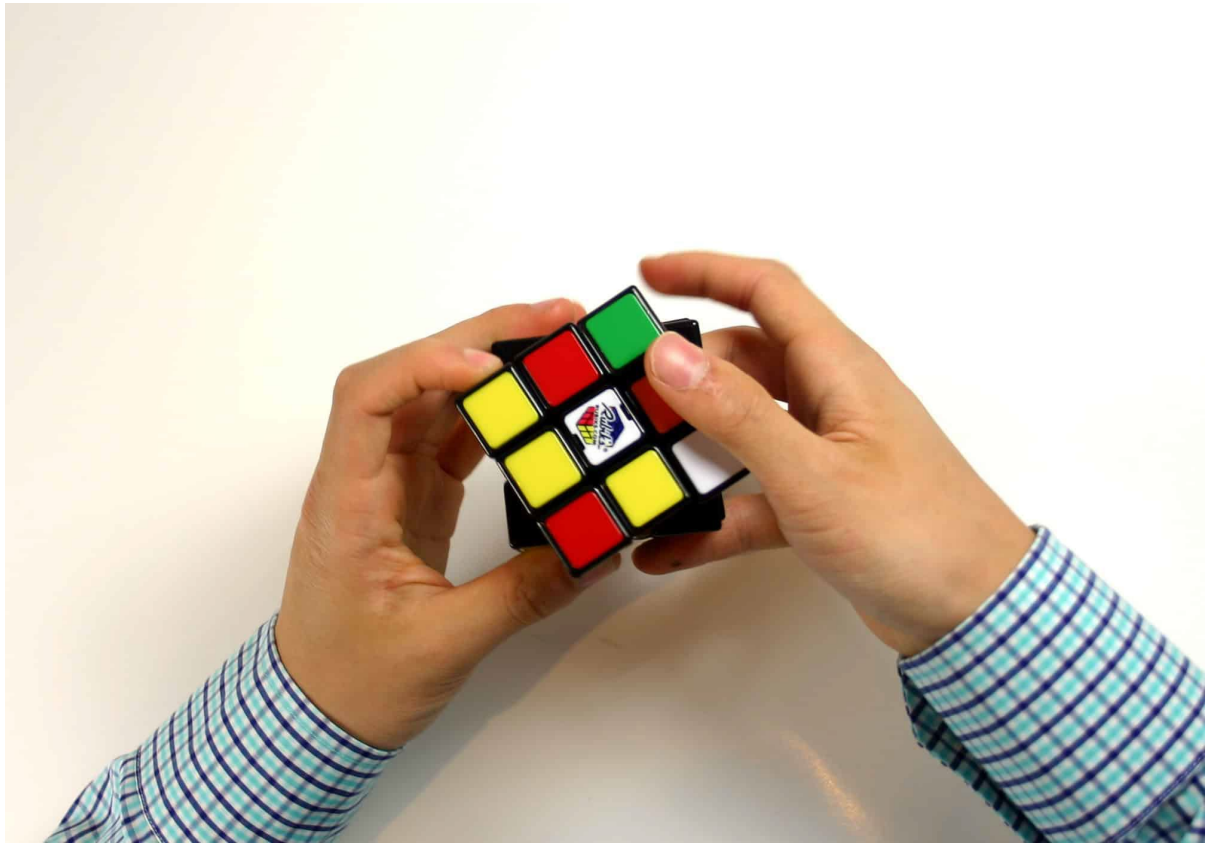
Positioning of Medical Therapies in the Treatment of Crohn's Disease



Brian G. Feagan MD
Professor of Medicine, Epidemiology and Biostatistics
Western University
Senior Scientific Director, Alimentiv Inc.
London, Ontario, Canada

Disclosures

Grant/Research Support	
Consultant	AbbVie, Abivax, Adiso, AgomAB Therapeutics, Allianthera, Amgen, AnaptysBio, Arena Pharma, Avoro Capital Advisors, Atomwise,, BioJamp, Biora Therapeutics, Blackbird Laboratories,Boehringer-Ingelheim, Boxer Capital, Celsius Therapeutics, Celgene/BMS, Celltrion, Connect BioPharma, Cytoki, Disc Medicine, Duality, EcoR1, Eli Lilly, Equillium, Ermium, First Wave, Forbion, Galapagos, Galen Atlantica, Genentech/Roche, Gilead, Gossamer Pharma, GSK, Hinge Bio, Index Pharma, Imhotex, Immunic Therapeutics, Intercept, JAKAcademy, Janssen, Japan Tobacco Inc., Kaleido Biosciences, Klick Health, Landos Biopharma, Lenczner Slaght, LifeSci Capital, Lument AB, Mage Biologics, Mestag, Millennium, MiroBio, Monte Rose Tx, Morgan Lewis, Morphic Therapeutics, Mylan, Nexys Therapeutics, Nimbus Therapeutics, OM Pharma, OrbiMed Origo BioPharma, Orphagen, Pandion Therapeutics, Pendopharm, Pfizer, Prometheus Therapeutics and Diagnostics (Merck), Progenity, Protagonist, PTM Therapeutics, Q32 Bio, Rebiotix, REDX, Roche, Roivant/Televant, Sandoz, Sanofi, Seres Therapeutics, Silverback Therapeutics, Sobi, Spyre Therapeutics, Surrozen Inc., Sun Pharma, Synedgen, Takeda, Teva, Thelium, Tigenix, Tillotts, Triastek, TR1X Inc. Ventyx Biosciences, Zagbio, Zealand Pharma
Speakers Bureau	AbbVie, Janssen, Takeda
Patent Holder	
Member, Scientific Advisory Board	AbbVie, Amgen, AMT, AnaptysBio, Boehringer-Ingelheim, Celgene/BMS Eli Lilly, Genentech/Roche, Janssen, MiroBio, Origo BioPharma, Pfizer, Prometheus, REDX Pharma, Sanofi, Takeda,Tillotts Pharma, Teva, Progenity, Index, Ecor1Capital, Morphic, GSK, Axio Research
Member, Board of Directors	Senior Scientific Director – Alimentiv Inc, London
Stock Shareholder	Connect BioPharma, EnGene
Other Financial Support	
Other Relationship/Affiliation	

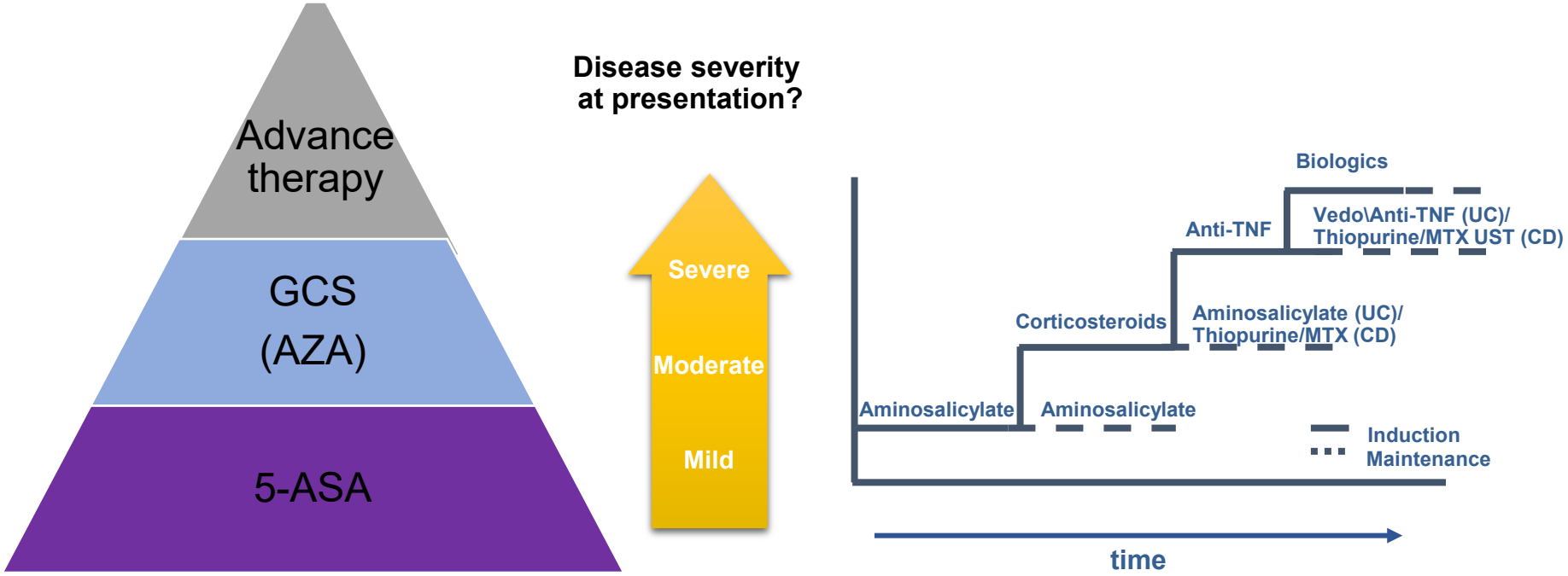
Topics to be Discussed

1. Treatment Algorithms in CD

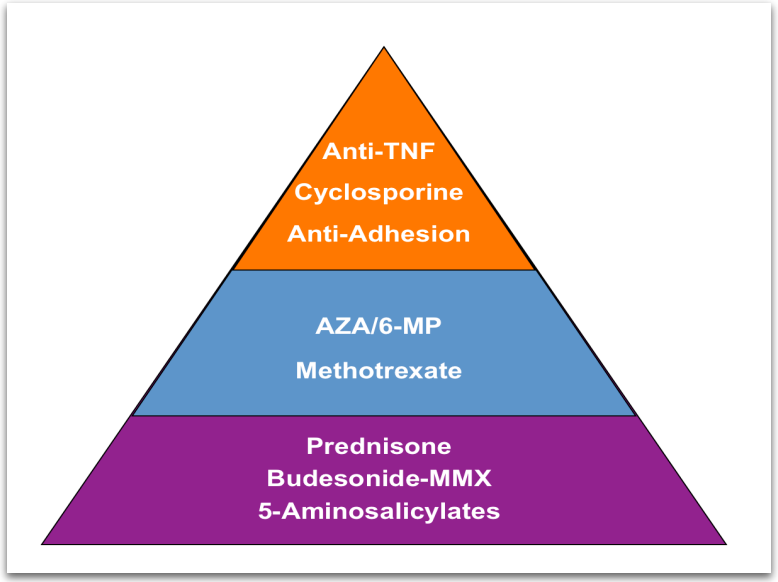
2. Key learnings for existing drug classes
   (TNF antagonists, vedolizumab, Il12-23s, JAKs)

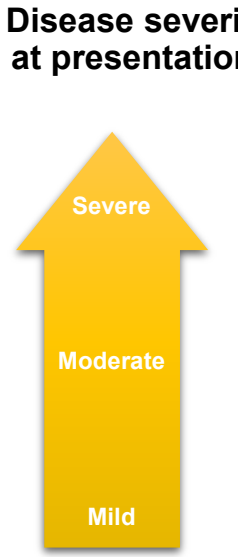
3. Combination therapy

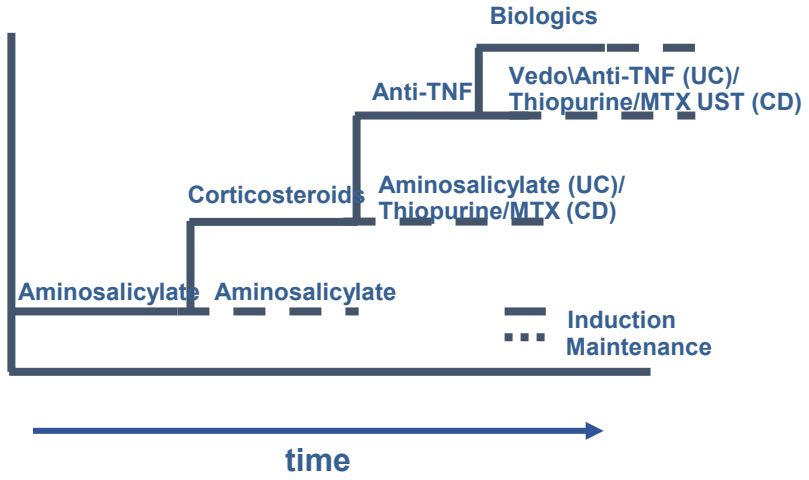
The concept of step-care in UC remains however…..



