

A Case of Complex Crohn's Disease

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OAG Winter Meeting

Jan 19-21 2024

Conflict of Interest Disclosure

(over the past 24 months)

Commercial or Non-Profit Interest	Relationship
None	Committee member, Chair
Abbvie, Takeda, Eli Lilly, Janssen	Advisory board
Abbvie, Eli Lilly	Speaker
None	Stockholder, employee
Abbvie	Research support for Clinical Trial

CanMEDS Roles Covered

✓	Medical Expert (as <i>Medical Experts</i> , physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <i>Medical Expert</i> is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
✓	Communicator (as <i>Communicators</i> , physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
✓	Collaborator (as <i>Collaborators</i> , physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
✓	Leader (as <i>Leaders</i> , physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
✓	Health Advocate (as <i>Health Advocates</i> , physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
✓	Scholar (as <i>Scholars</i> , physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
✓	Professional (as <i>Professionals</i> , physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Objectives

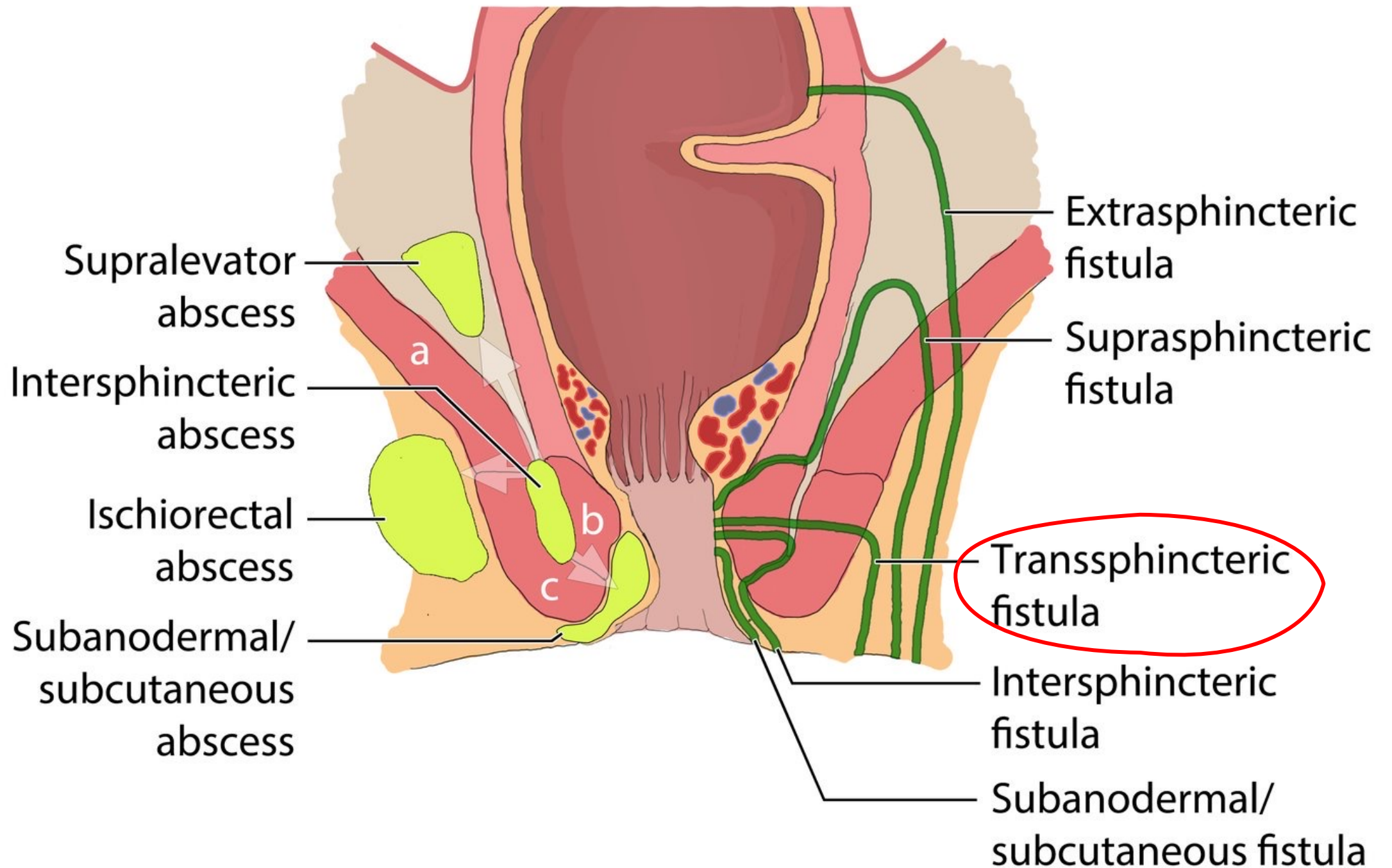
- To use patient case studies based on real-life scenarios to aid clinical decision-making
- To consider a systematic approach to management of complex inflammatory bowel disease
- To evaluate the role of newer therapies (small molecules and anti IL-23) in our current strategies

Patient KS

- 30 year old female, accountant, single, non smoker
 - 6 month history of poor appetite and RLQ abdominal pain
 - 1 month prior: perianal abscess drained by local surgeon
 - 4/52 course of metronidazole
 - Referred to GI with suspicion for Crohn's disease

Investigations

- Infectious work-up negative
- MRI pelvis revealed 2 transphincteric fistulae
- Colonoscopy showed moderate ileocolonic CD



Treatment Considerations:

- ? Steroids while perianal abscess is treated with antibiotics
- ? Immunomodulators
- ? Biologic
- ? Other Rx

Patient has a number of questions

- How common is fistulizing disease in Crohn's?
- How will it heal?
- Can it get worse?

