant medications
- Histologic efficacy at Week 52 favored vedolizumab over adalimumab
- Improvements in clinical response with vedolizumab versus adalimumab emerged between Weeks 6 and 14
- Both drugs were generally safe and well tolerated, consistent with known profiles
- These results provide the most direct evidence to date on the comparative efficacy of biologics to support clinical decision making in the management of moderately to severely active UC

Slide 20 corticosteroid; UC, ulcerative colitis; TNFi, tumor necrosis factor inhibitor.

Amsterdam UMC
Universitair Medische Centra

Vagus Nerve Stimulation Reduces Disease Activity and Modulates Serum and Autonomic Biomarkers in Biologic-Refractory Crohn's Disease

Geert D'Haens, Amsterdam, Netherlands; Zeljko Cabrijan, Osijek, Croatia; Michael Eberhardson, Stockholm, Sweden; Remco van den Bergh, Amsterdam, Netherlands, Mark Lowenberg, Amsterdam, Netherlands, Silvio Danese, Milan, Italy; Gionata Fiorino, Milan, Italy; Rik Schuerman, Amsterdam, Netherlands; Yaakov Levine, Valencia, CA; David Chernoff, Valencia, CA.

Digestive Disease Week 2019

This study was sponsored by SetPoint Medical

IBD Amsterdam UMC

THE INFLAMMATORY REFLEX IN THE GUT

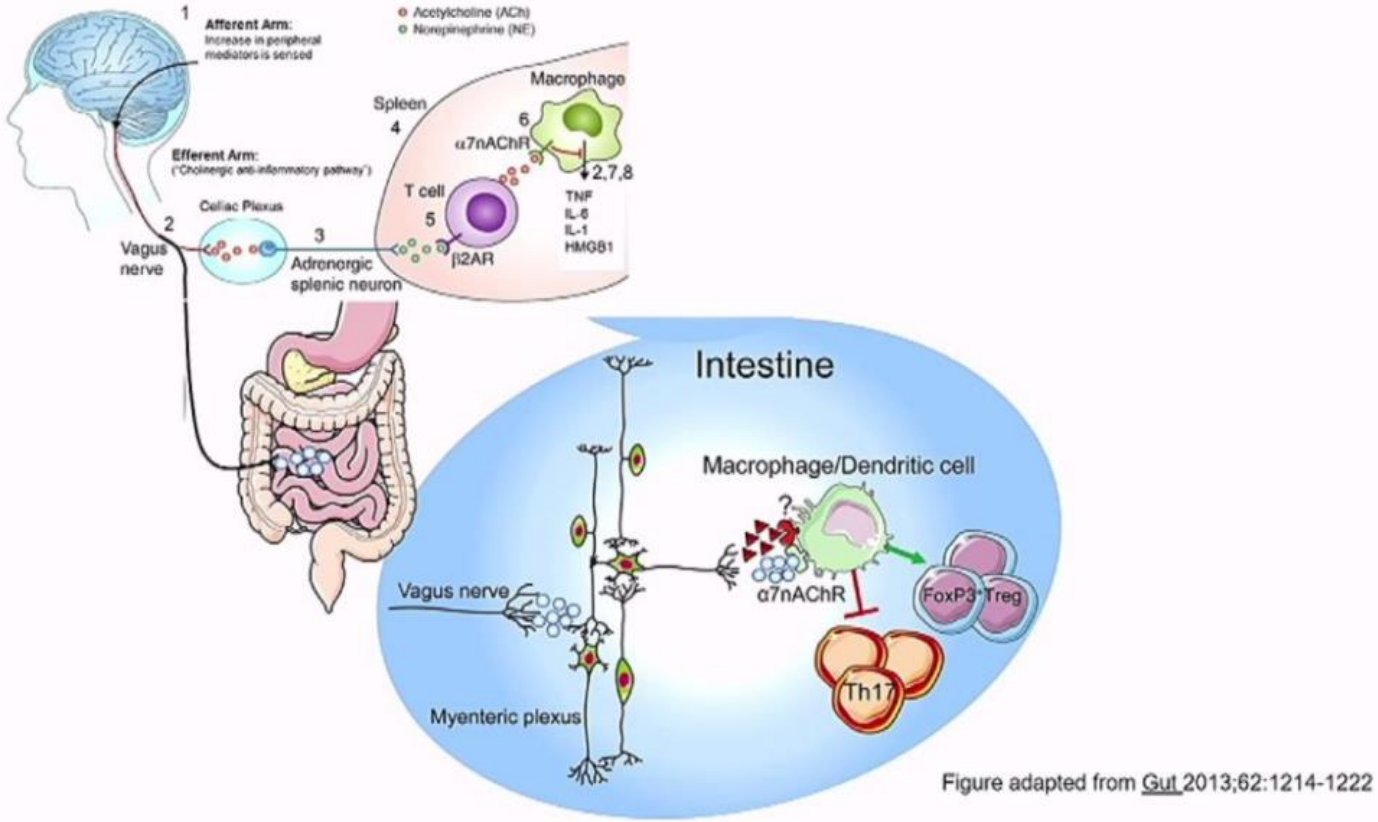
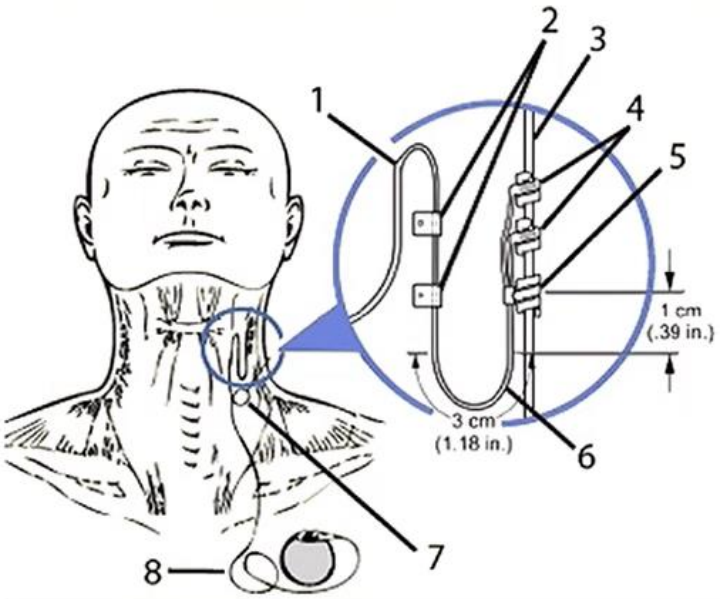


