2022 Rising Star Award

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# **Designing Fit-for-Purpose Clinical Trials in IBD**

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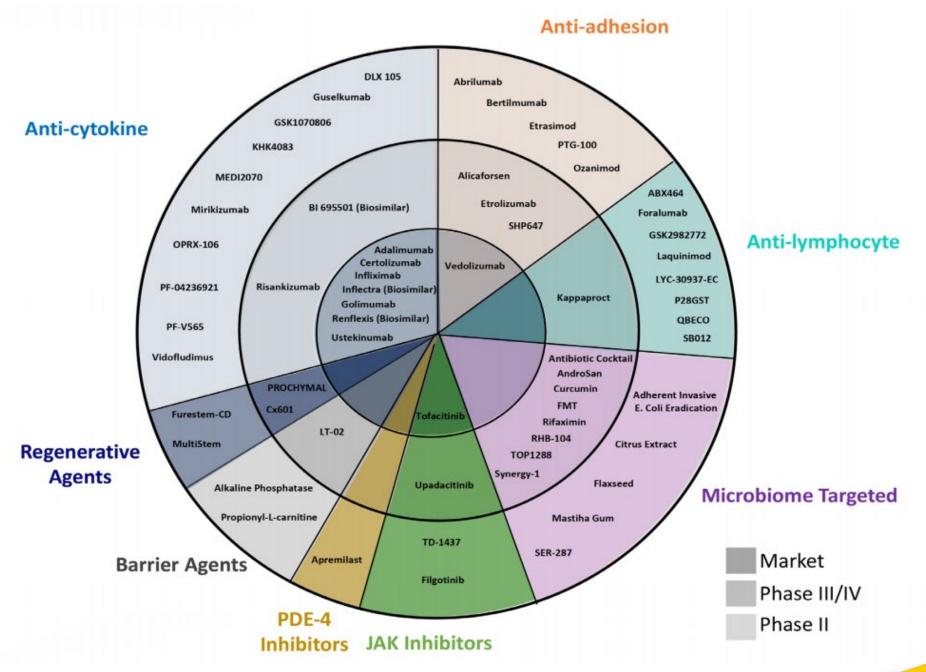




- Consulting: AbbVie, Alimentiv, American College of Gastroenterology, Amgen,
  AVIR Pharma Inc, BioJAMP, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi,
  Janssen, McKesson, Mylan, Takeda, Pendopharm, Pfizer, Roche, Sanofi
- **Speaking:** AbbVie, Amgen, AVIR Pharma Inc, Alimentiv, Bristol Myers Squibb, Ferring, Fresenius Kabi, Janssen, Takeda, Pendopharm, and Pfizer
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We would like to acknowledge the traditional territories of the people of the Treaty 7 region in Southern Alberta, which includes the Blackfoot Confederacy (comprising the Siksika, Piikani, and Kainai First Nations), as well as the Tsuut'ina First Nation, and the Stoney Nakoda (including the Chiniki, Bearspaw, and Wesley First Nations). The City of Calgary is also home to Métis Nation of Alberta, Region 3.