Rates of Fistulizing Disease In CD

- Mayo population based study
 - Incidence 21% at 1 yr post diagnosis
 - Prevalence rates up to 30%
- Difficult to treat
- Almost 70% relapse

Schwartz DA et al. *Gastroenterology* 2002, 122, 875–880
Sandborn WJ et al. *Gastroenterol.* 2003;125:1508–1530

Question for audience:

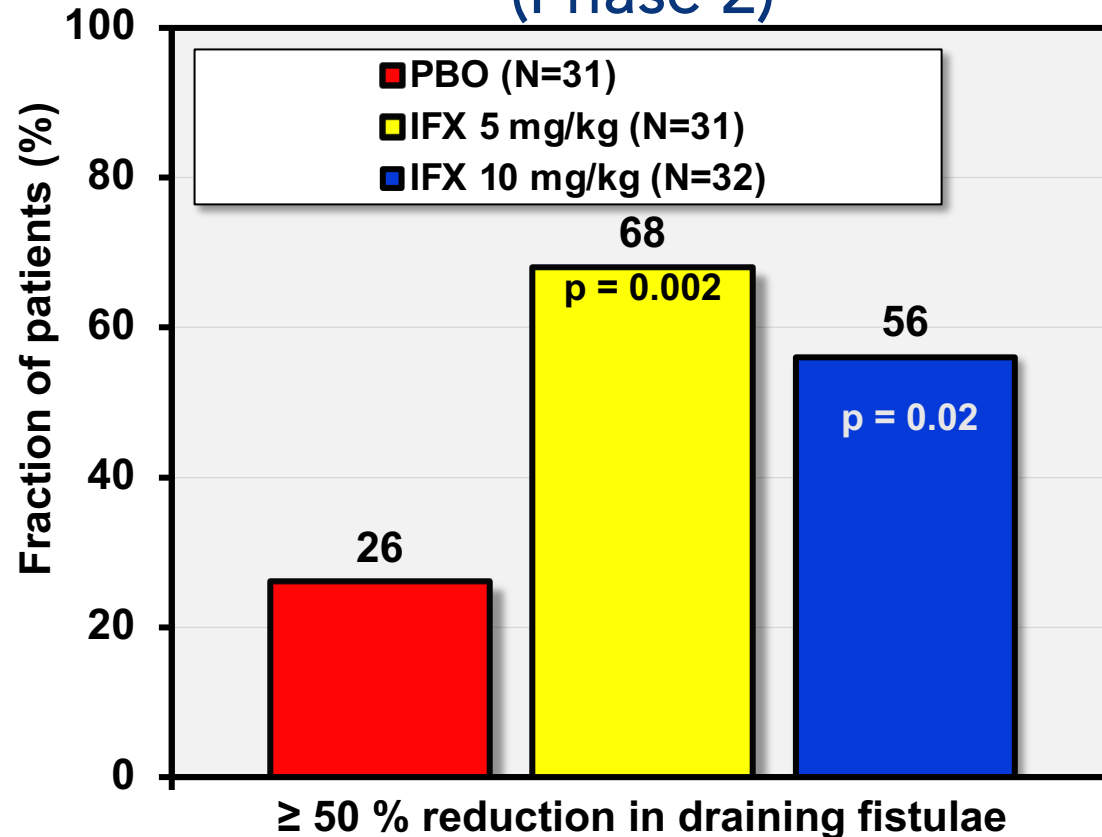
Does a biologic with fistulizing RCT data influence your 1st choice?

Considerations for Fistulizing CD

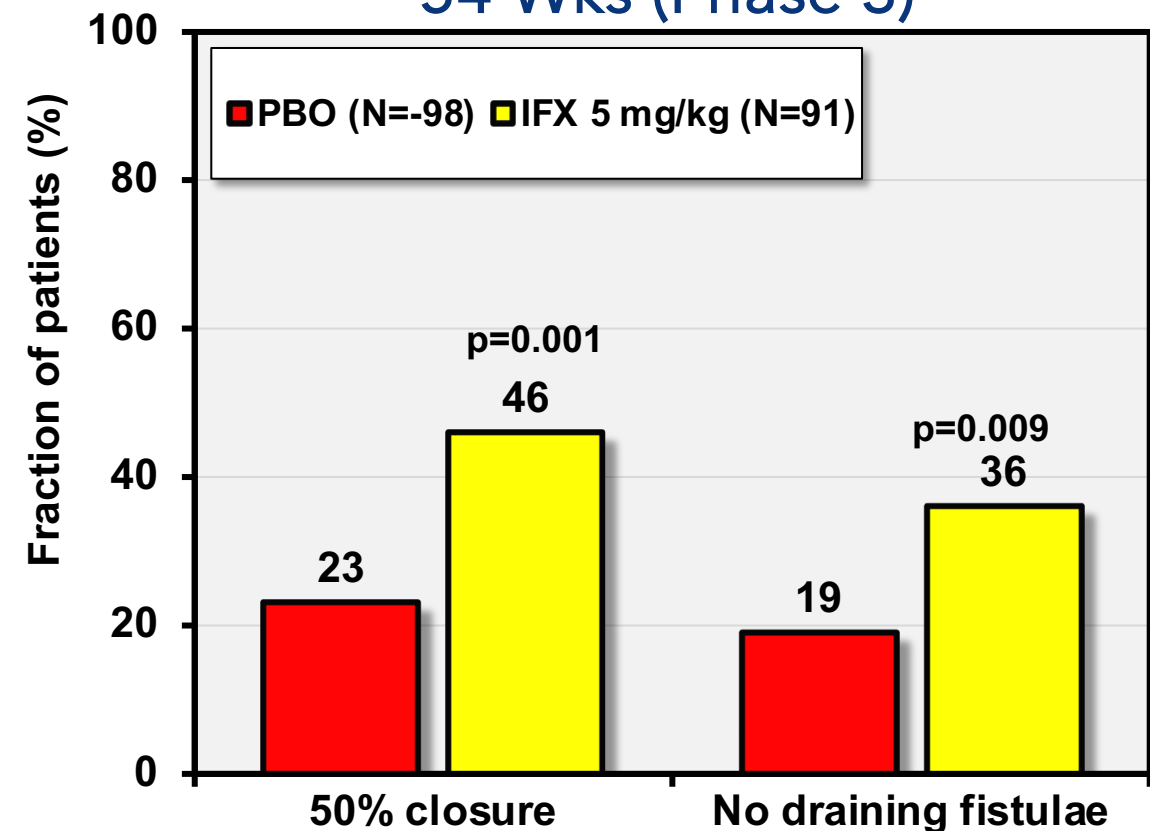
- The only prospective trial with a biologic aimed specifically at fistulizing CD pts was conducted with IFX
- Only biologic with indication for fistulizing CD

Infliximab Induces and Maintains Closure in Fistulizing CD

Induction in TNF-Naïve (Phase 2)



Maintenance in TNF-Naïve to 54 Wks (Phase 3)