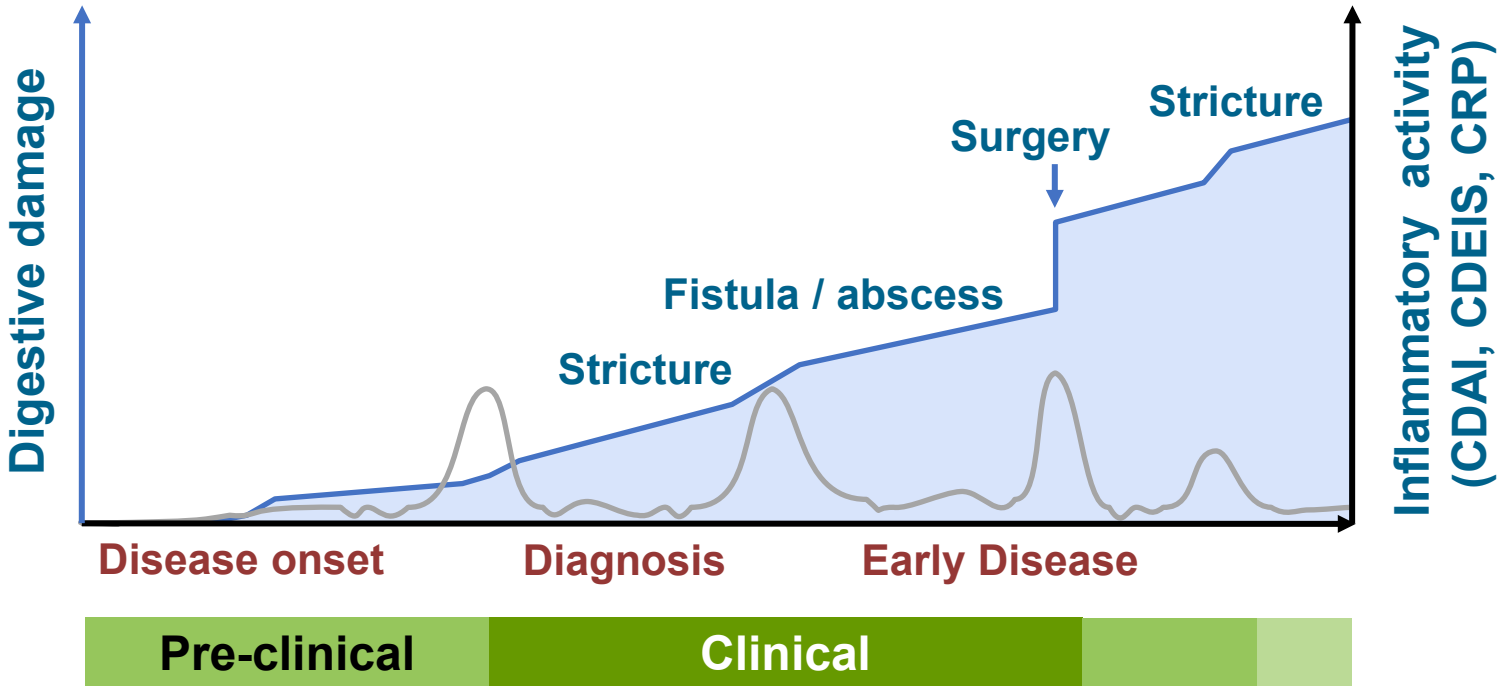
Step-Care in CD is Flawed





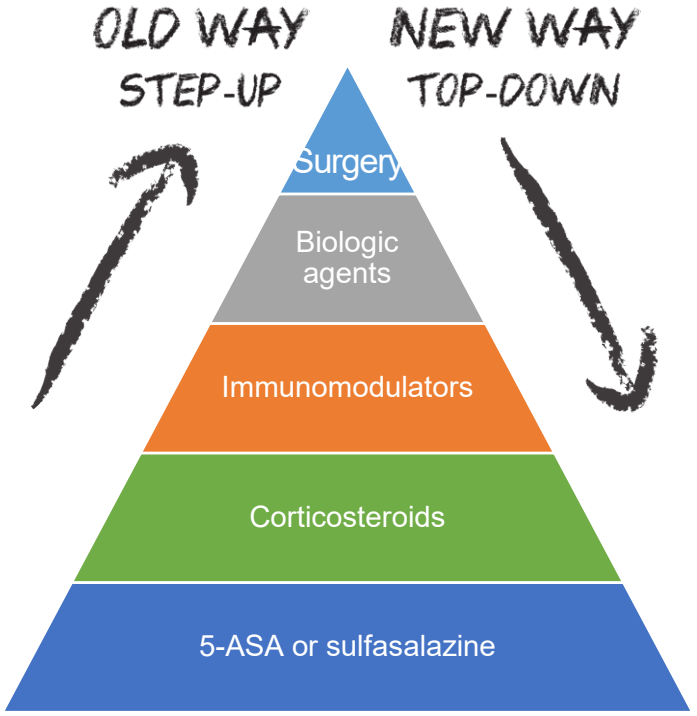


Because CD is Inexorably Progressive!



Pariente B, *et al. Inflamm Bowel Dis* 2011;17:1415–22

‘Top-down’ vs ‘Step-up’ Trial 2008



THE LANCET

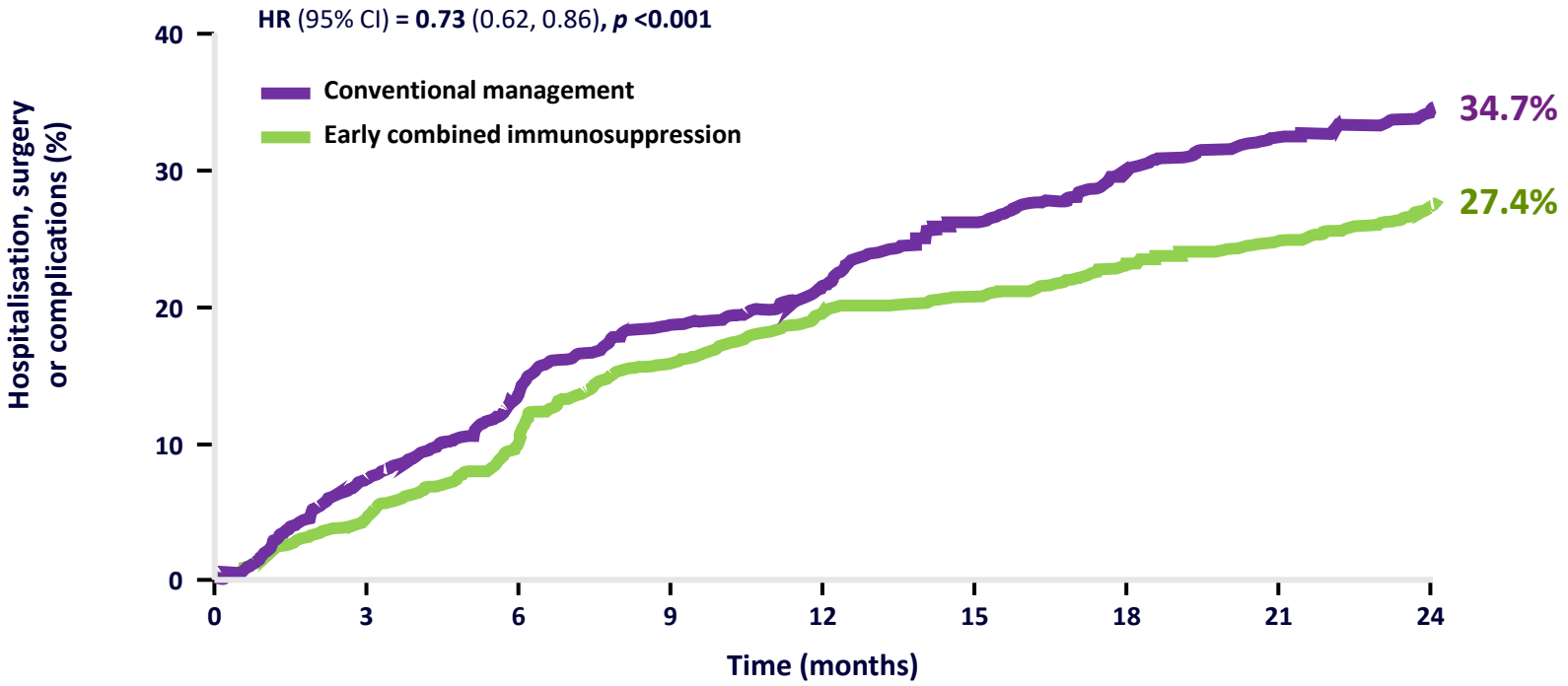
Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn’s disease: an open randomised trial

Geert D’Haens, Filip Baert, Gert van Assche, Philip Caenepeel, Philippe Vergauwe, Hans Tuynman, Martine De Vos, Sander van Deventer, Larry Stitt, Allan Donner, Severine Vermeire, Frank J Van De Mierop, Jean-Charles R Coche, Janneke van der Woude, Thomas Ochsenkühn, Ad A van Bodegraven, Philippe P Van Hootegem, Guy L Lambrecht, Fazia Mana, Paul Rutgeerts, Brian G Feagan, Daniel Hommes, for the Belgian Inflammatory Bowel Disease Research Group and the North-Holland Gut Club

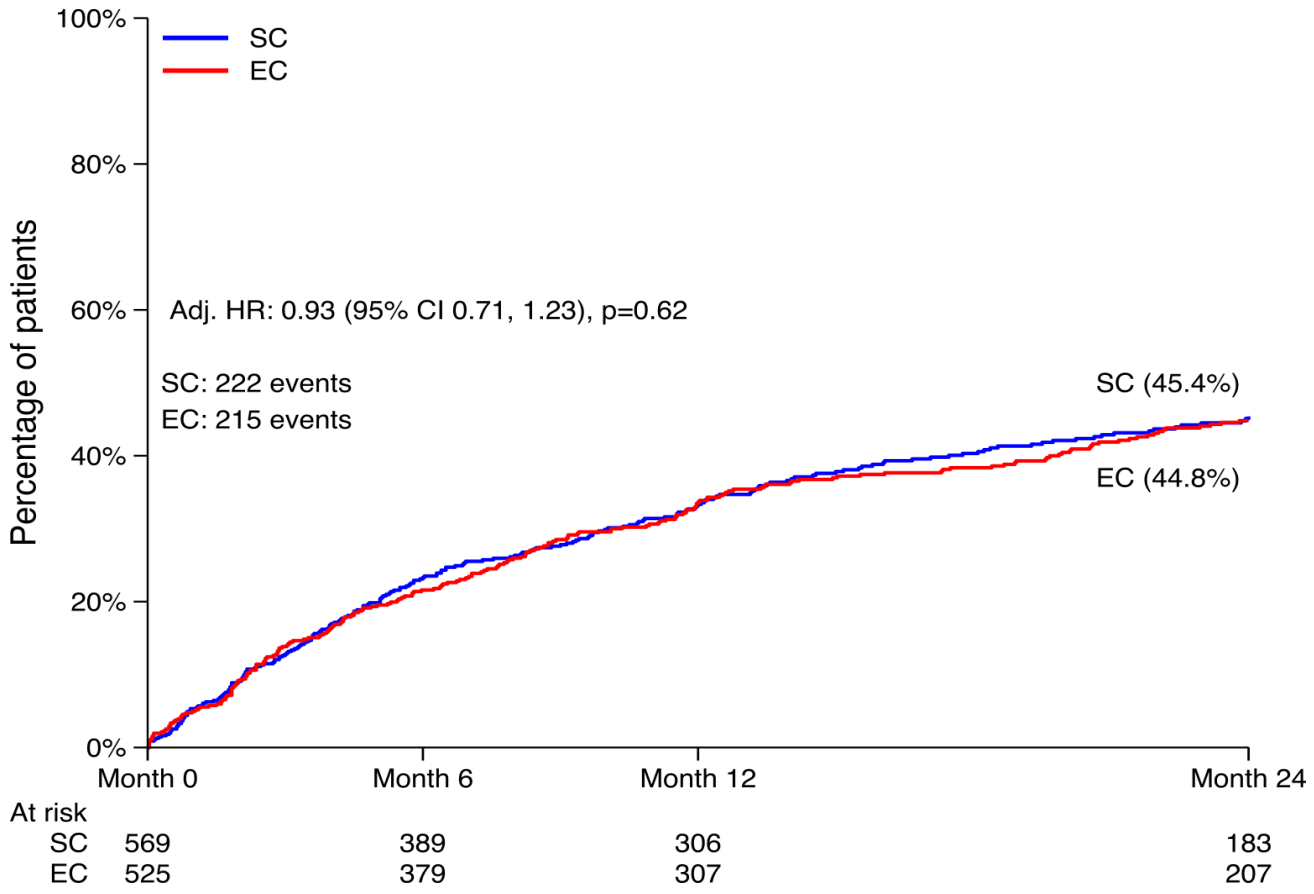
Image adapted from Aloi, M et al. *Nat Rev Gastroenterol Hepatol* 2014;11:99-108
D’Haens G et al. *Lancet* 2008;371:660-667. doi: 10.1016/S0140-6736(08)60304-9

Cluster Randomization Trials

REACT
Time to hospitalization/surgery/complication



REACT 2 -Primary Outcome: CD-Related Complications



Model-Based Cumulative Incidence Rate (EC vs SC)