Figure adapted from Gut 2013;62:1214-1222

Gut 2013;63(6):938
J Immunol 2011;187:2677
Neurogastroenterol Motil 2012;24(2):191
Am J Physiol 2007;293(3):G560

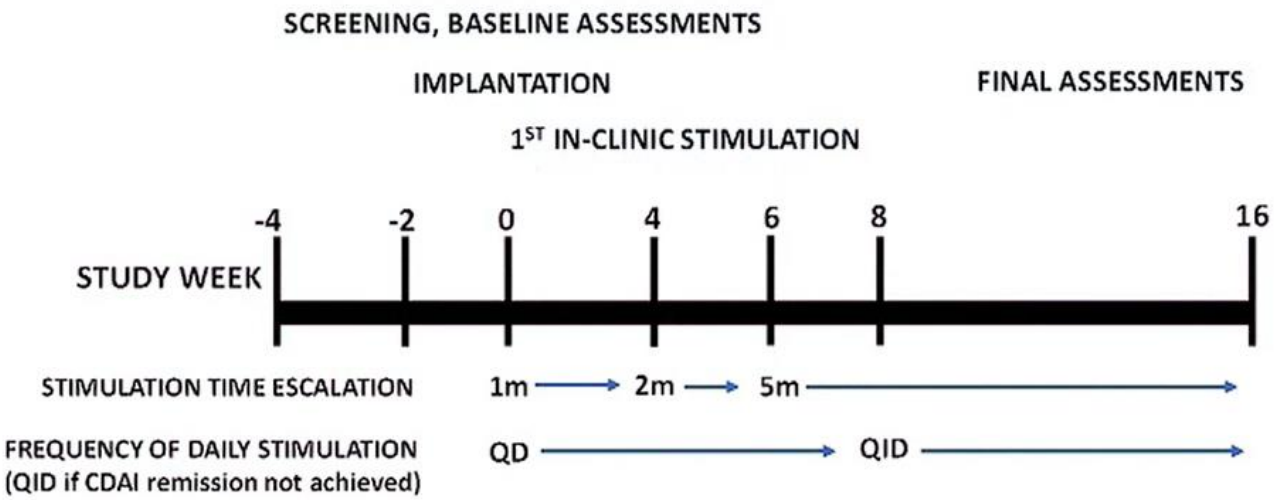
Slide 4

CLINICAL EPILEPSY DEVICE WAS USED FOR PROOF-OF-CONCEPT STUDY



1 Lead
2 Tie-Downs
3 Vagus Nerve
4 Helical Electrodes
5 Anchor Tether
6 Strain Relief Bend
7 Strain Relief Loop
8 Coiled Extra Lead