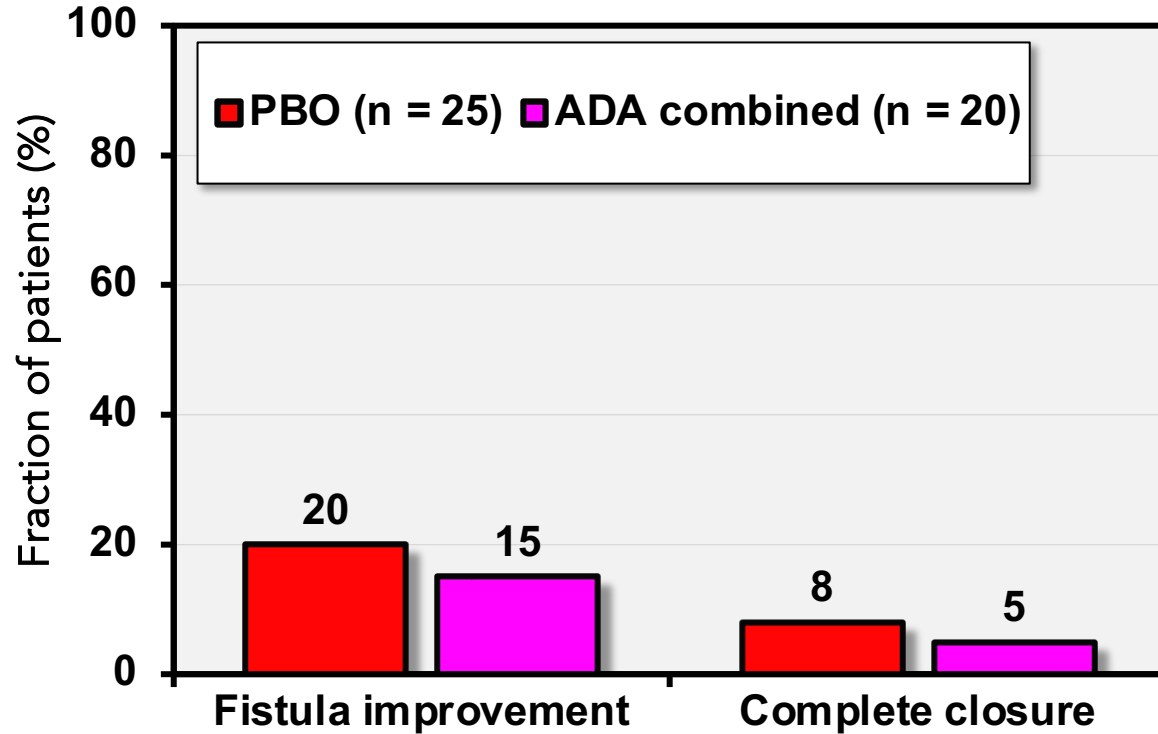


- Only biologic prospectively tested & indicated in fistulizing CD
 - Phase 2: 3 IV doses (0, 2, 6) and were followed for 26 weeks
 - Phase 3: OL induction (5 mg/kg 0/2/6), randomized at week 14

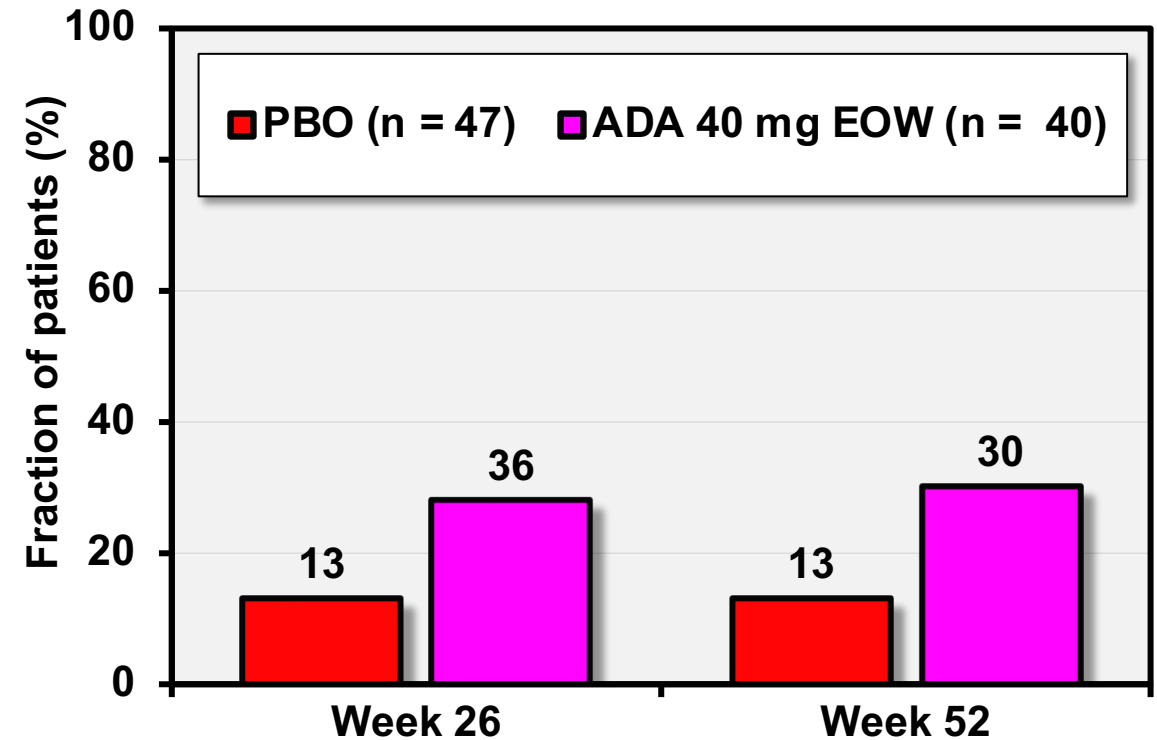
How do other Anti TNFs fare in fistulizing disease?