40.9% vs 43.1%

Adjusted Risk Difference

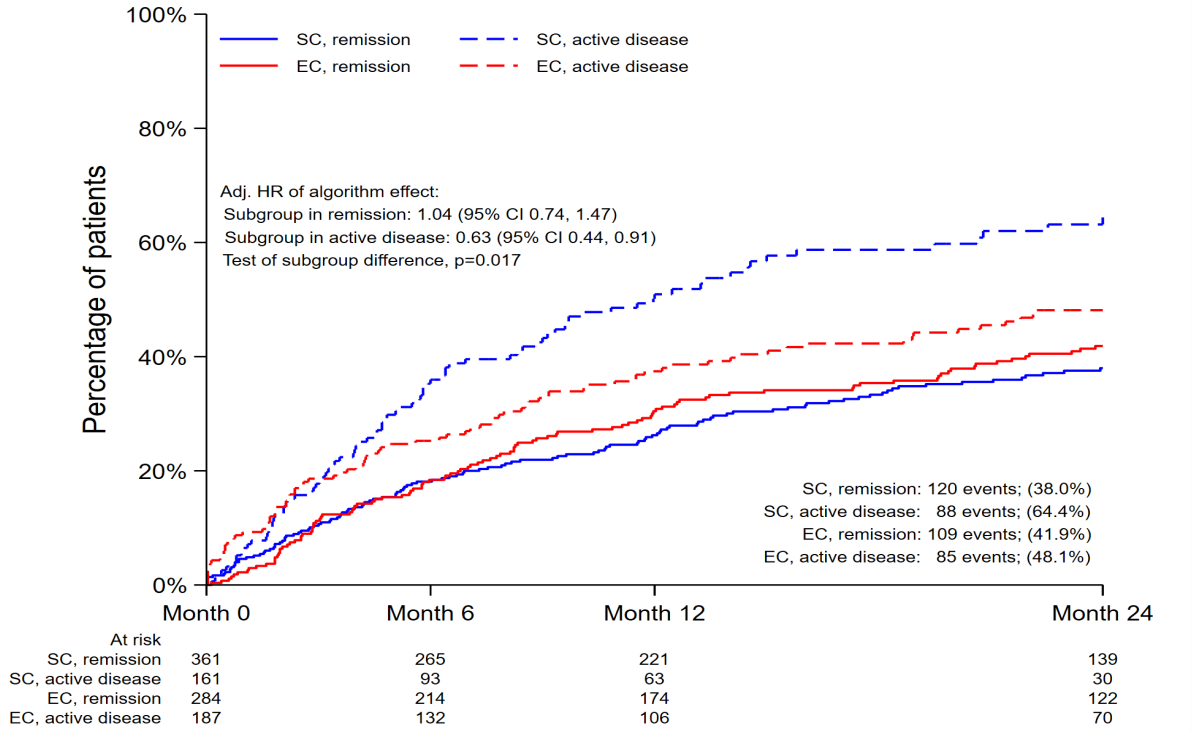
-1.5% (95% CI: -10.2% to 7.2%, p=0.73)

Risk Ratio

0.95 (95% CI: 0.79 to 1.15, p=0.59)

Jairath V et al DDW 2022

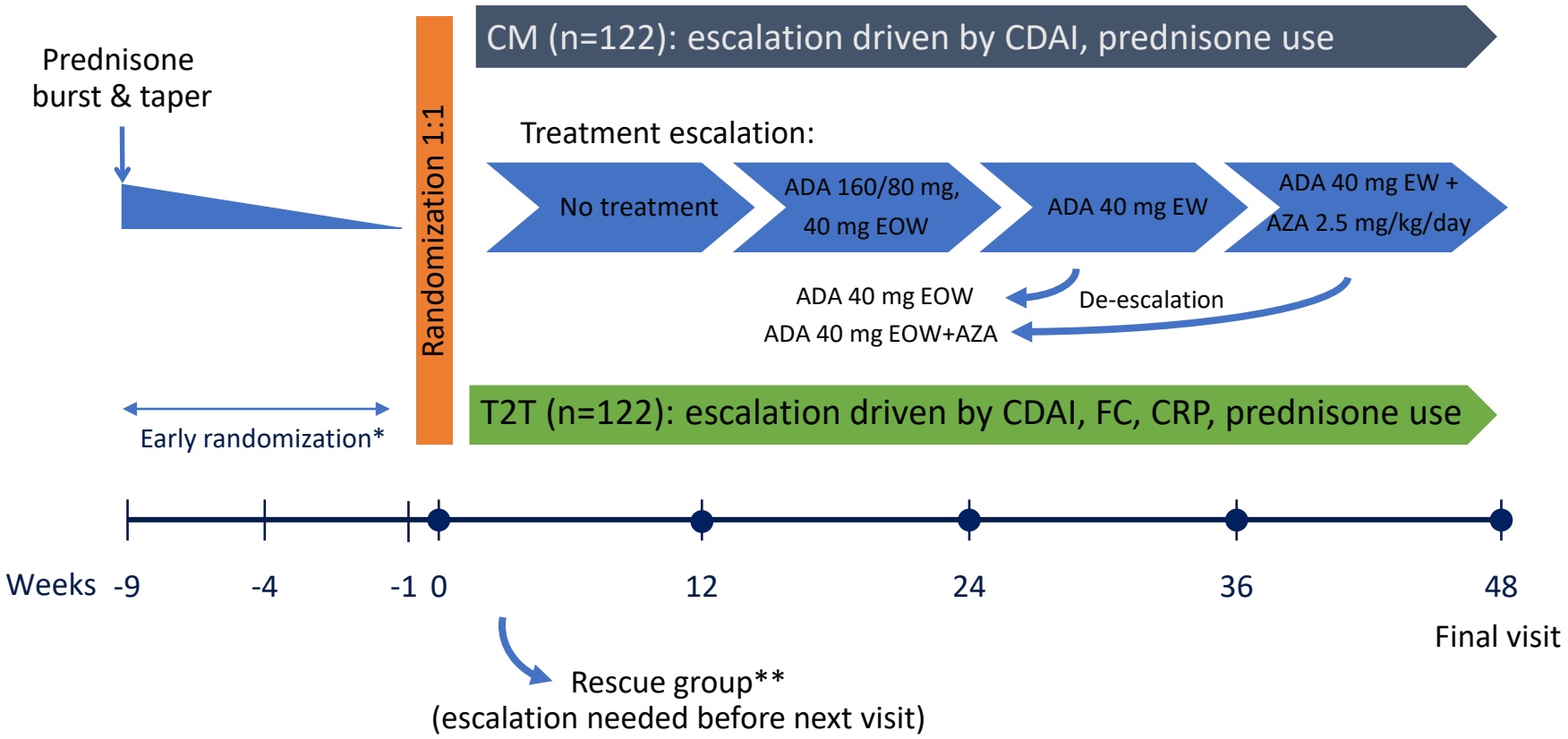
CD-Related Complications in Patients with Active* Disease



Model-Based Cumulative Incidence Rate (EC vs SC, Active Disease)
44.1% vs 58.7%
Adjusted Risk Difference (Active Disease)
-15.1% (95%CI -27.8% to -2.4%)
Risk Ratio
0.75 (95%CI 0.60 to 0.95)

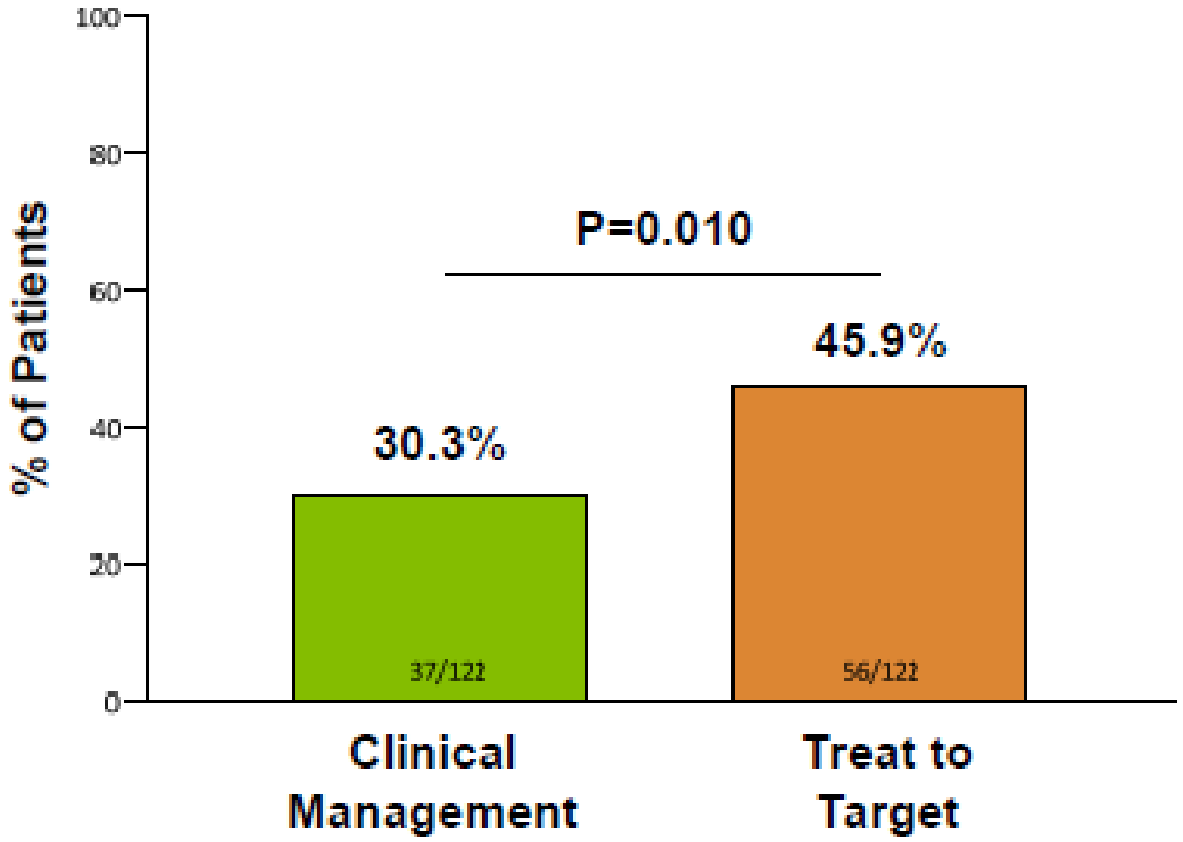
Jairath V et al DDW 2022

CALM: Treat To Biomarker Remission



Colombel JF. Lancet 2017

CALM: Primary Endpoint at Week 48
CDEIS<4 and No Deep Ulcerations



Colombel JF. Lancet 2017

CD Therapies 2024: Summary of Key Concepts

- For most patients TNF antagonist are no longer the initial treatment of choice
- Newer agents are not TNF antagonists with respect to dose-response optimization or immunogenicity
- Safety is important to patients – two classes of agents are completely safe (vedolizumab/Il-12-23)
- IL-23 antagonists and upadacitinib appear to have greater efficacy than other agents for endoscopic outcomes
- Efficacy ceiling is an enormous problem –combination therapy is the most promising solution

Origins

Bert Derkx, Jan Taminiau, Sandra Radema, Arnold Stronkhorst, Cees Wortel, Guido Tytgat, Sander van Deventer

Departments of Paediatric Gastroenterology, Nutrition, and Gastroenterology, Academic Medical Centre, 1105 AZ Amsterdam, Netherlands

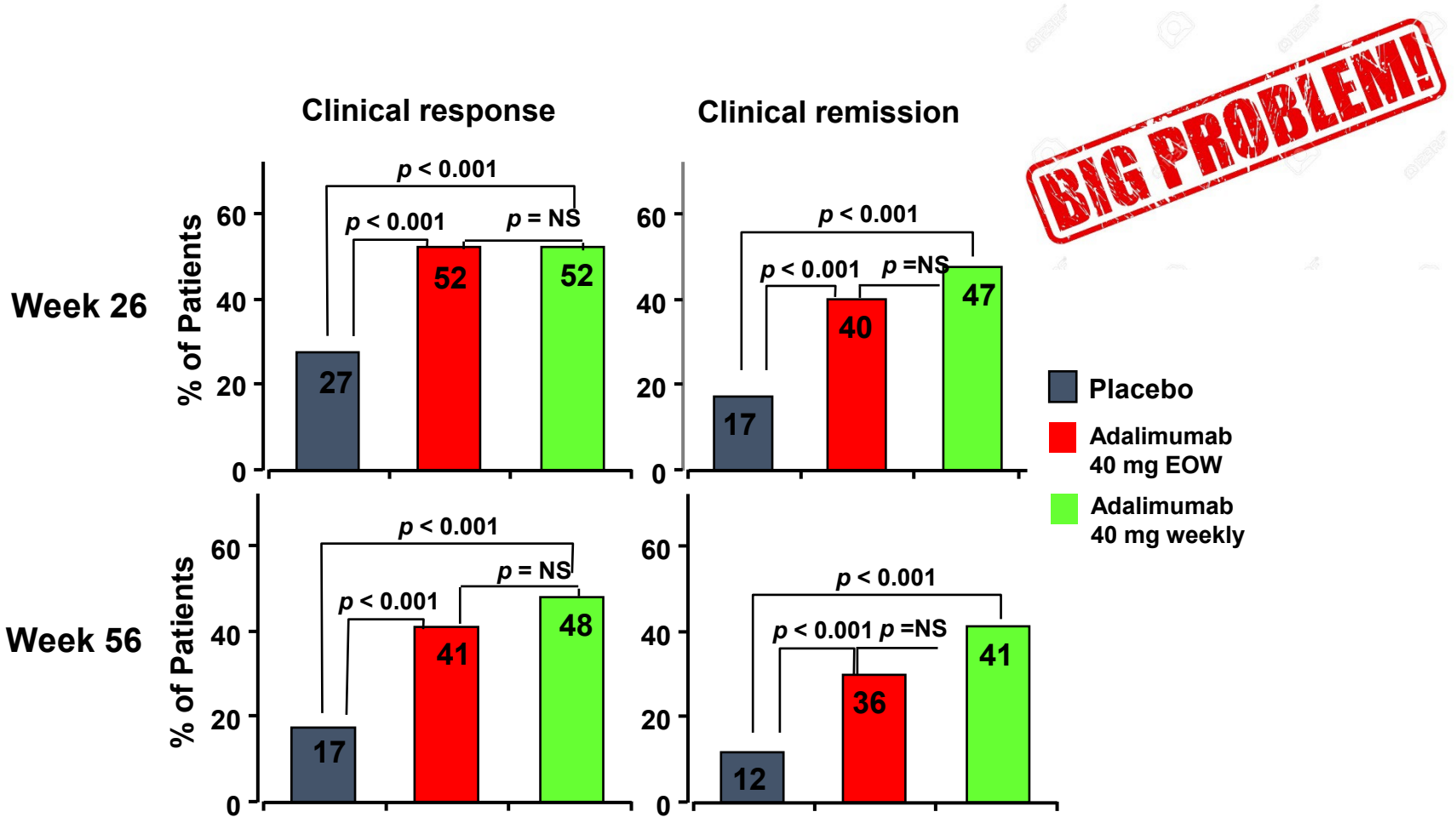
Tumour-necrosis-factor antibody treatment in Crohn's disease

SIR—We report a girl with Crohn's disease who was not responsive to medical therapy but in whom complete but temporary remission could be achieved by treatment with tumour necrosis factor (TNF) monoclonal antibodies.