STUDY DESIGN: SINGLE-ARM OPEN LABEL TWO COHORTS



Subject Cohorts

I. VNS Monotherapy, n=8: 8 week washout of TNF alpha inhibitors, vedolizumab or natalizumab

II. Adjunctive Therapy, n=8 : Subjects remain on biologic to which they have insufficient response

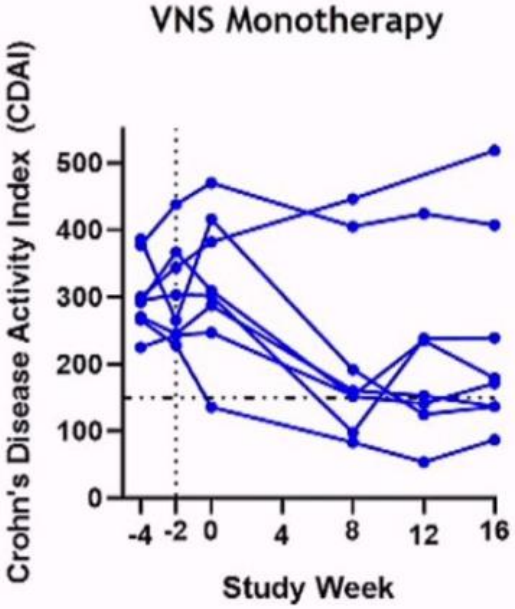
- 4 centers: Amsterdam, Stockholm, Zagreb, Milan
- Standard disease endpoints: CDAI, SES-CD, biomarkers

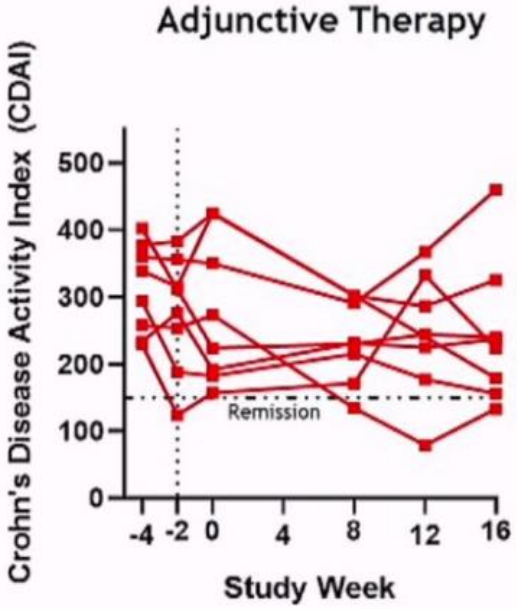
MAJOR INCLUSION / EXCLUSION CRITERIA

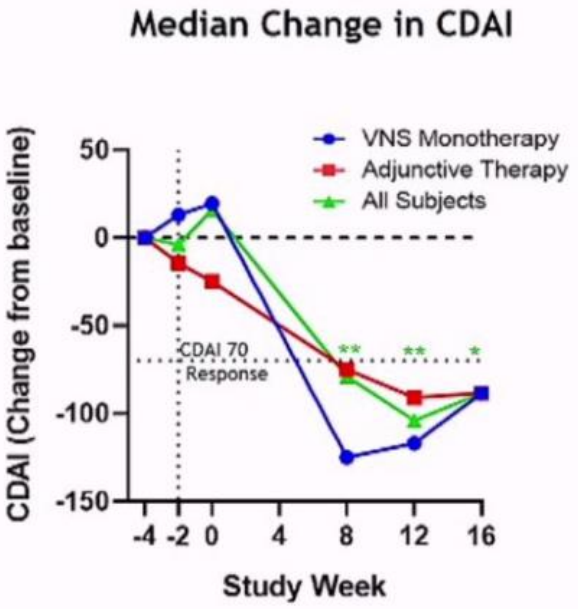
- **Major Inclusion Criteria**
  - M/F subjects age 18-75
  - Moderately-to-severely active Crohn's disease
    - CDAI: 220-450, SES-CD ulcer score ≥ 2 in at least 1 segment
  - Fecal Calprotectin ≥ 200µg/g
  - Inadequate response and/or intolerance to one or more TNF inhibitors

- **Major Exclusion Criteria**
  - Celiac disease, ulcerative colitis, pelvic fistulae, bowel surgery within 4 months, extensive colonic resection
  - Use of prohibited medications without washout
    - TNF inhibitors; Glucocorticoids >10 mg prednisone (or equivalent) QD
    - Azathioprine, 6-mercaptopurine, methotrexate **allowed** on stable dose
  - History of vagotomy, recurrent vaso-vagal syncope
  - Previously implanted active electrical device (e.g. cardiac pacemaker)