Adalimumab In Fistulizing CD

Short term Effect in TNF-Failures at Wk 4
GAIN



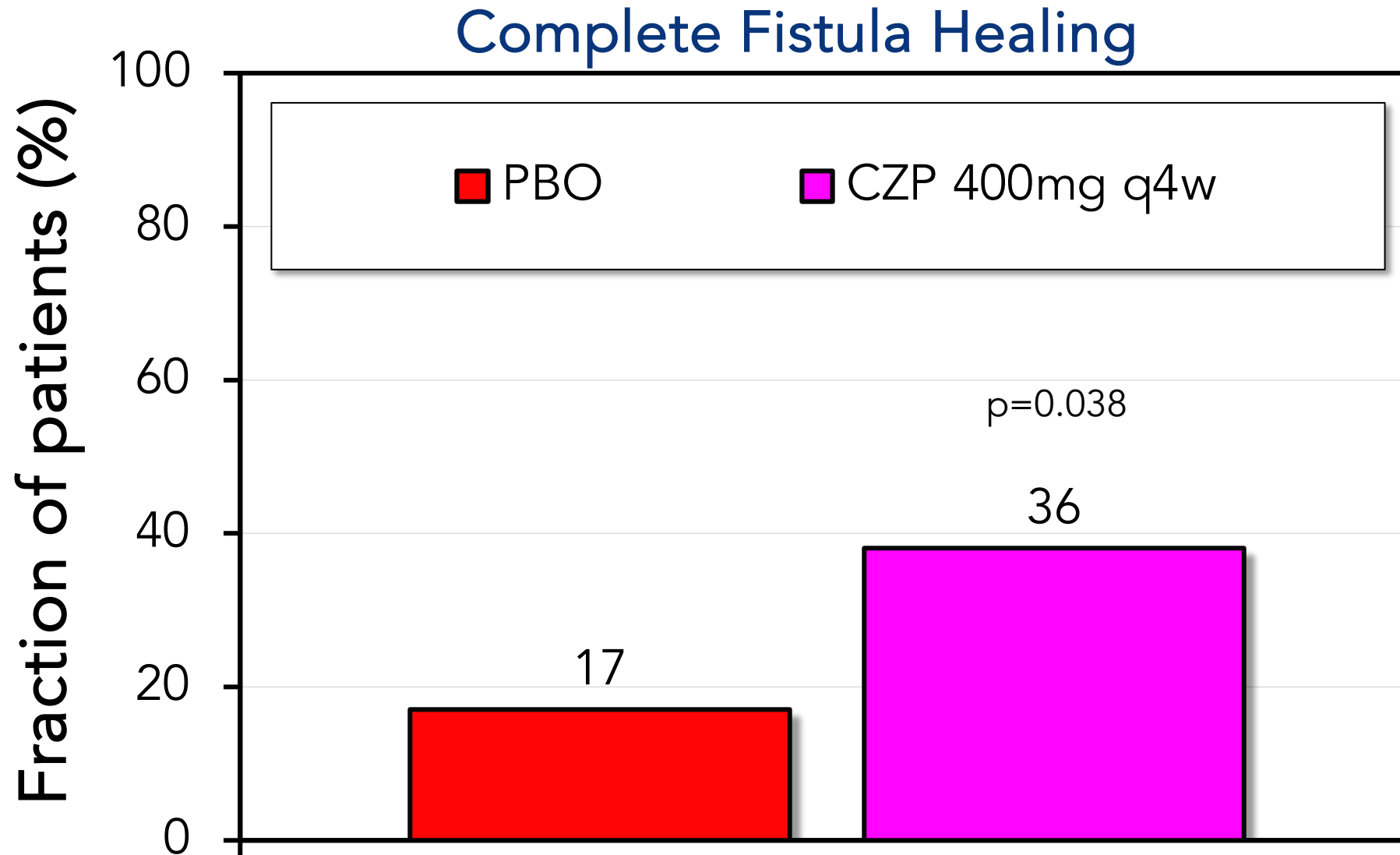
Long-term Healing#
(50% TNF-Naïve) CHARM



- First sc Bx approved for CD in Canada: 160/80 mg sc wk 0/2, then 40 mg sc eow
- Post-hoc analyses and other uncontrolled studies suggestive of effectiveness in treatment of fistula (no protocolized removal of setons)

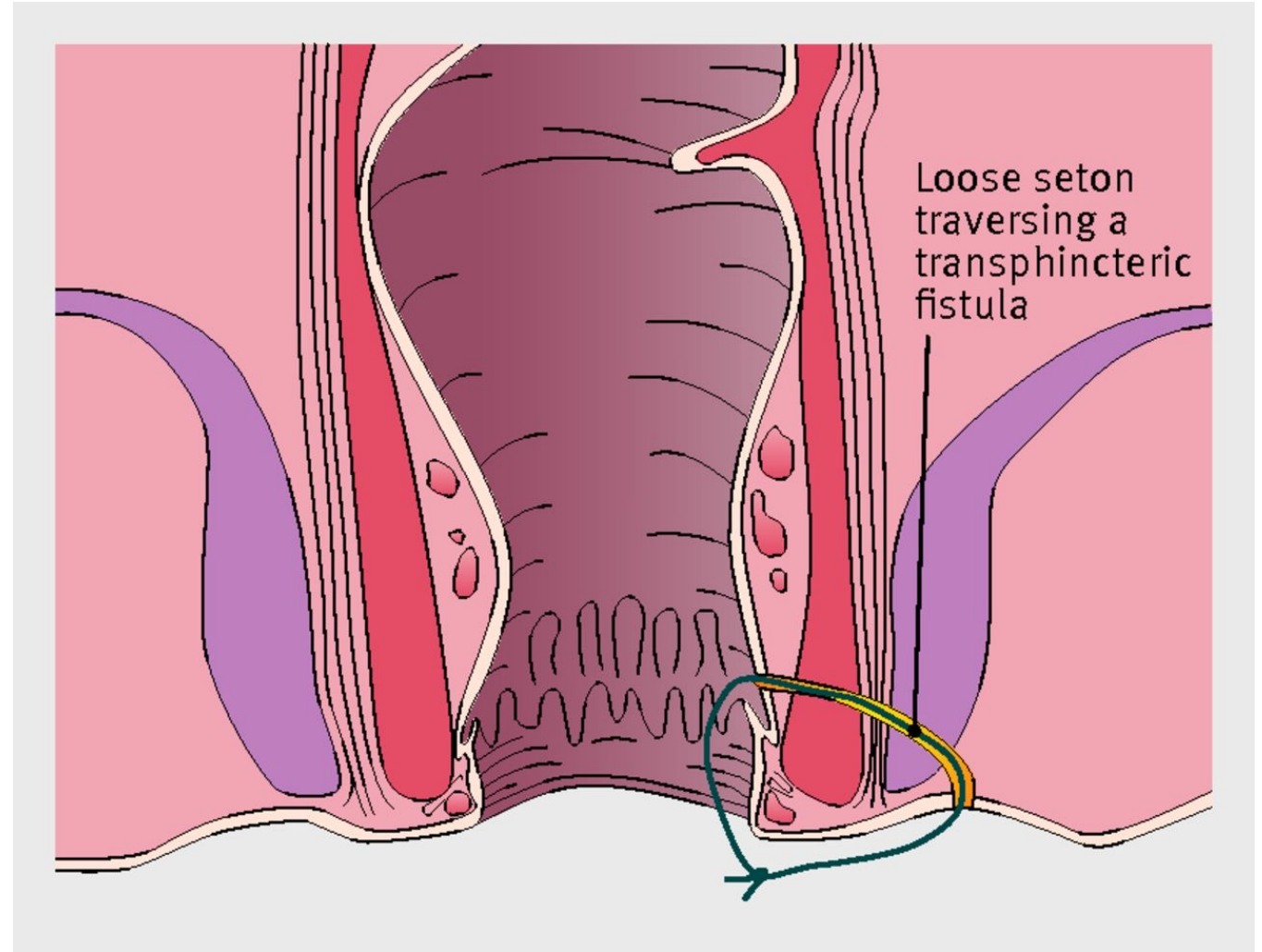
#Healing = no draining fistulas for at least 2 consecutive post-baseline evaluations