At age 12 years the patient was examined because of diarrhoea of 4 months' duration, rectal blood loss, abdominal pain, fever, and loss of 4·5 kg. Colonoscopy showed multiple aphthoid lesions, skip lesions, erythema, friability, and granularity in the distal 70 cm of the colon extending into the anus. Biopsy specimens revealed severe inflammation, crypt abscesses, and granulomas. A small bowel follow-through was normal. Prednisone 30 mg per day, mesalazine 250 mg three times a day, and enemas containing 2 g aspirin and 40 mg prednisone were started. Her complaints initially abated but the disease soon relapsed despite continued anti-inflammatory treatment. Because of severe side-effects the prednisone dose had to be reduced. Colonoscopy 3 months after diagnosis showed no improvement. The treatment was intensified by raising the dose of mesalazine and adding azathioprine. Some clinical improvement was noted but her growth stunted, and it was not possible to withdraw any medication. A semi-elemental diet for 2 months and the addition of metronidazole had no effect. A year after diagnosis, she had increasing anorexia, abdominal pain, and frequent bloody diarrhoea. Colonoscopy again showed extensive colitis and perianal lesions. Over the next 14 months the patient was treated with prednisone (daily alternating up to 40 mg a day), azathioprine 75 mg a day, mesalazine 500 mg three times a day, and enemas containing beclomethasone and aspirin.

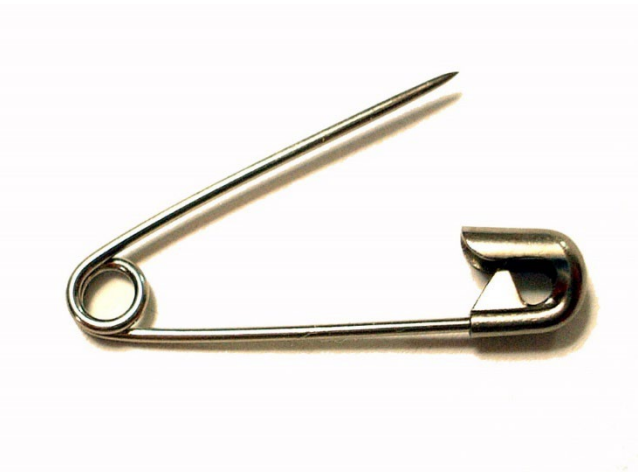
Because of unresponsive disabling disease, the possibility of anti-TNF treatment was discussed with the patient and her parents. Written consent was obtained. She was infused twice over a fortnight with anti-TNFα (chimeric monoclonal cA2,

Greater Efficacy is Needed: Positive Yet Sub-optimal Results with TNF Antagonists



.
Colombel JF. et al. Gastroenterology 2007

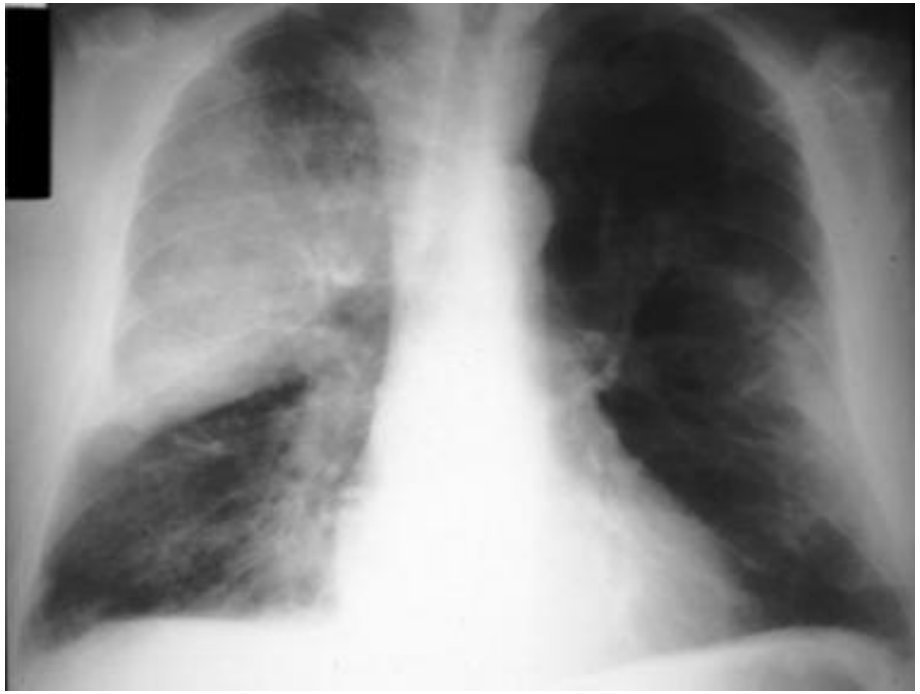
Safety is Important to Patients

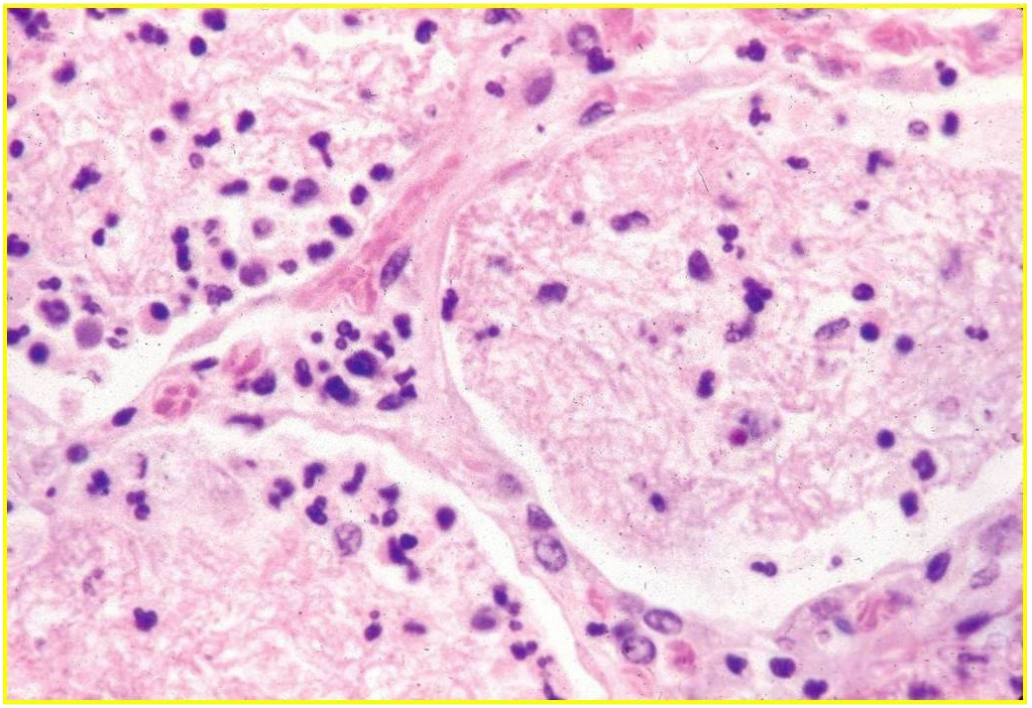


RFIPC Items Ranked	M0	M3	M6	M9	M12
Having an ostomy bag	1	2	1	1	1
Uncertain nature of disease	2	1	2	3	3
Energy level	3	4	4	4	4
Having surgery	4	3	3	2	2
Pain or suffering	5	5	6	7	8
Eating normally	6	10	10	10	12
Feelings about my body	7	6	5	5	5
Effects of medication	8	8	9	9	7
Moving difficulties	9	9	8	8	9
Loss of bowel control	10	7	7	6	6
Ability to achieve full potential	11	13	11	12	11
Leading a normal life	12	12	12	11	10
Being a burden on others	13	11	13	13	13
Developing cancer	14	15	15	14	15
Producing unpleasant odors	15	16	16	15	14
Intimacy	16	14	14	16	16
Financial difficulties	17	20	17	22	22
Loss of sex drive	18	18	18	17	17
Feeling out of control	19	22	19	19	21
Dying early	20	19	22	18	19
Feeling alone	21	21	20	20	20
Attractiveness	22	19	21	21	18
Ability to have a child	23	24	25	24	26
Ability to perform sexually	24	23	23	25	23
Being treated as different	25	25	26	26	25
Feeling dirty/smelly	26	26	24	23	24
Having access to quality medical care	27	27	27	27	27
Passing the disease to others	28	28	28	28	28

By Haragayato .wikimedia.org, Blondel-Kucharski F. et al. Am J Gastroenterol. 2001;96(10):2915-20