CDAI OVER TIME







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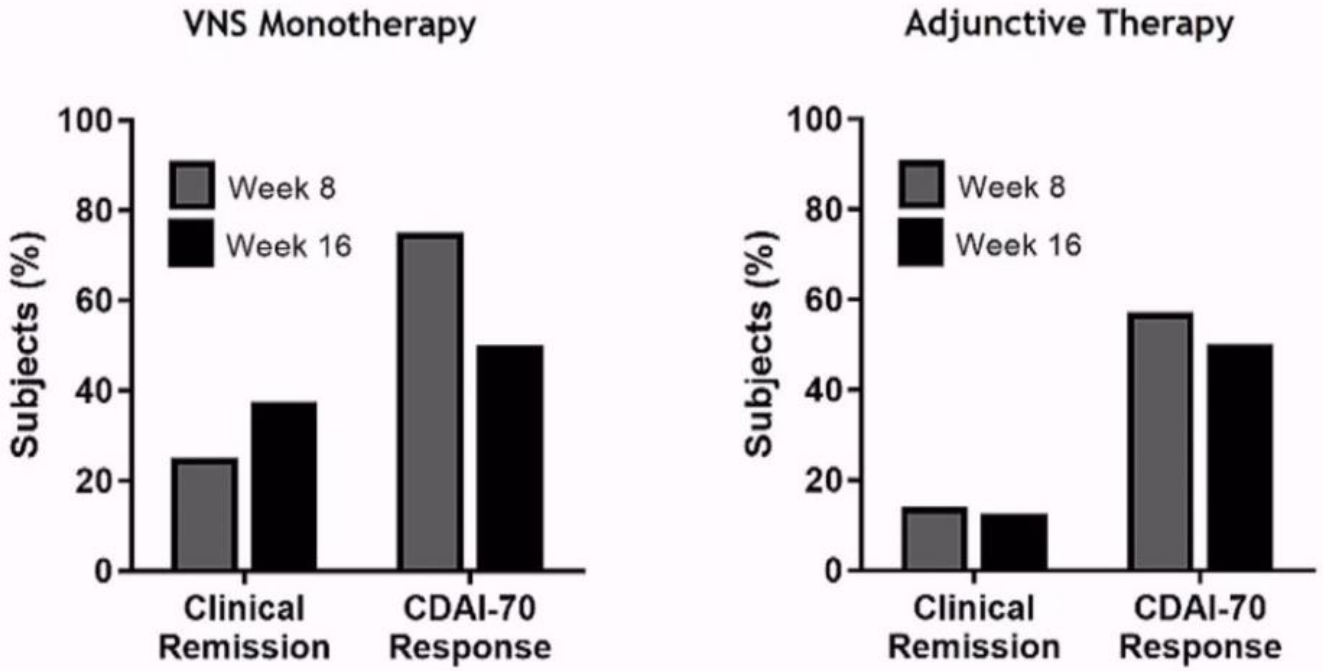
CDAI RESPONSE/REMISSION



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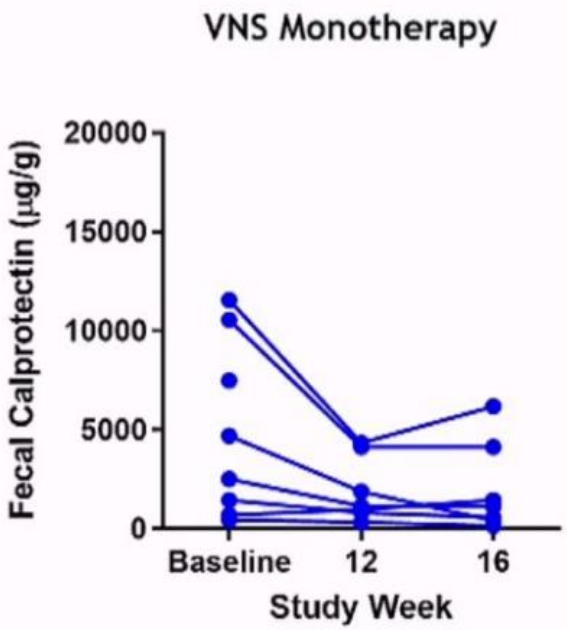
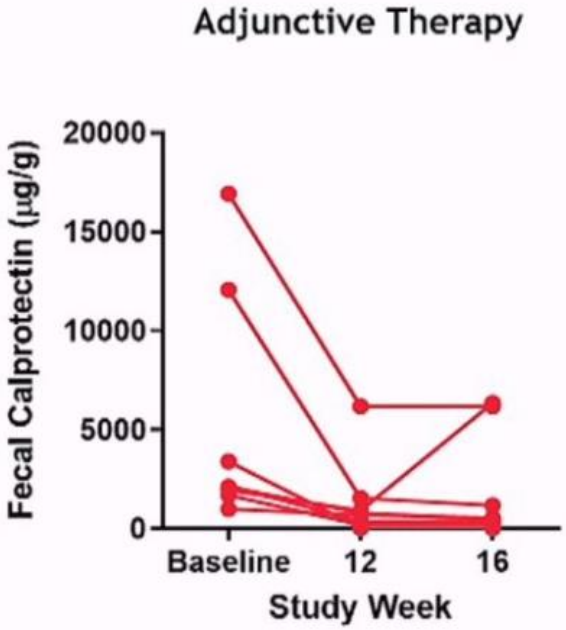
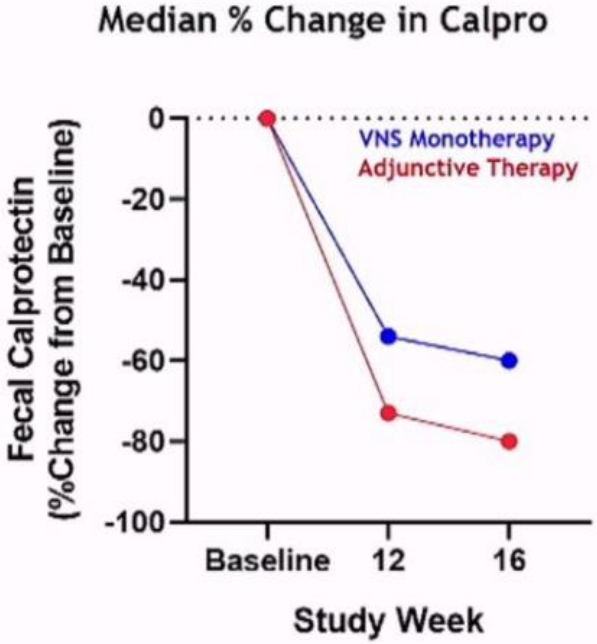
FECAL CALPROTECTIN