Certolizumab In Fistulizing CD

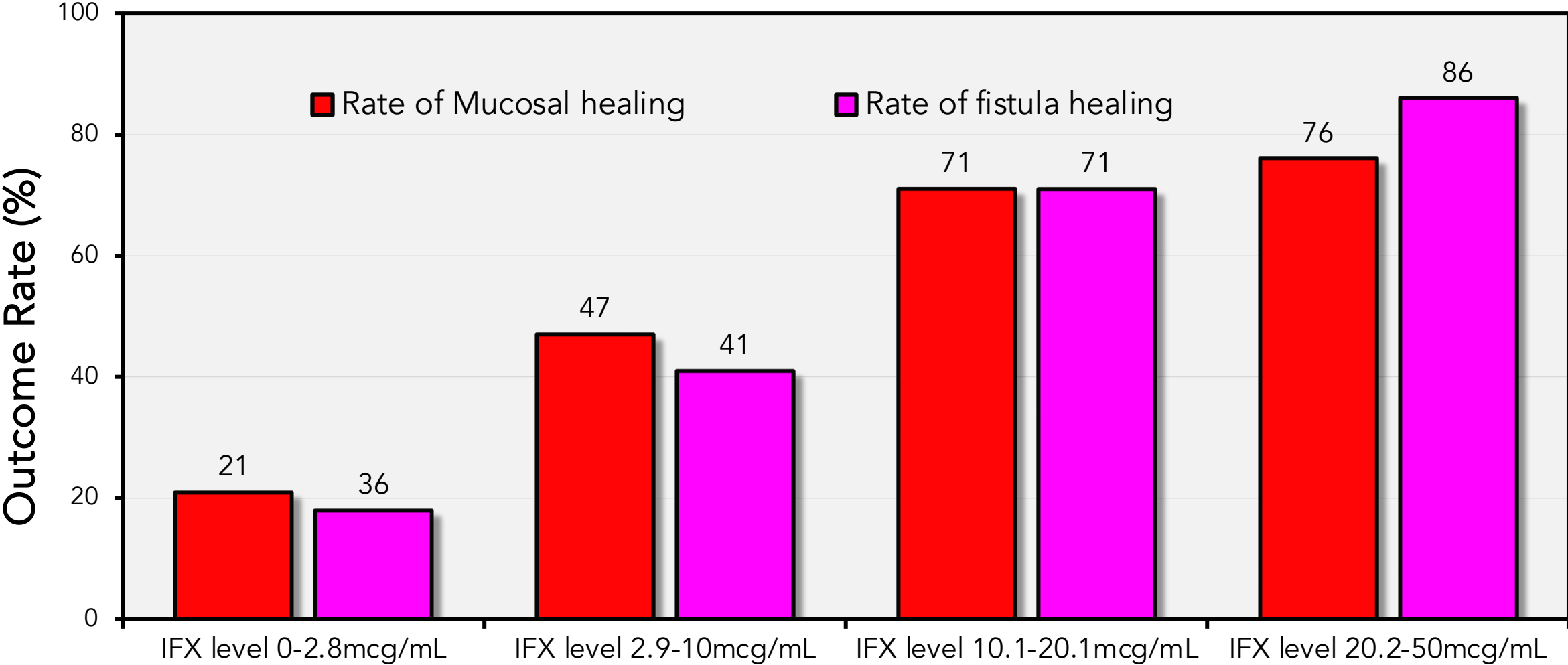


What did I do?

- Consulted with surgery
 - 2 setons inserted
- Remicade 5mg/kg q 8w
- Checked TDM wk 14
 - 6.5 mcg/mL
- What level should I aim for?



Higher infliximab trough levels are associated with fistula healing



IFX levels

- Patients with infliximab level in the **third quartile** (10.1–20.2 mcg/mL) had almost a **three-fold chance** of achieving fistula healing when compared to the first quartile (0–2.8 mcg/mL)
 - [OR: 2.7 (95% CI: 1.1–6.7), $P = 0.03$]
- Patients with infliximab level in the **fourth quartile** (20.3–50 mcg/mL) had an **eight-fold chance** of achieving fistula healing when compared to the first quartile
 - [OR: 8.2 (95% CI: 2.6–25.6), $P < 0.0001$]

Back to the patient

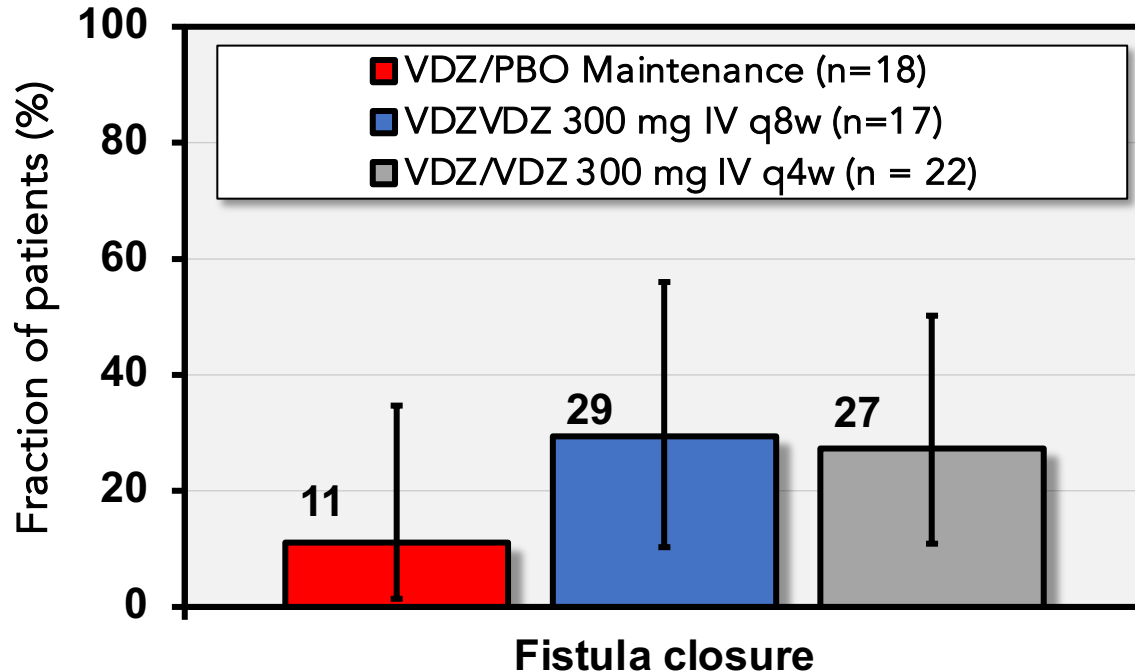
- Increased dose to 10mg/kg
- TDM remeasured after 2 cycles
 - 15 mcg/mL
- Setons fell out naturally
- 1 yr later:
 - Symptomatic: abdo pain, nocturnal BMs, anorexia, fistula drainage
 - Fcal 600, TDM levels good
 - MRI pelvis shows very minimal improvement in fistulae
 - MRE and Colonoscopy show active small and large bowel disease

Now what?