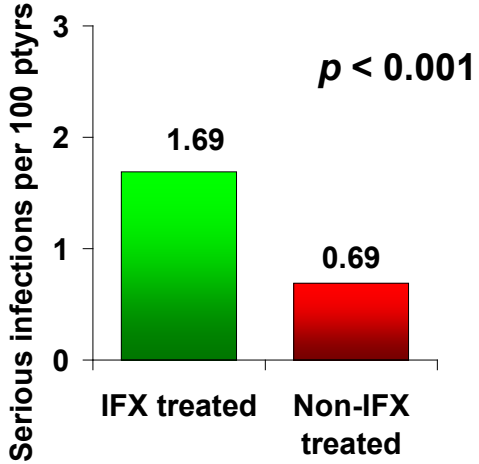
Lobar Pneumonia with Pneumococcus



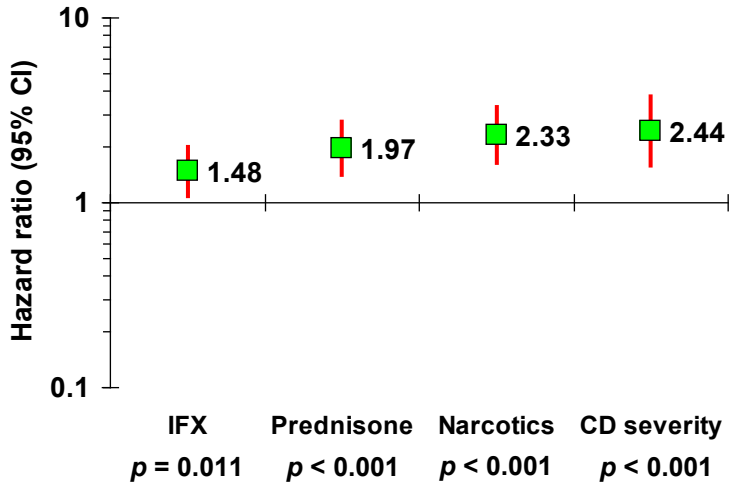


TREAT: Risk Factors for Serious Infections

Univariate



Multivariate predictors of serious infection

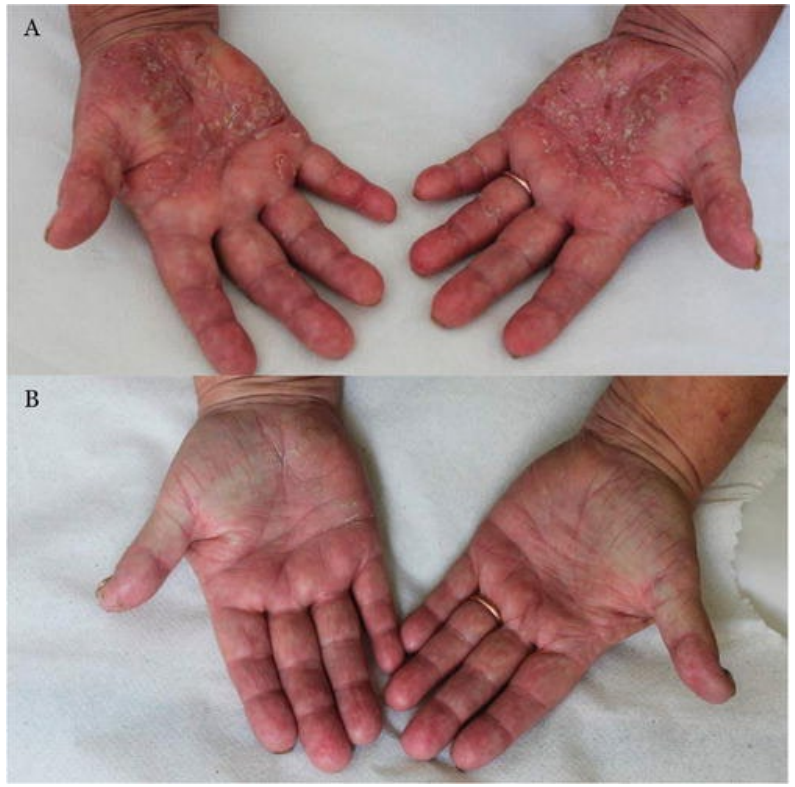


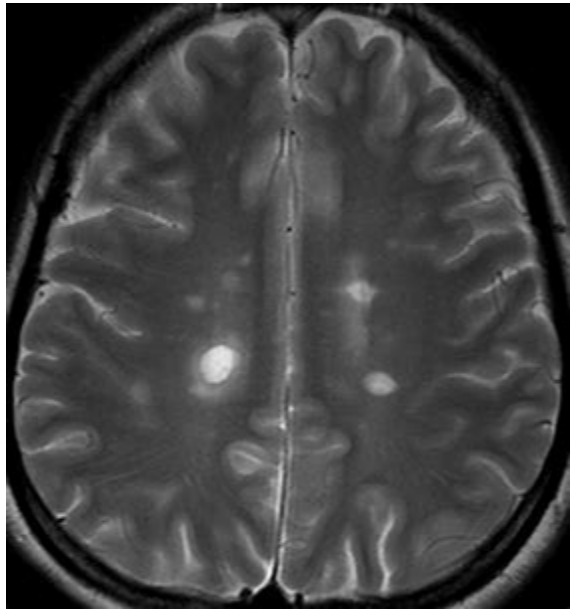
IFX use was associated with an increased incidence of serious infections (unadjusted)

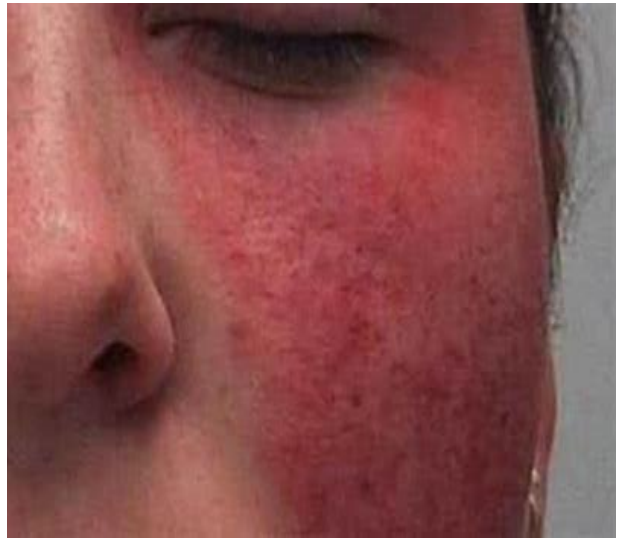
(RR=2.47, 95% CI=1.55-3.93, p<0.001)

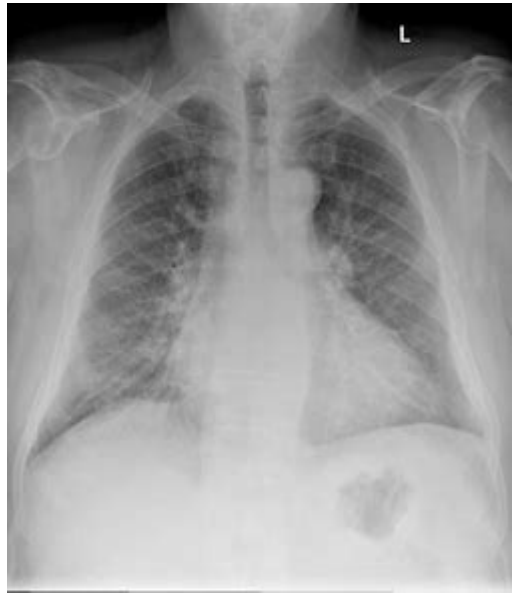
Lichtenstein, et al. DDW 2010: Abstract #T1040

TNF Antagonists - Additional Grief

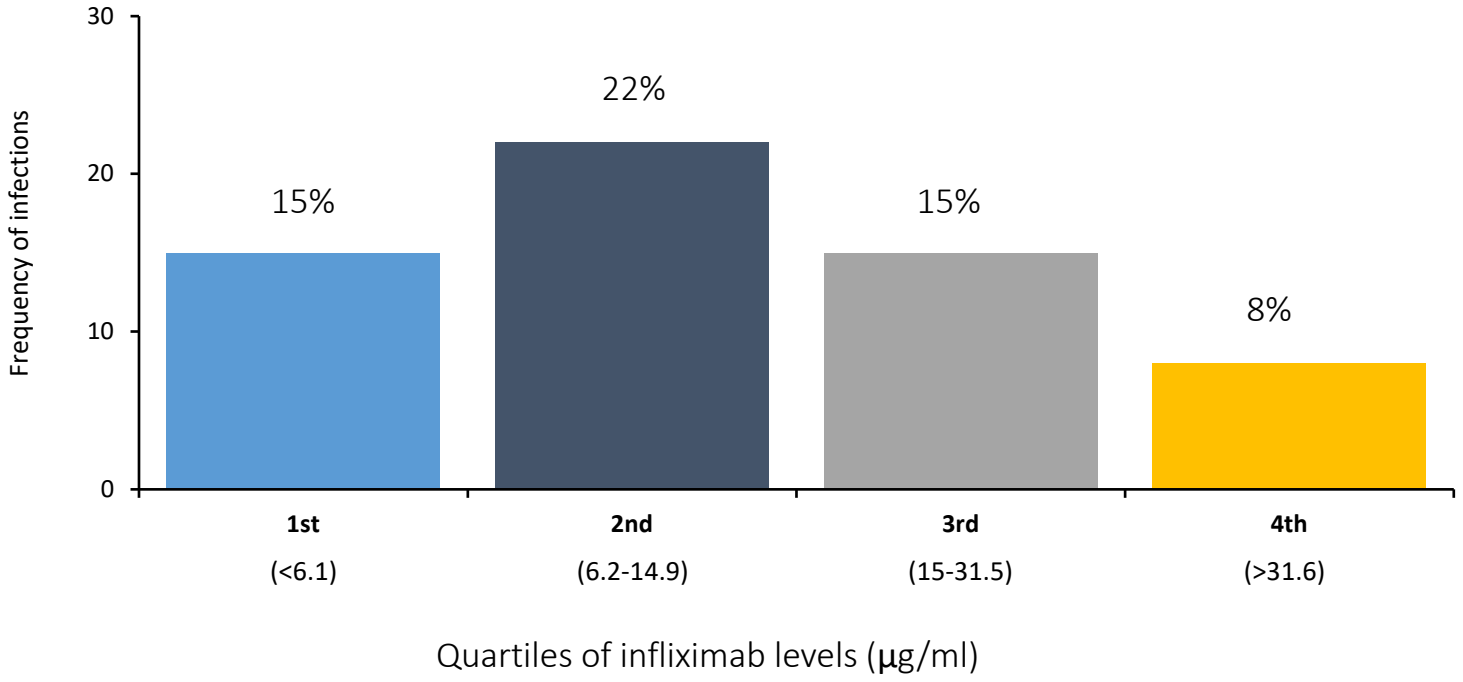








Higher Infliximab Exposure is NOT Associated with an Increased Risk of AEs

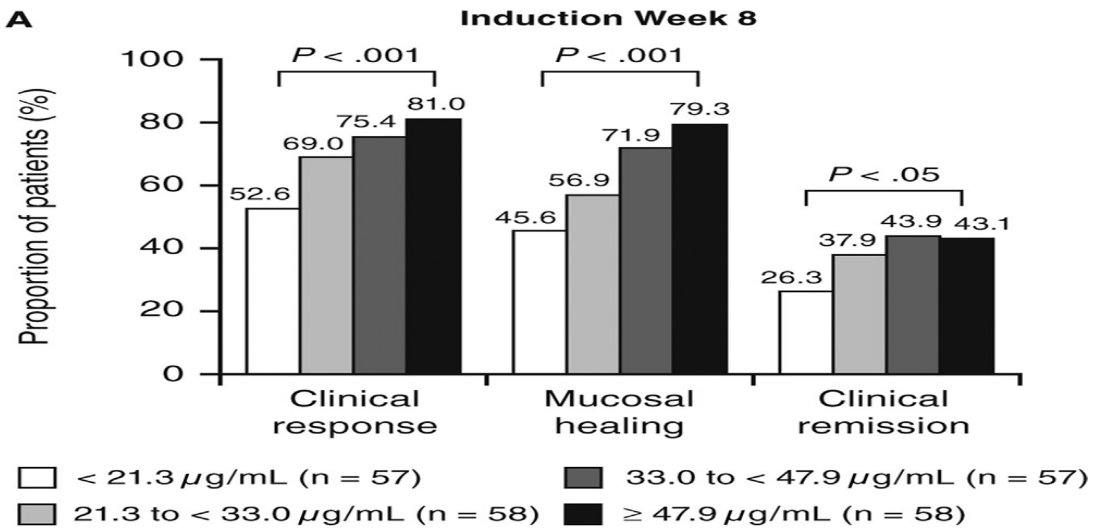


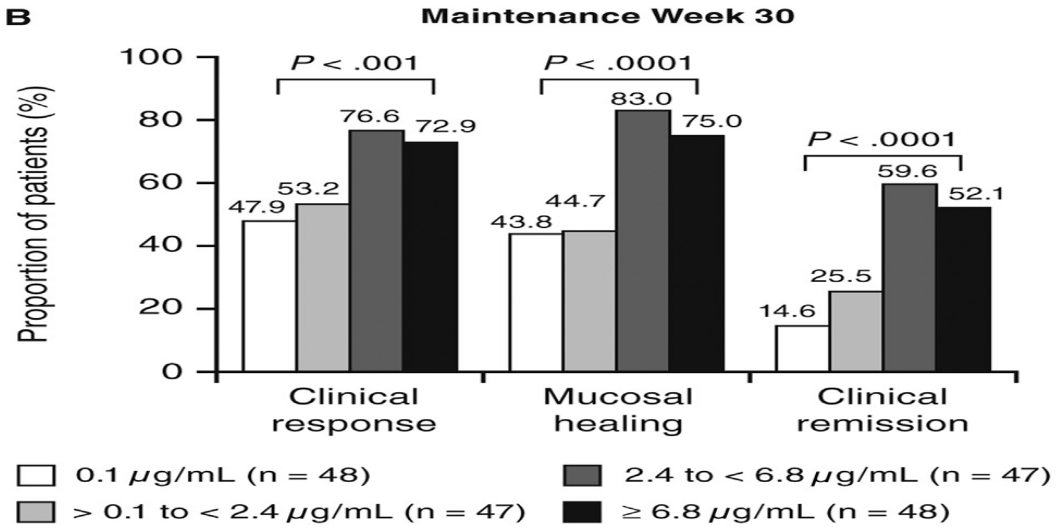
Reference. Inflamm Bowel Dis. 2018;24(8):1808-1814

Exposure –Response Relationship (IFX-UC)
A Decade of Quartile Analyses!