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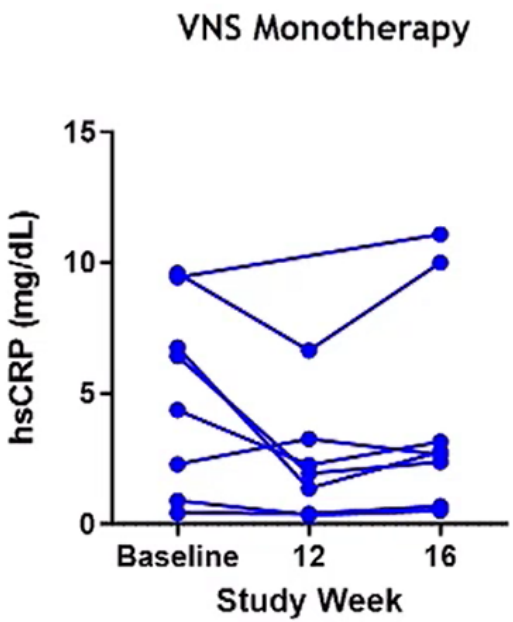
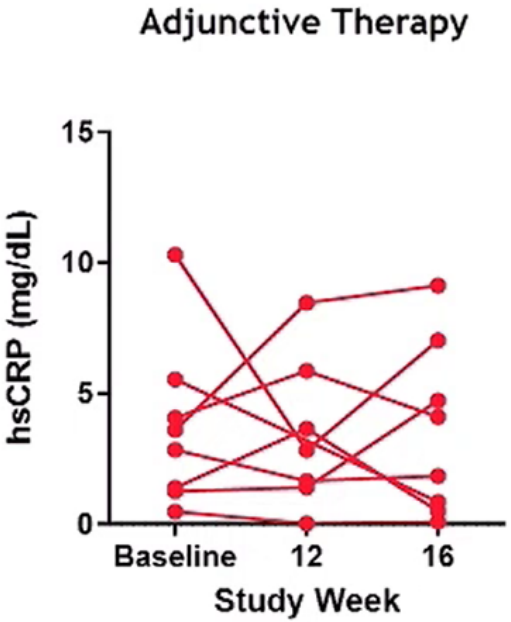
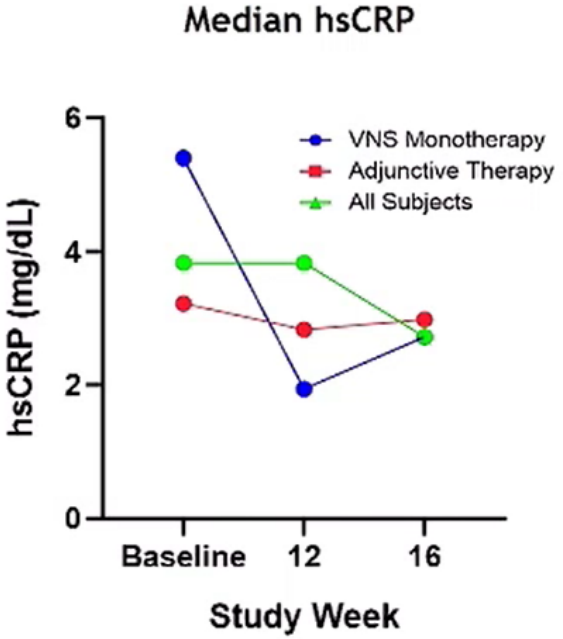
SERUM C-REACTIVE PROTEIN