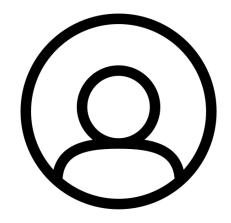






# The "typical" IBD RCT



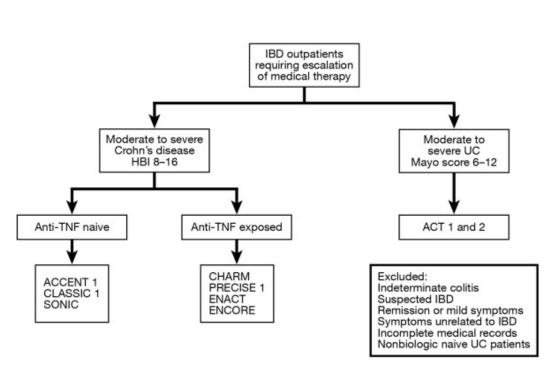


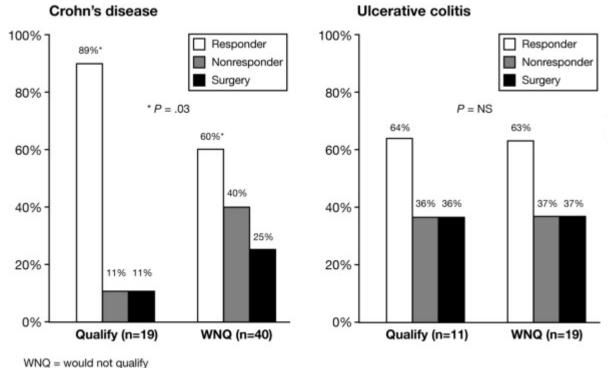


Moderate-to-severe adult UC or CD with inadequate response or intolerance to conventional therapy Parallel group, induction responders then rerandomized into maintenance Strict inclusion and exclusion criteria: pregnancy, comorbidities, phenotype, etc.

# Historically, RCTs have not represented patients we see in clinic





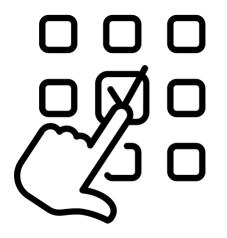




The "typical" IBD RCT vs. the "typical" IBD patient

### What are the considerations for being more inclusive?











What are the appropriate eligibility criteria?

What is the appropriate trial design? Do we have the right tools?

What are the logistical implications of the trial design?

What are the patient and treatment characteristics that are appropriate?

# **Unmet Needs: Mild to Moderate Disease**



Considerations	Pros	Cons
Drug and patient factors	May be more suitable for some mechanisms of action	Uncertain natural history of milder disease phenotypes
Enroll patients on the basis of endoscopically active disease	Reduce placebo rate Increase trial efficiency	Burdensome for patients Defining "mild-to-moderate" IBD endoscopically
Allowance and handling of corticosteroids	Avoids masking relatively milder symptoms	Enrolment logistics and barriers
Using a placebo comparator	Improves assay sensitivity	Appropriateness of placebo vs. active vs. historical comparator
Defining remission and response using existing instruments	Consistency in outcome definitions	Unknown operating properties of our existing tools for mild-to-moderate disease

Sedano R *et al.* Gastroenterology. 2022;162(4) Hanzel J *et al.* Gastroenterology. 2021;162(7)

#### **Unmet Needs: Mild to Moderate Disease**



# STUDY POPULATION

Mild-to-moderate ulcerative colitis definitions

Other Inclusion Criteria

#### MCS 4-9 with:

- MES ≥2, RBS ≥1, and SFS ≥1 (recommended) OR
- MES ≥1 AND (Geboes score >2B.0 or RHI ≥10 and/or FC >250 ug/g)

Corticosteroids excluded at enrolment or lower maximum allowable dose (15-20 mg/day) during induction

Failure or intolerance to 5-ASA, ± biologic failure or intolerance

# COMPARATOR

First-line indication

Second-line indication

Active comparator with standard firstline treatment: **5-ASA** 

Placebo comparator

#### **Unmet Needs: Mild to Moderate Disease**



Clinical Outcomes

Endoscopic Outcomes

Histologic Outcomes

Mucosal Healing

Clinical response: ≥1-point reduction in SFS and RBS, total MCS reduction ≥2 and ≥30% from baseline