Post hoc analysis ACT 1 & 2

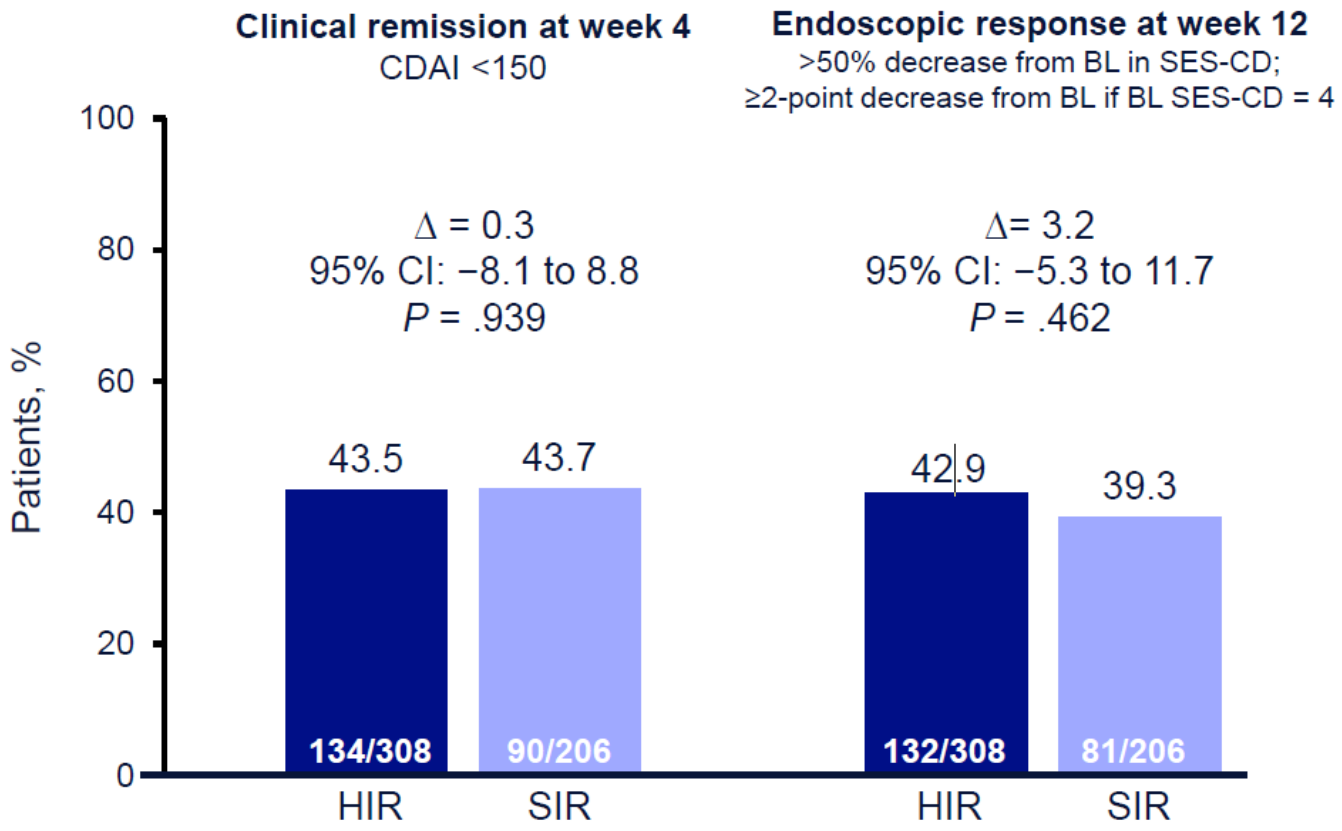
- 242 patients with UC
- IFX 5 mg/kg at weeks 0-2-6
  - 5 mg/kg q8 w
- IFX trough concentration quartile analysis at week 8, 30 and 54





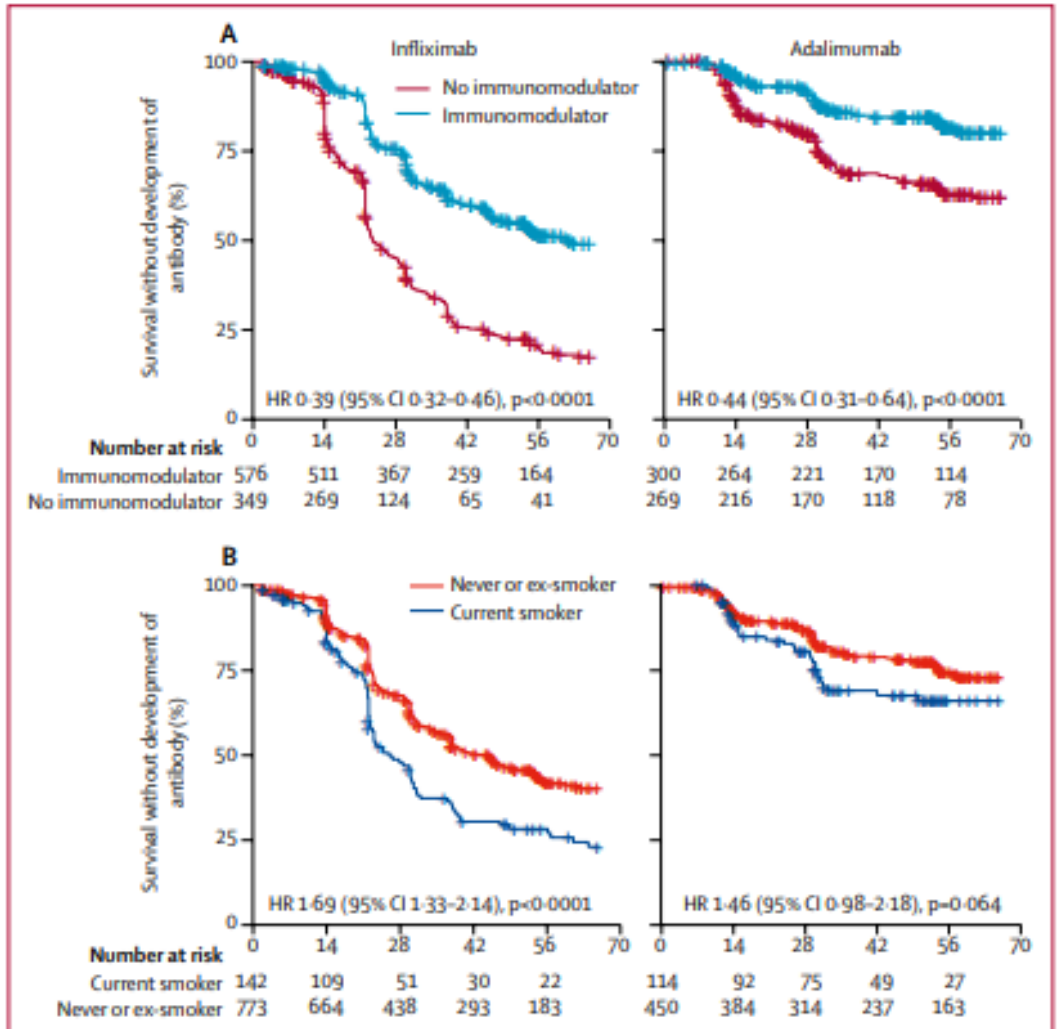
Reference: Adedokun OJ, *et al. Gastroenterology* 2014;147(6):1296-1307

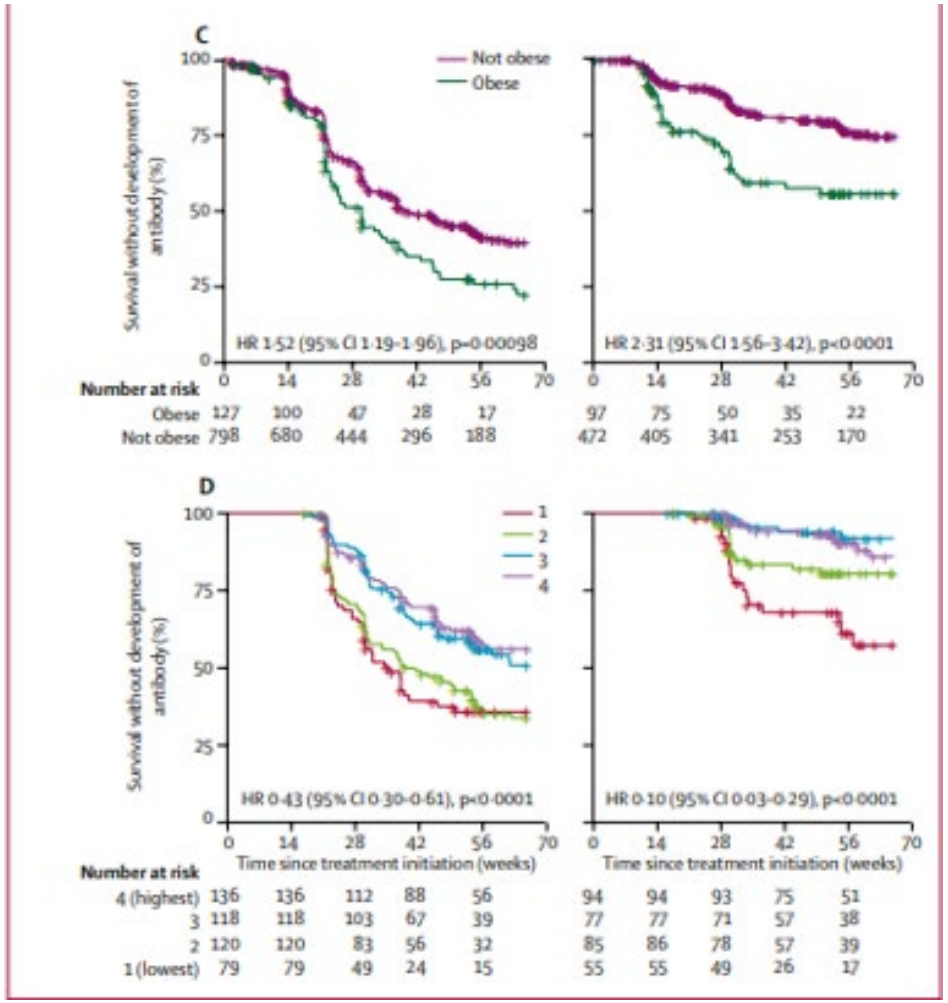
Clinical Remission at Week 4 and Endoscopic Response at Week 12
SERENE CD



D'Haens et al. Gastroenterology 2022. 162:1876-1890.

Univariable associations of time to immunogenicity using Kaplan-Meier and Cox proportional hazards methods – PANTS Study





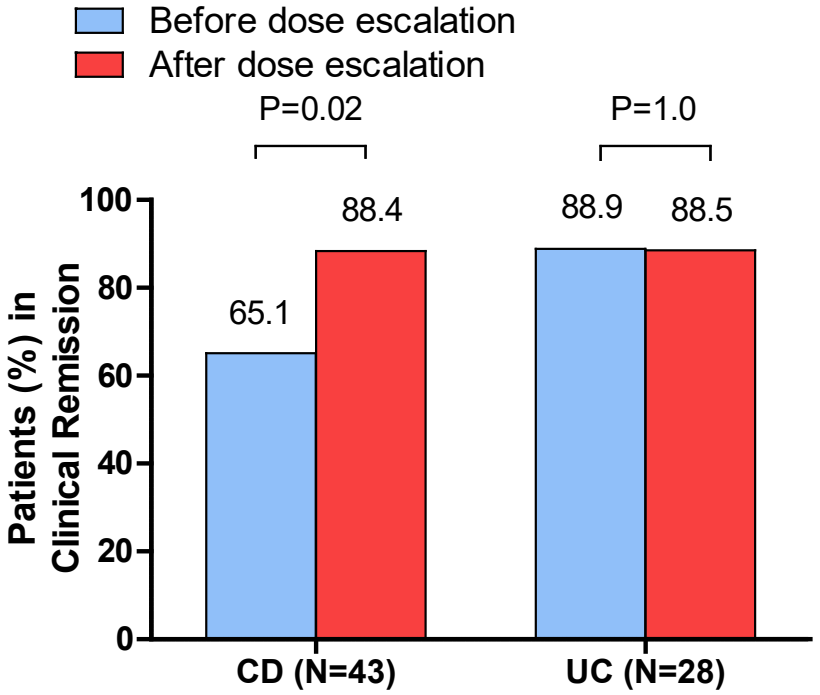
Kennedy, NA. et al. Lancet Gastroenterol Hepatol 2019; 4:341–53

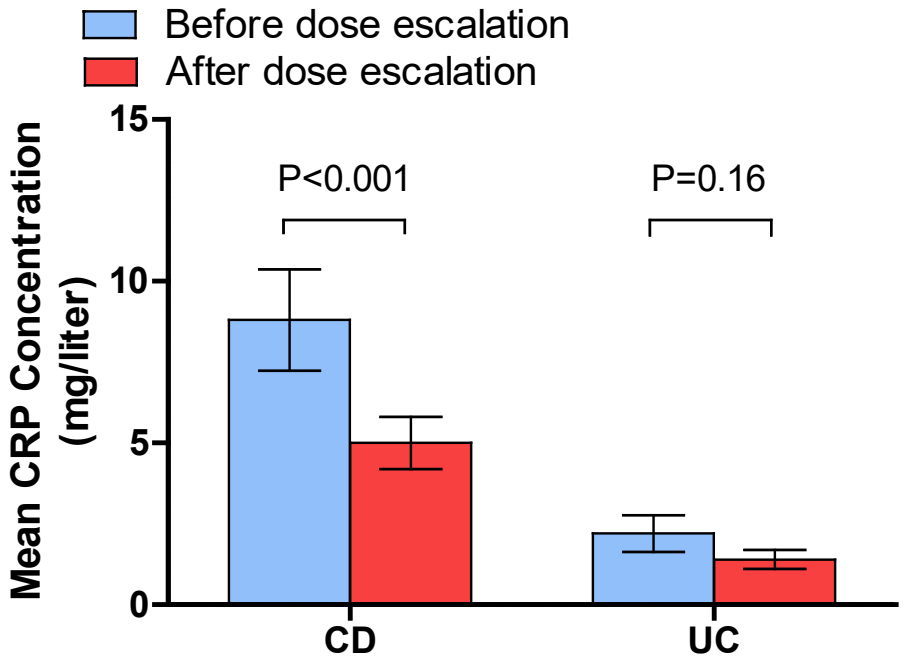
TDM for Secondary Loss of Response

Drug Concentration / Anti-drug Abs	Subtherapeutic drug trough concentration	Therapeutic drug trough concentration
Undetectable ADAb	**Nonimmune-mediated pharmacokinetic failure** **51%** ↓ Dose escalate by either increasing the dose or decreasing the interval between drug administrations	**Mechanistic or pharmacodynamic failure** **25%** ↓ Switch to drug out of class
Detectable ADAb	**Immune-mediated pharmacokinetic failure** **19%** ↓ Switch to drug in class and consider adding an immunomodulator	**Mechanistic or pharmacodynamic failure** **5%** ↓ Switch to drug out of class and consider adding an immunomodulator

Vande Casteele N, *et al. Gastroenterology* 2017;153(3):835-857.e6.