SAFETY

Serious Adverse Events	SAEs in Subjects	Early Terminations	Disease Related	Implantation Related
VNS Monotherapy	8 in 5/9	1	7	1
Adjunctive Therapy	4 in 3/8	2	4	0

Disease Related

Crohn's Disease
Gastroenteritis
Ileus
Dehydration
Prerenal failure
Inflammation
Cachexia

Implantation Related

Postoperative surgical wound infection
(This patient had device removed before therapy was initiated)

CONCLUSIONS

- The inflammatory reflex maintains immunologic homeostasis and can be driven non-pharmacologically with electrical vagus nerve stimulation (VNS).
- 16 weeks of VNS in 16 patients with extremely refractory Crohn's disease led to:
  - ✓CDAI-70 response > **50%**
  - ✓CDAI remission in **3/8** VNS monotherapy patients and **1/8** adjunctive therapy patients
- Centrally read SES-CDs showed >25% reductions in **5/15** patients, with **1/15** in endoscopic remission; longer treatment may result in more complete healing.
- Improvements were observed in biomarkers of disease activity:
  - ✓Fecal calprotectin levels reduced in 14/16 patients, median reduction **-63%**
  - ✓Serum CRP (not elevated at baseline in many patients) declined on average
  - ✓Reductions in circulating proinflammatory cytokines
- Improvements in patient reported outcome (QoL) metrics (IBDQ, SHS).
- Improvements in autonomic tone as assessed by heart rate variability.
- SAEs occurred in a number of patients, all related to severe Crohn's disease and one patient had surgical infection

Dr. Philip Grunert
Department of Internal Medicine IV
Gastroenterology - Hepatology – Infectiology

LONG-TERM MULTIDONOR FECAL MICROBIOTA TRANSFER (FMT) BY ORAL CAPSULES FOR ACTIVE ULCERATIVE COLITIS

Microbiome as Therapy in IBD and CDI

50th Digestive Disease Week
San Diego, 21st of May 2019

Fecal Microbiota Transfer (FMT) for Treatment of Ulcerative Colitis

Meta Analysis:
4 RCT
n=277

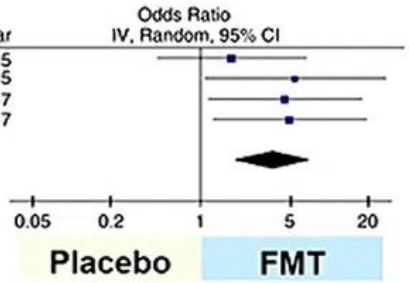
Clinical Remission
FMT **28%** vs. Placebo 9%
(OR: 3.67 95%CI: 1.82- 7.39; ***P*<.01**)

Endoscopic Remission
FMT **14%** vs. Placebo 5%
(OR: 2.69 95%CI: 1.07-6.74; **P=.04**)

Clinical Remission

Study or Subgroup	Donor transplant Events	Total	Placebo Events	Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Rossen 2015	7	23	5	25	28.2%	1.75 (0.47, 6.57)	2015
Moayyedi 2015	9	38	2	37	19.0%	5.43 (1.09, 27.15)	2015
Paramsothy 2017	11	41	3	40	26.5%	4.52 (1.16, 17.70)	2017
Costello 2017	12	38	3	35	26.4%	4.92 (1.25, 19.31)	2017
Total (95% CI)		140		137	100.0%	3.67 (1.82, 7.39)	
Total events	39		13				

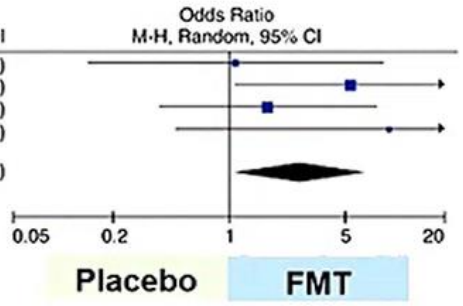
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.70$, df = 3 (P=.64); $I^2 = 0\%$
Test for overall effect: $Z = 3.63$ (P=.0003)