Endoscopic improvement: MES=0/1 if baseline MES for enrolment ≥2

Histologic response: RHI decrease ≥7 points from baseline

Clinical remission: MCS ≤2 with SFS=0/1 and RBS=0

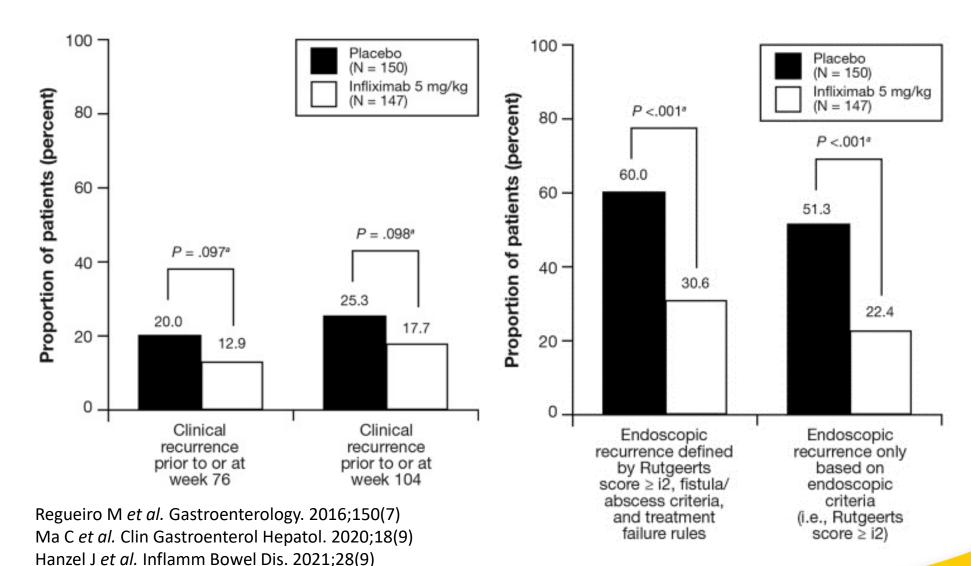
Endoscopic remission: MES=0 if baseline MES for enrolment ≥1

Histologic remission: Geboes ≤2B.0, RHI ≤3 with no lamina propria neutrophils or neutrophils in epithelium

Mucosal healing: histologic remission with MES=0/1 or MES=0 (depending on baseline endoscopy requirement)

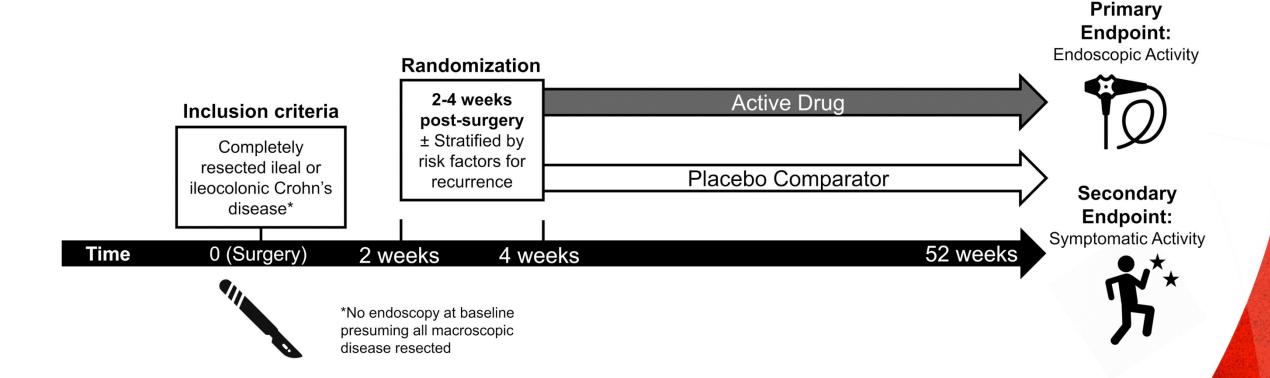






## **Unmet Needs: Postoperative Crohn's Disease**





Regueiro M *et al.* Gastroenterology. 2016;150(7) Ma C *et al.* Clin Gastroenterol Hepatol. 2020;18(9) Hanzel J *et al.* Inflamm Bowel Dis. 2021;28(9)



# **Unmet Needs: Postoperative Crohn's Disease**

	Reliability (ICC with 95% CI)		
Item	Inter-rater	Intra-rater	
Anastomotic lesions			
Aphthous ulcer(s) <5mm	0.12 [0.02, 0.21]	0.48 [0.30, 0.62]	
Large ulcer(s) ≥5mm	0.37 [0.24, 0.49]	0.60 [0.52, 0.69]	
Neoterminal ileum lesions			
Aphthous ulcer(s) <5mm	0.17 [0.04, 0.27]	0.48 [0.25, 0.64]	
Large ulcer(s) ≥5mm	0.40 [0.24, 0.55]	0.60 [0.48, 0.71]	
CI confidence interval, ICC intraclass correlation coefficient			