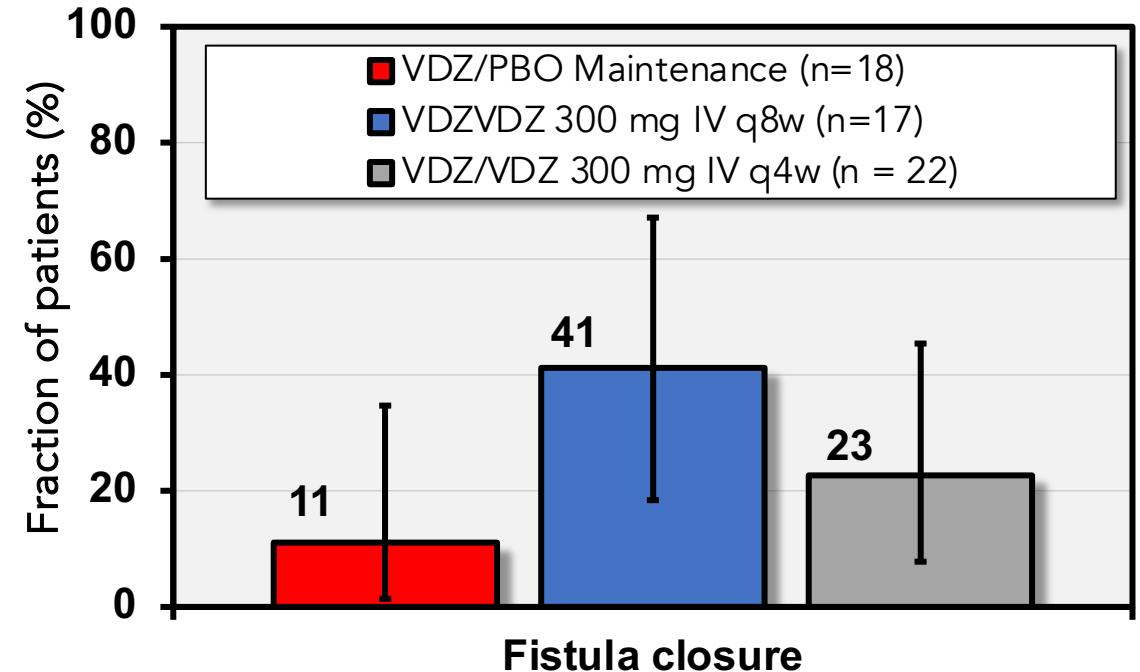
- Vedolizumab?
- Stelara?

Vedolizumab in Fistulizing CD

Short term Effect in Mixed Population
(Week 14)

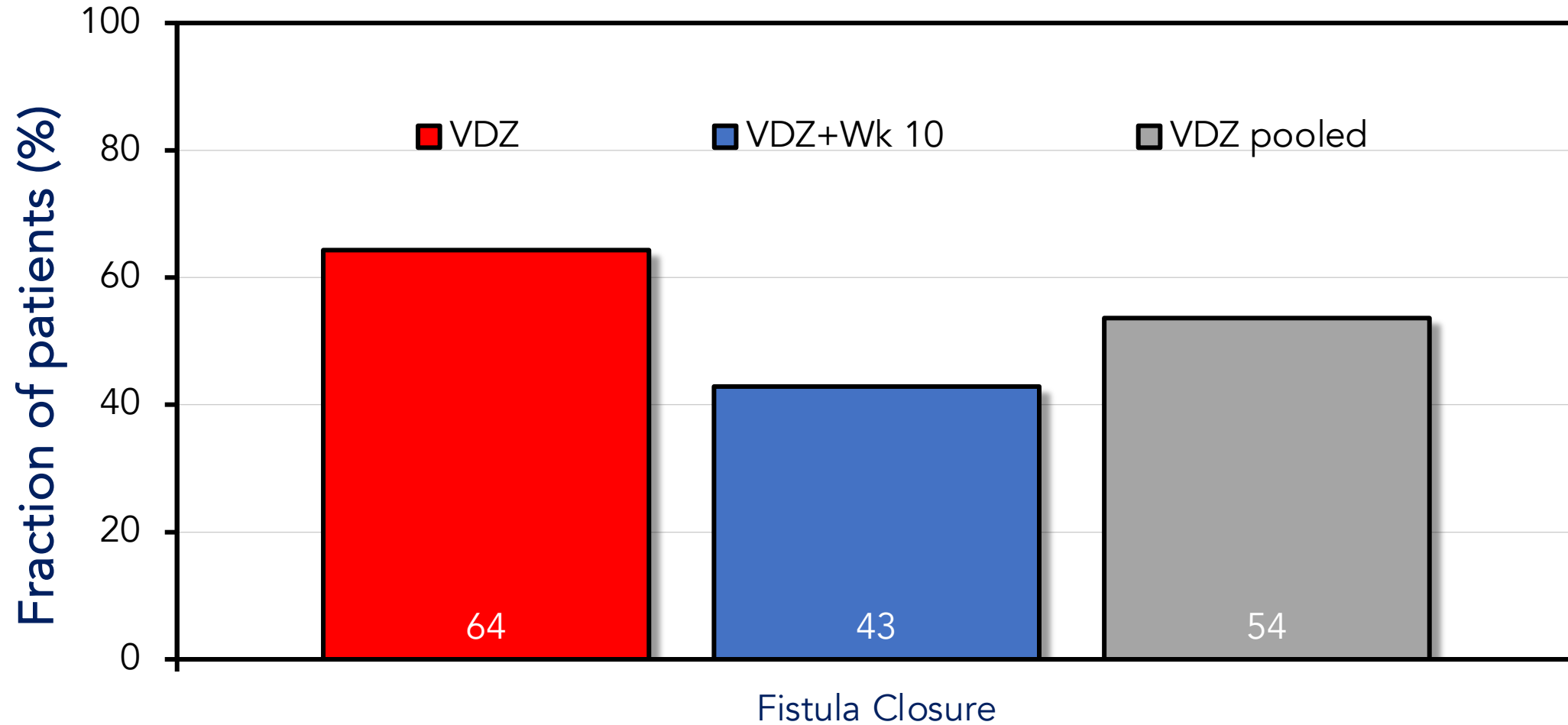


Long-term Healing In Mixed Population
(Week 52)