Endoscopic Remission

Study or Subgroup	Donor FMT Events	Total	Placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Rossen 2015	2	23	2	25	20.2%	1.10 (0.14, 8.48)
Moayyedi 2015	9	38	2	37	32.7%	5.43 (1.09, 27.15)
Paramsothy 2017	5	41	3	40	37.5%	1.71 (0.38, 7.70)
Costello 2017	4	38	0	35	9.7%	9.26 (0.48, 178.55)
Total (95% CI)		140		137	100.0%	2.69 (1.07, 6.74)
Total events	20		7			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.54$, df = 3 (P=.47); $I^2 = 0\%$
Test for overall effect: $Z = 2.11$ (P=.04)



Costello SP et al. Aliment Pharmacol Ther 2017;46

Fecal Microbiota Transfer (FMT) – Intensity

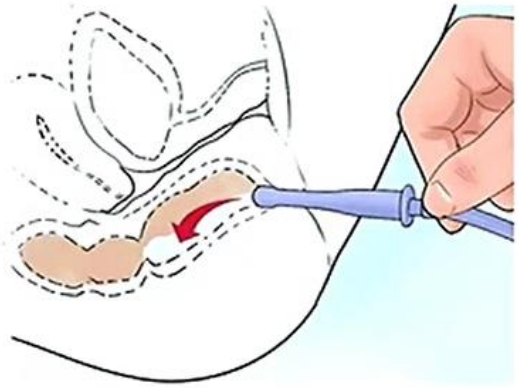
Disease	CDI	UC	UC	UC
Author	van Nodd et al. 2012	Rossen et al. 2015	Moayyedi et al. 2015	Paramsothy et al. 2017
Trial	RCT	RCT	RCT	RCT
Donor	1	1	1	3-7
FMT Intensity	1x enema	2x nasoduodenal tube	6x enemas	40x (1 colonoscopy, 39 enemas)
Remission FMT vs. control	81% vs. 23%	30% vs. 20 % ns	24% vs. 5%	44% vs. 20% *steroid free

Van Nood E et al. N Engl J Med 2013;368
Rossen NG et al. Gastroenterology 2015;149
Moayyedi P et al. Gastroenterology 2015;149
Paramsothy et al. Lancet 2017;389

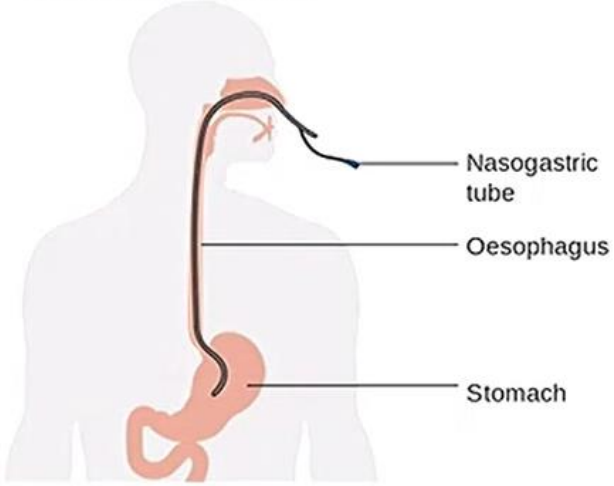
Introduction

Mode of Application

Enema



Nasogastric/ -duodenal tube



Oral intake - Capsule

Health care utilization, potential complications, costs

Picture: creative commons + https://www.fpv.org.au

Materials and Methods: FMT Capsules

FMT Capsule Preparation

Fresh donated stool (75-100g)

Homogenization + Filtration

200ml 0.9% sodium chloride w/ 10% glycerol

Double encapsulation

acid-resistant hypromellose capsules
(DRcaps Capsugel, Cambridge, MA)

Materials and Methods: Patient Selection

Eligibility Criteria

Inclusion	Exclusion
Active UC despite treatment with - corticosteroids (<30 mg prednisone/day), - immunosuppressive and/or - TNF or integrin antibody treatment agents	Pregnancy
Active UC (Mayo ≥ 4)	Unable to give written consent
Endoscopic Subscore ≥ 1	

Materials and Methods: Diagnostics

Treatment Protocol - Diagnostic Assessment

Clinical Assessment + AE + pMayo + Fecal Calpro	BL	d1	w4	w8	w12
Colonoscopy	BL				w12