TAXIT Optimization Phase
Dose Escalation



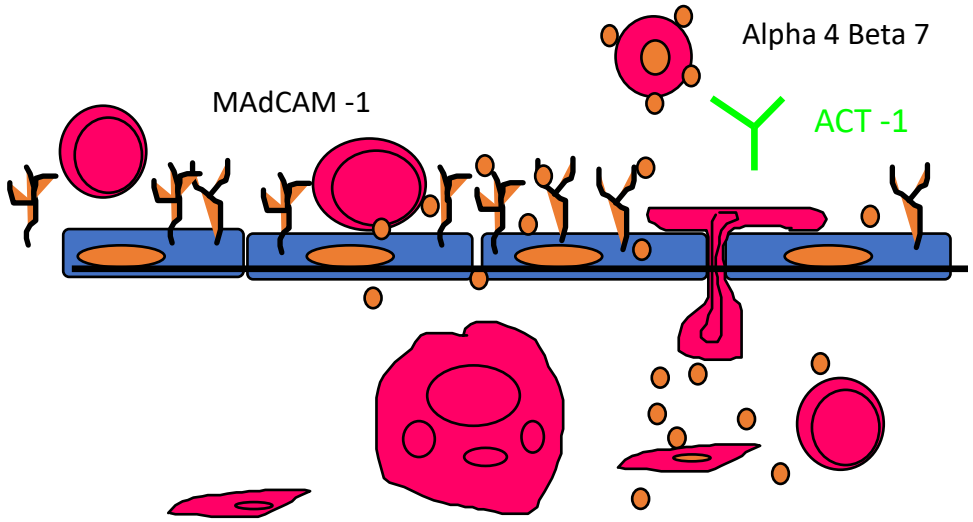


Dose escalation in Crohn's disease patients with subtherapeutic concentrations resulted in better disease control

Vande Casteele N, *et al. Gastroenterology* 2015;148(7):1320-1329.e3.

Vedolizumab: Background

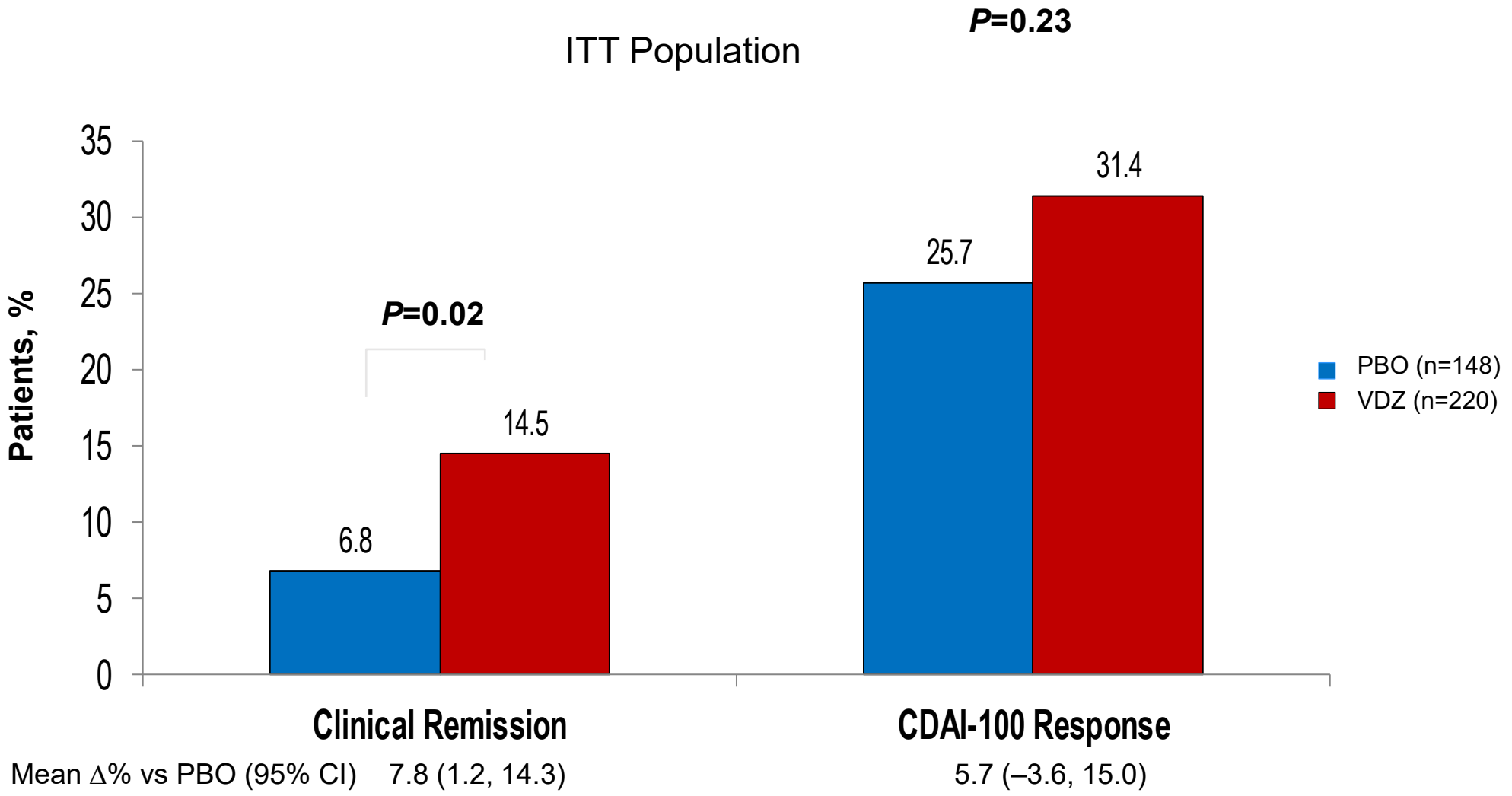
- Ligand for $\alpha_4\beta_7$ is MAdCAM
- Animal models show that ACT-1 selectively blocks trafficking of $\alpha_4\beta_7$ positive lymphocytes to the gut
- Raises possibility of gut specific immune modulation
- Striking benefit in cotton-top tamarin model



Hesterberg PE et al. Gastroenterology 1996;111:1373-80

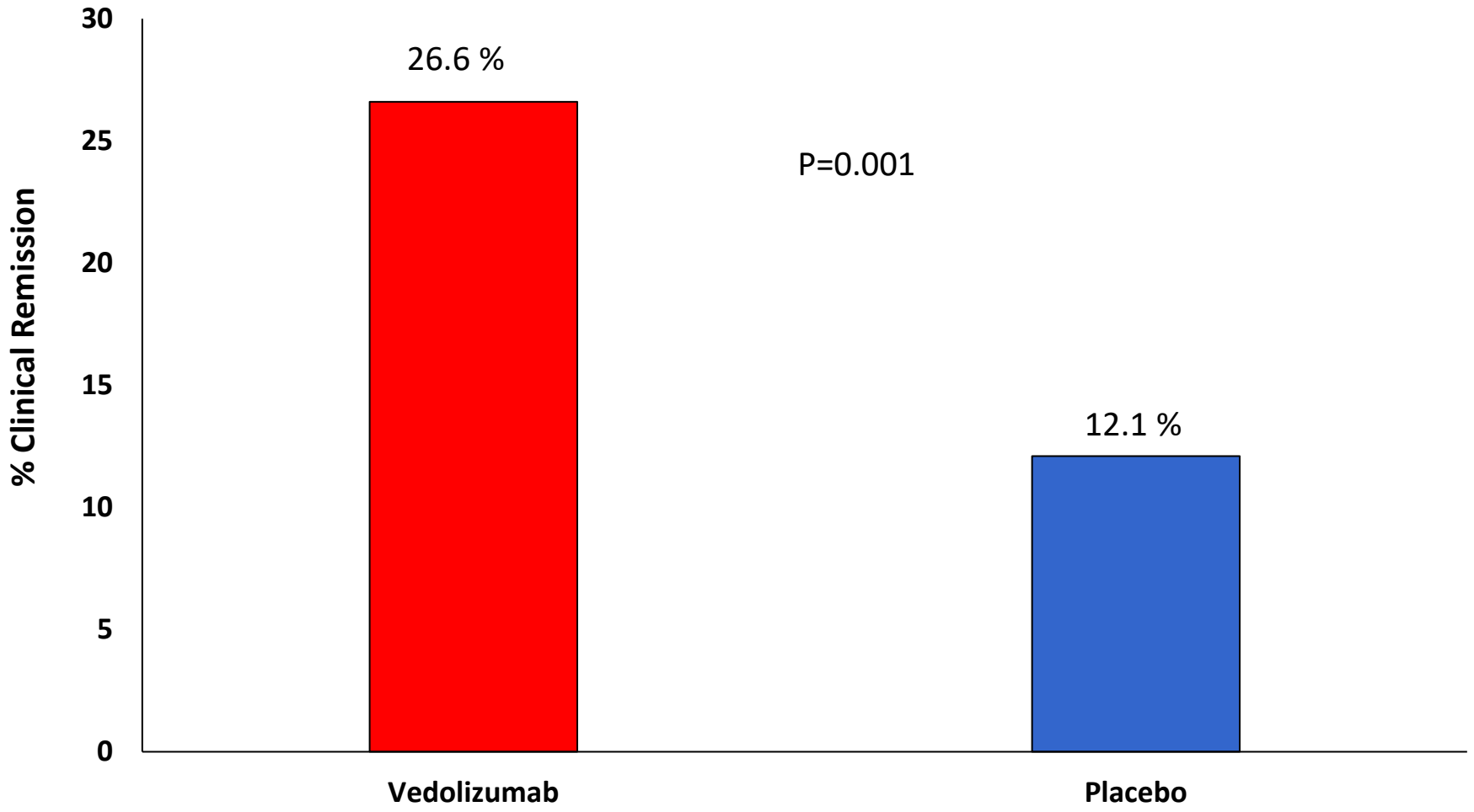
Podolsky et al. JCI 1993;92:372-80

GEMINI II CD: Clinical Remission and CDAI-100 Response at Week 6



Sandborn WJ. et al. New Eng J Med 2013;369(8):711-21.

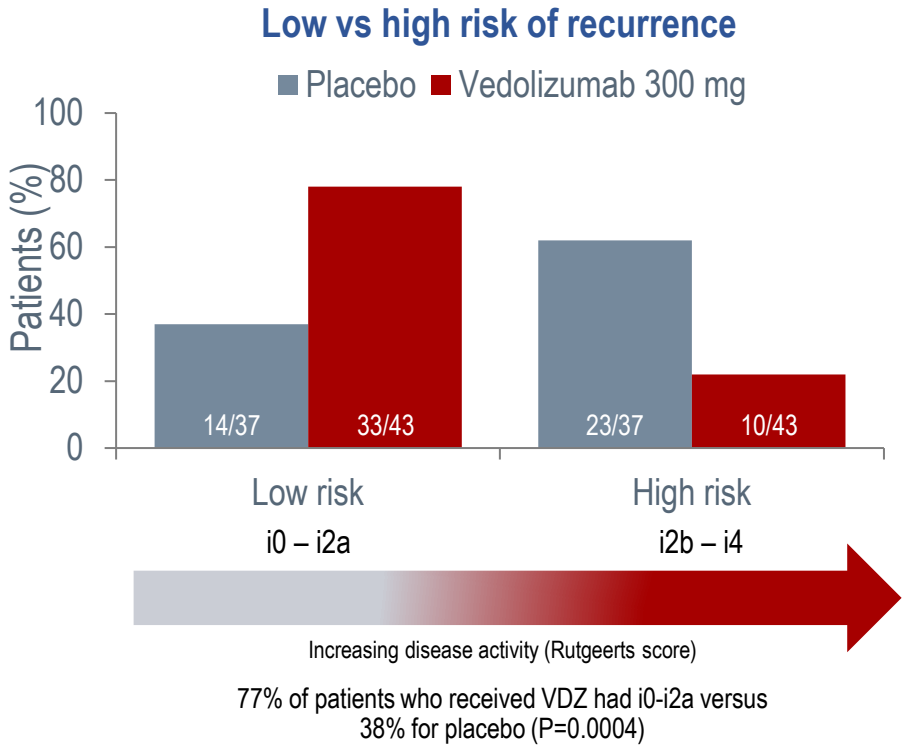
Vedolizumab Induction Therapy for Crohn's Disease Patients: TNF Antagonist Failure Population– 10 Week Data



Sands BE et al. Gastroenterology. 2014;147:618-627.