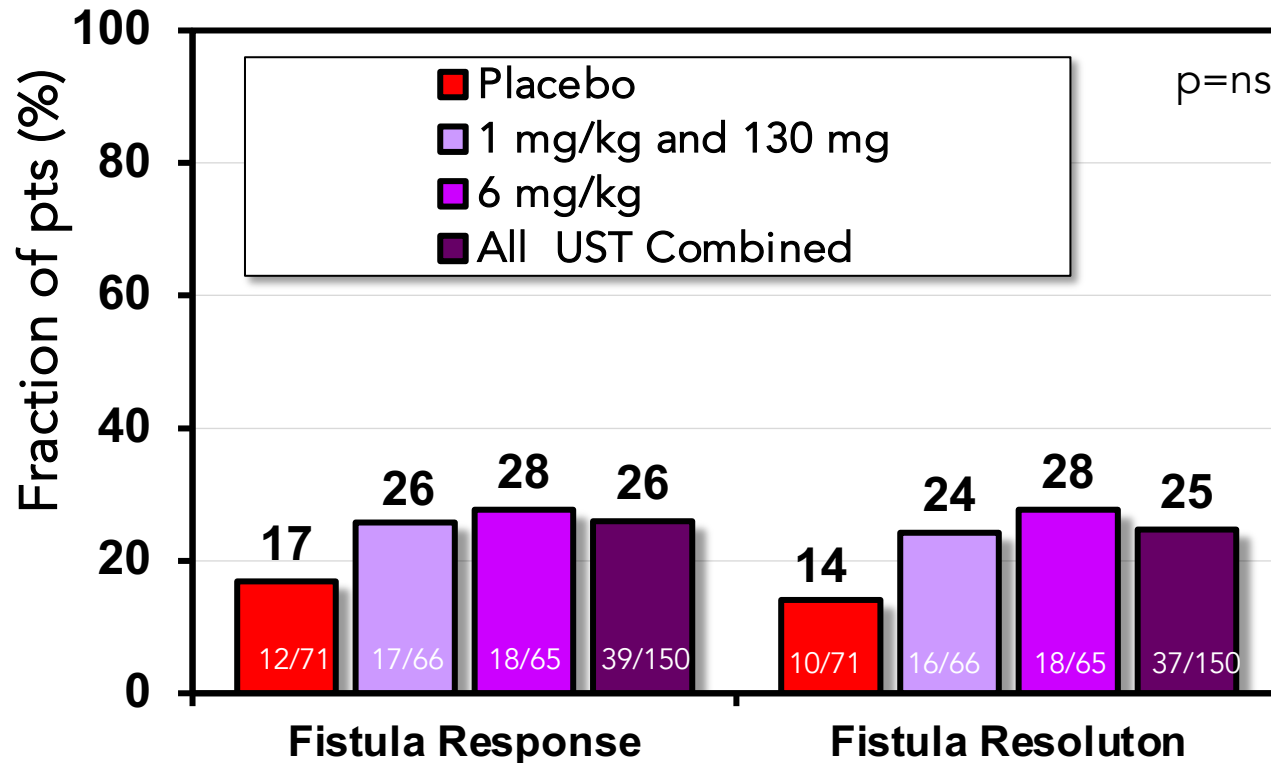
- Humanized, IgG1 monoclonal antibody against the $\alpha 4\beta 7$ integrin: 300 mg IV at wks 0/2/6, then 300 mg IV q8w
- Sub-analyses of GEMINI suggest some effectiveness in fistula closure

Enterprise Study: VDZ

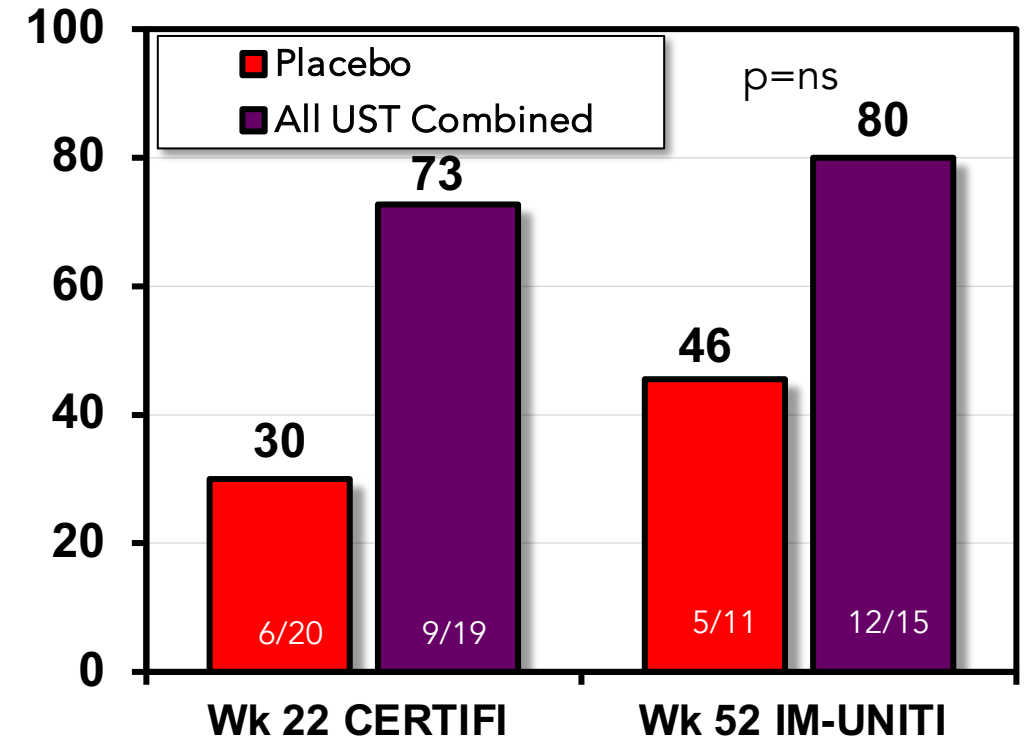


Ustekinumab in Fistulizing CD

Pooled Data on Fistula Response and Fistula Resolution at Week 8



Fistula Response in UST Responders



- 12.3% (161/1306) of pts had active fistulas at BL in the UNITI and CERTIFI studies
- Fistulas assessed by physical exam at each study visit, analyzed for fistula response and resolution
- Consistent trends for improvement in fistula healing but not stat sig