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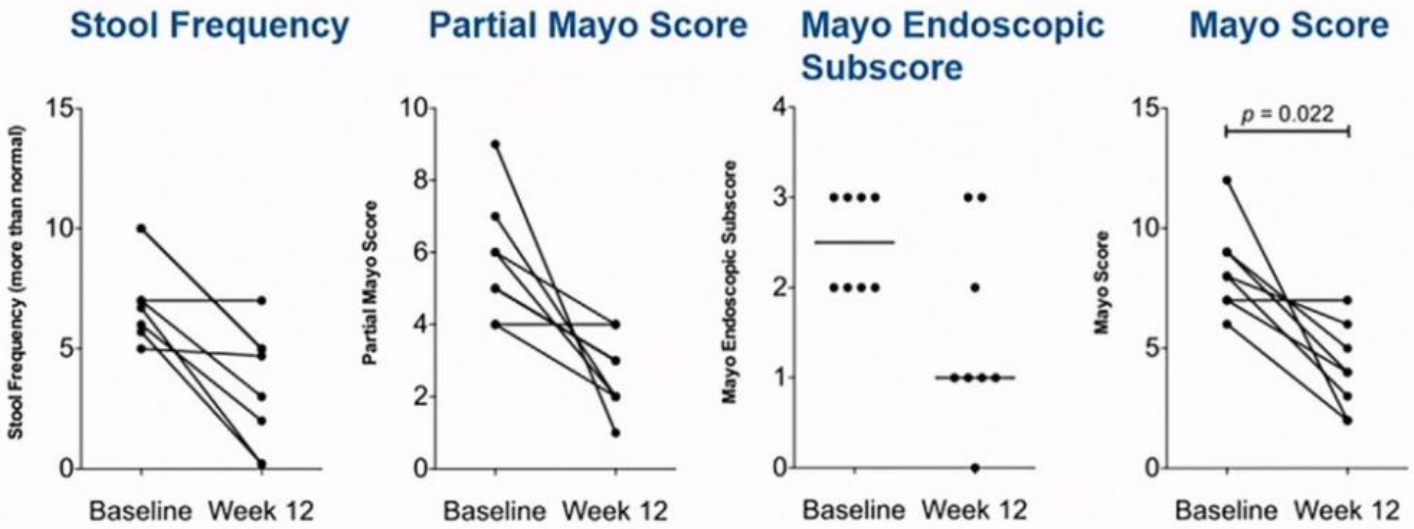
Results – Patient Characteristics

Number of patients enrolled	10
Demographics	
Male	8 (80%)
Mean age	37 ±7
Disease location	
Pancolitis	6 (60%)
Left-sided colitis	2 (20%)
Proctosigmoiditis	2 (20%)
Therapy	
Concomitant corticosteroids	8 (80%)
Biologic experienced	7 (70%)

Results – Clinical Impact

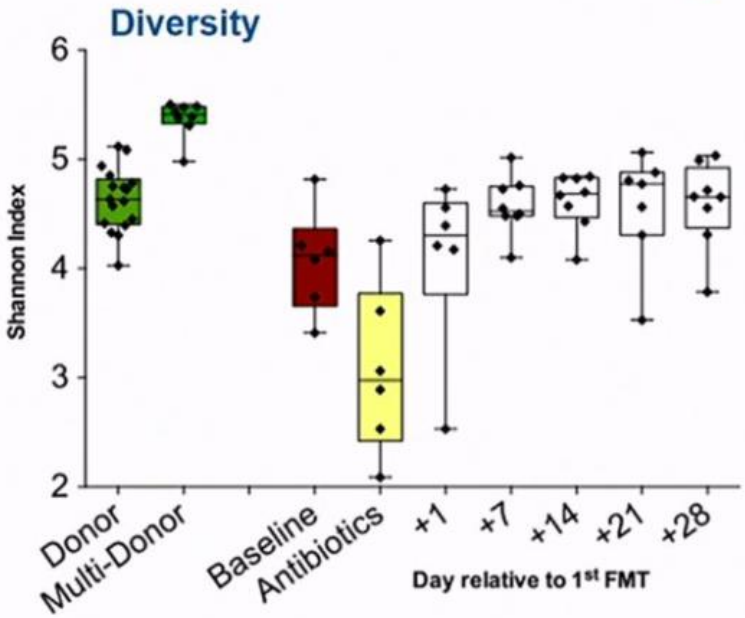
Clinical Outcomes



Serious Adverse Events: 2 – worsening of colitis, discontinuation within 5 days of study
Adverse Events: minor bloating/flatulence within first week

Results – Microbial Impact

Fecal Microbiota Diversity and Community Structure



- Lower diversity of UC patients at BL
- Anbiotics decreased diversity
- Capsule FMT increased diversity

Summary

- First study to evaluate clinical and microbial impact of capsule based long-term FMT
- Capsule stability sufficient to facilitate intestinal release
- Safe and effective to rapidly modulate microbial diversity
- Engraftment of multidonor community structure with Prevotellaceae becoming dominant members
- Beneficial clinical response with significant reduction of Mayo Score
- Limitations: single-center, small sample size, no control group

Thank You