Primary
Endpoint:

Endoscopic Activity



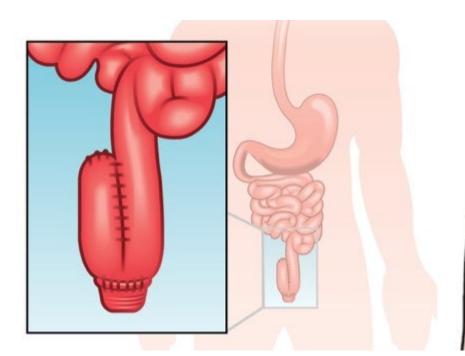
Secondary
Endpoint:
Symptomatic Activity

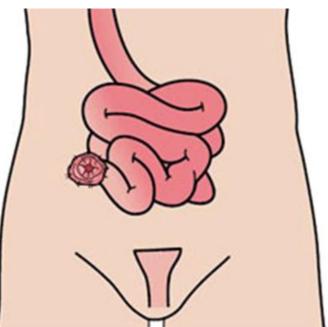


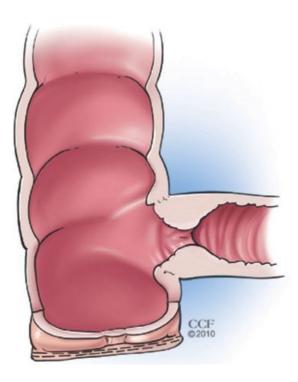


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#### **Unmet Needs: Different Anatomy, Different Phenotypes**

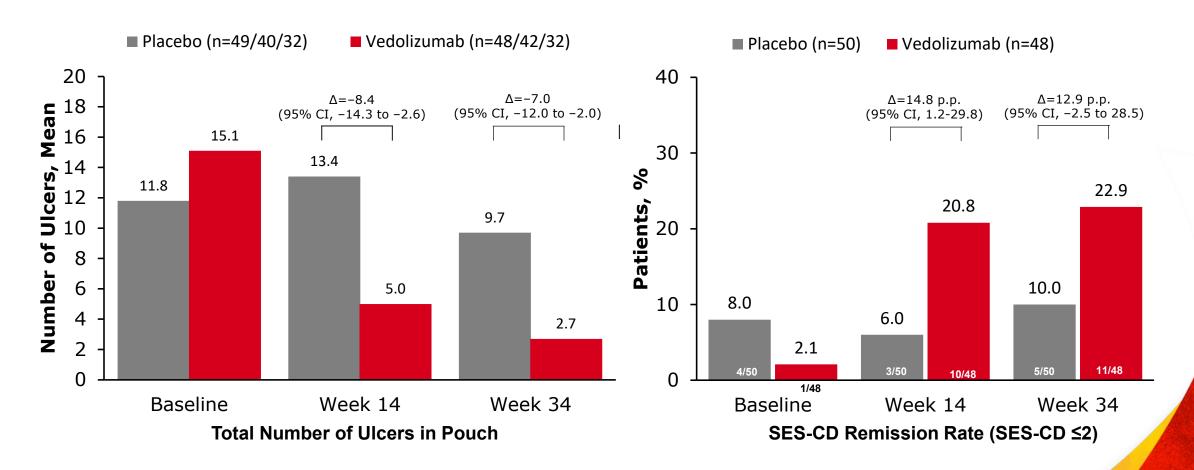






Sedano R *et al.* Aliment Pharmacol Ther. 2021;53(10) Goodsall T *et al.* J Crohns Colitis. 2020;15(1) Rieder F *et al.* Aliment Pharmacol Ther. 2018;48(3)





Travis S et al. J Crohns Colitis. 2022;16(S1)