Fistula Response: $\geq 50\%$ Reduction in the number of draining fistulas

Fistula Resolution: 100% Reduction in the number of draining fistulas

UNITI sub-analysis, CERTIFI

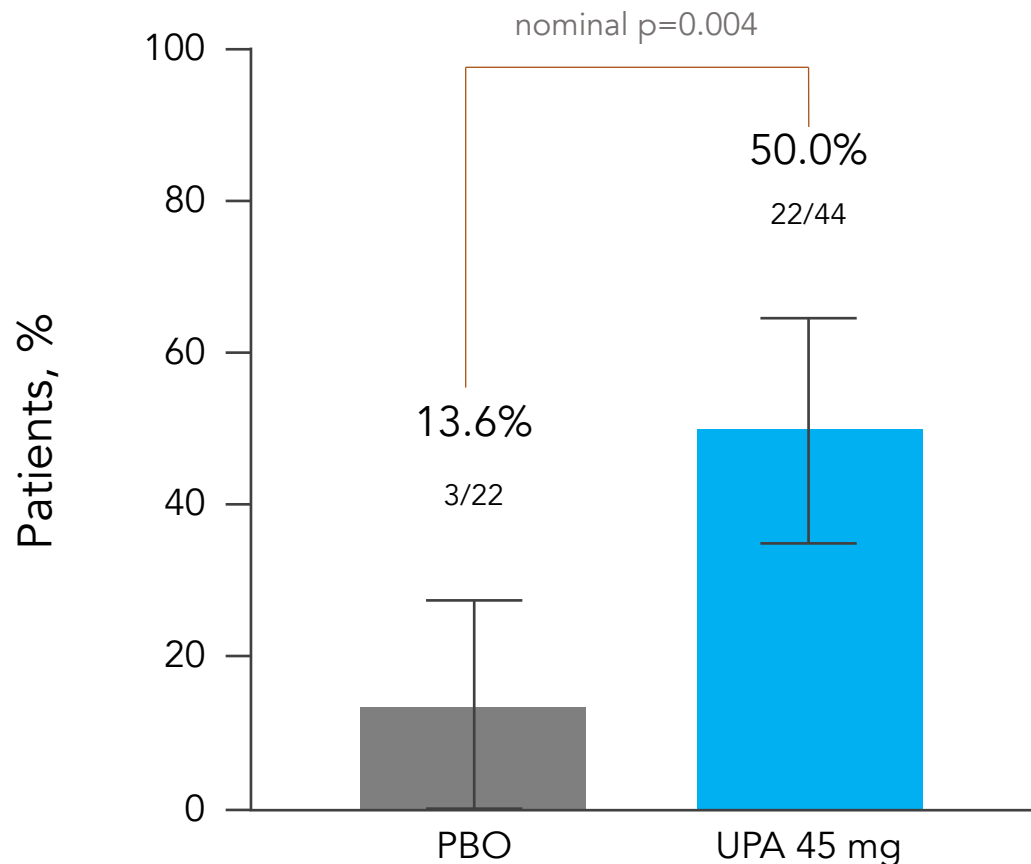
Sands et al. DDW 2017, 981

What about small molecules?

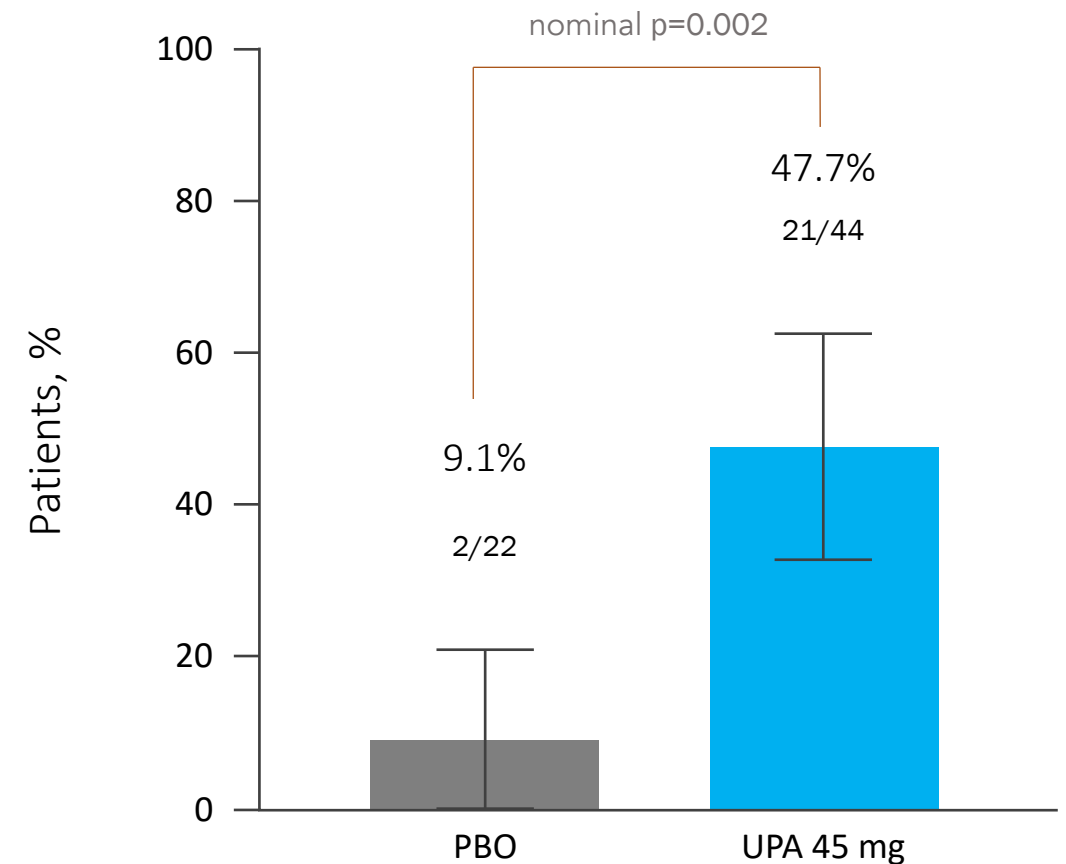
- ? Upadacitinib

Proportion of patients who achieved resolution of draining fistulas at Week 12 with UPA vs PBO

≥50% resolution of draining



Complete resolution of draining



What about Anti IL-23?

Risankizumab

In phase 3 induction trials, among patients with draining fistulas at baseline, no significant difference between RZB IV and PBO in patients with no draining fistulae at week 12

Patients with No Draining Fistula at Week 12 in Patients with Draining Fistula at Baseline ADVANCE			
	PBO iv	RZB 600mg iv	RZB 1200mg iv
Draining fistula at baseline, n	9	18	24
No draining fistula at Week 12, % (95% CI)	22.2 (0, 49.4)	27.8 (7.1, 48.5)	29.2 (11, 47.4)

Source: Data on file, ABVRRTI73680

Back to the patient

- Secondary loss of response to Infliximab
- Wants to start a family in near future
- Switched to Stelara
- Now on q 4w



Halder-Game Code:

CHALET

Questions?