REPREVIO: Vedolizumab for Post-Operative CD

- VDZ illustrates efficacy in a difficult to treat patient population
- Confers striking efficacy in an area of unmet medical need



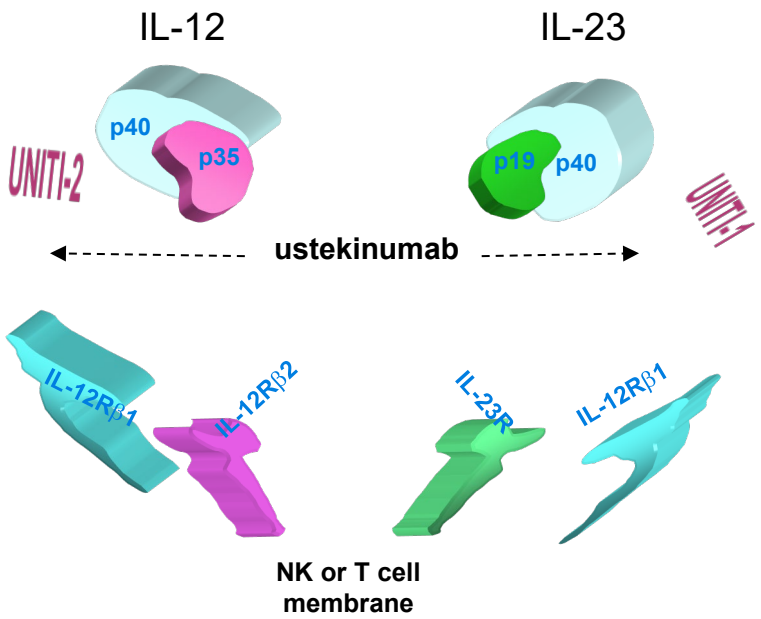
D'Haens et al presented at ECCO 2023 OP14. Copenhagen, Denmark; Not approved by Health Canada in the Product Monograph

Exposure-Adjusted Incidence Rates of Infections in the Overall Safety Population

	Placebo		Vedolizumab	
	UC and CD (n = 504)[a]		UC and CD (n = 2830)[d]	
Adverse event: Infection	No. of patients with event	No. of patients with event/100 PY (95% CI)	No. of patients with event	No. of patients with event/100 PY (95% CI)
Any infection[e]	139	82.9 (68.3-97.5)	1606	63.5 (59.6-67.3)
Upper respiratory tract infections	67	34.7 (26.0-43.3)	967	28.6 (26.6-30.6)
Lower respiratory tract and lung infections	16	7.7 (3.9-11.5)	270	6.1 (5.3-6.8)

Colombel JF et al. GUT 2016 Feb 18

Anti-p40 Ustekinumab: Background



No IL-12 or IL-23 intracellular signal

- IL-12 & IL-23 are key cytokines in the pathogenic immune cascade of Crohn's disease
- Ustekinumab is a fully human IgG1k monoclonal antibody binding the **p40 subunit** of interleukin-12 and -23
- Inhibits IL-12- and IL-23-mediated signaling, cellular activation, and downstream cytokine production
- Approved for moderate to severe psoriasis and psoriatic arthritis
- Induction efficacy recently demonstrated in a broad CD population in UNITI-1[1] and UNITI-2[2]

[1] *Sandborn W, et al. Oral presentation. CCFA 2015 and Rutgeerts P, et al . Oral presentation. ECCO 2016.*
[2] *Feagan B, et al. Oral presentation. ACG and UEGW 2015.*

Sandborn W.J., et al. DDW 2016. Presentation 768.

The Evolution of Psoriasis Therapy 2000-2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Ustekinumab and Etanercept for Moderate-to-Severe Psoriasis

Christopher E.M. Griffiths, M.D., Bruce E. Strober, M.D., Ph.D., Peter van de Kerkhof, M.D., Vincent Ho, M.D., Roseanne Fidelus-Gort, Ph.D., Newman Yeilding, M.D., Cynthia Guzzo, M.D., Yichuan Xia, Ph.D., Bei Zhou, Ph.D., Shu Li, M.S., Lisa T. Dooley, Dr.P.H., Neil H. Goldstein, M.D., and Alan Menter, M.D., for the ACCEPT Study Group*

From the University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom (C.E.M.G.); New York University Medical Center, New York (B.E.S.); University Hospital Nijmegen, Nijmegen, the Netherlands (P.K.); University of British Columbia, Vancouver, BC, Canada (V.H.); Incyte Corporation, Wilmington, DE (R.F.-G.); Centocor Research and Development (N.Y., C.G., Y.X., B.Z., S.L., L.T.D.) and Precision Research (N.H.G.) — both in Malvern, PA; and the Psoriasis Research Unit, Baylor University Medical Center, Dallas (A.M.). Address reprint requests to Dr. Griffiths at the Dermatology Centre, Salford Royal Hospital, University of Manchester, Manchester M6 8HD, United Kingdom, or at christopher.griffiths@manchester.ac.uk.

*The investigators participating in the Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial (ACCEPT) study group are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

This article (10.1056/NEJMoa0810652) was updated on January 25, 2010, at NEJM.org.

N Engl J Med 2010;362:118-28.

ABSTRACT

BACKGROUND

Biologic agents offer a range of new therapeutic options for patients with psoriasis; however, the relative benefit–risk profiles of such therapies are not well known. We compared two biologic agents, ustekinumab (an interleukin-12 and interleukin-23 blocker) and etanercept (an inhibitor of tumor necrosis factor α), for the treatment of psoriasis.

METHODS

We randomly assigned 903 patients with moderate-to-severe psoriasis to receive subcutaneous injections of either 45 or 90 mg of ustekinumab (at weeks 0 and 4) or high-dose etanercept (50 mg twice weekly for 12 weeks). The primary end point was the proportion of patients with at least 75% improvement in the psoriasis area-and-severity index (PASI) at week 12; a secondary end point was the proportion with cleared or minimal disease on the basis of the physician's global assessment. Assessors were unaware of the treatment assignments. The efficacy and safety of a crossover from etanercept to ustekinumab were evaluated after week 12.

RESULTS

There was at least 75% improvement in the PASI at week 12 in 67.5% of patients who received 45 mg of ustekinumab and 73.8% of patients who received 90 mg, as compared with 56.8% of those who received etanercept (P=0.01 and P<0.001, respectively). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.6% of patients who received 90 mg of ustekinumab had cleared or minimal disease according to the physician's global assessment, as compared with 49.0% of those who received etanercept (P<0.001 for both comparisons). Among patients who did not have a response to etanercept, 48.9% had at least 75% improvement in the PASI within 12 weeks after crossover to ustekinumab. One or more adverse events occurred through week 12 in 66.0% of patients who received 45 mg of ustekinumab and 69.2% of patients who received 90 mg of ustekinumab and in 70.0% who received etanercept; 1.9%, 1.2%, and 1.2%, respectively, had serious adverse events. Safety patterns were similar before and after crossover from etanercept to ustekinumab.

CONCLUSIONS

The efficacy of ustekinumab at a dose of 45 or 90 mg was superior to that of high-dose etanercept over a 12-week period in patients with psoriasis. (ClinicalTrials.gov number, NCT00454584.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis

M. Lebwohl, B. Strober, A. Menter, K. Gordon, J. Weglowska, L. Puig, K. Papp, L. Spelman, D. Toth, F. Kerdel, A.W. Armstrong, G. Stingl, A.B. Kimball, H. Bachelez, J.J. Wu, J. Crowley, R.G. Langley, T. Blicharski, C. Paul, J.-P. Lacour, S. Tyring, L. Kircik, S. Chimenti, K.C. Duffin, J. Bagel, J. Koo, G. Aras, J. Li, W. Song, C.E. Milmont, Y. Shi, N. Erondu, P. Klekotka, B. Kotzin, and A. Nirula

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Lebwohl at the Icahn Medical Institute, 2nd Fl., 1425 Madison Ave., New York, NY 10029, or at mark.lebwohl@mountsinai.org.

N Engl J Med 2015;373:1318-28.
DOI: 10.1056/NEJMoa1503824

ABSTRACT

BACKGROUND

Early clinical studies suggested that the anti–interleukin-17 receptor A monoclonal antibody brodalumab has efficacy in the treatment of psoriasis.

METHODS

In two phase 3 studies (AMAGINE-2 and AMAGINE-3), patients with moderate-to-severe psoriasis were randomly assigned to receive brodalumab (210 mg or 140 mg every 2 weeks), ustekinumab (45 mg for patients with a body weight ≤100 kg and 90 mg for patients >100 kg), or placebo. At week 12, patients receiving brodalumab were randomly assigned again to receive a brodalumab maintenance dose of 210 mg every 2 weeks or 140 mg every 2 weeks, every 4 weeks, or every 8 weeks; patients receiving ustekinumab continued to receive ustekinumab every 12 weeks, and patients receiving placebo received 210 mg of brodalumab every 2 weeks. The primary aims were to evaluate the superiority of brodalumab over placebo at week 12 with respect to at least a 75% reduction in the psoriasis area-and-severity index score (PASI 75) and a static physician's global assessment (sPGA) score of 0 or 1 (clear or almost clear skin), as well as the superiority of brodalumab over ustekinumab at week 12 with respect to a 100% reduction in PASI score (PASI 100).

RESULTS

At week 12, the PASI 75 response rates were higher with brodalumab at the 210-mg and 140-mg doses than with placebo (86% and 67%, respectively, vs. 8% [AMAGINE-2] and 85% and 69%, respectively, vs. 6% [AMAGINE-3]; P<0.001); the rates of sPGA scores of 0 or 1 were also higher with brodalumab (P<0.001). The week 12 PASI 100 response rates were significantly higher with 210 mg of brodalumab than with ustekinumab (44% vs. 22% [AMAGINE-2] and 37% vs. 19% [AMAGINE-3], P<0.001). The PASI 100 response rates with 140 mg of brodalumab were 26% in AMAGINE-2 (P=0.08 for the comparison with ustekinumab) and 27% in AMAGINE-3 (P=0.007). Rates of neutropenia were higher with brodalumab and with ustekinumab than with placebo. Mild or moderate candida infections were more frequent with brodalumab than with ustekinumab or placebo. Through week 52, the rates of serious infectious episodes were 1.0 (AMAGINE-2) and 1.3 (AMAGINE-3) per 100 patient-years of exposure to brodalumab.

CONCLUSIONS

Brodalumab treatment resulted in significant clinical improvements in patients with moderate-to-severe psoriasis. (Funded by Amgen; AMAGINE-2 and AMAGINE-3 ClinicalTrials.gov numbers, NCT01708603 and NCT01708629.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis

Kim A. Papp, M.D., Ph.D., Andrew Blauvelt, M.D., Michael Bukhalo, M.D., Melinda Gooderham, M.D., James G. Krueger, M.D., Ph.D., Jean-Philippe Lacour, M.D., Alan Menter, M.D., Sandra Philipp, M.D., Howard Sofen, M.D., Stephen Tyring, M.D., Ph.D., Beate R. Berner, M.D., Sudha Visvanathan, Ph.D., Chandrasena Pamulapati, Ph.D., Nathan Bennett, Ph.D., Mary Flack, M.D., Paul Scholl, M.B., B.Chir., and Steven J. Padula, M.D.

From K. Papp Clinical Research and Probity Medical Research, Waterloo, ON (K.A.P.), School of Medicine, Queen's University, Kingston, ON (M.G.), and Centre for Dermatology and Probity Medical Research, Peterborough, ON (M.G.) — all in Canada; Oregon Medical Research Center, Portland (A.B.); Altman Dermatology Associates, Arlington Heights, IL (M.B.); Rockefeller University, New York (J.G.K.); Hôpital de l'Archet, University of Nice–Sophia Antipolis, Nice, France (J.-P.L.); Baylor Research Institute, Dallas (A.M.); Charité Universitätsmedizin Berlin, Berlin (S.P.), Boehringer Ingelheim Pharma, Biberach (B.R.B.), and Boehringer Ingelheim Pharma, Ingelheim, (S.J.P.) — all in Germany; University of Texas Health Science Center, Houston (S.T.); University of California, Los Angeles, School of Medicine, Los Angeles (H.S.); and Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (S.V., C.P., N.B., M.F., P.S.). Address reprint requests to Dr. Papp at Probity Medical Research, 135 Union St. E., Waterloo, ON N2J 1CE, Canada, or at kapapp@probity.medical.com.

N Engl J Med 2017;376:1551-60.
DOI: 10.1056/NEJMoa1607017

ABSTRACT

BACKGROUND

Interleukin-23 is thought to be critical to the pathogenesis of psoriasis. We compared risankizumab (BI 655066), a humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specifically targeting the p19 subunit and thus prevents interleukin-23 signaling, and ustekinumab, an interleukin-12 and interleukin-23 inhibitor, in patients with moderate-to-severe plaque psoriasis.

METHODS

We randomly assigned a total of 166 patients to receive subcutaneous injections of risankizumab (a single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg, according to body weight, at weeks 0, 4, and 16). The primary end point was a 90% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12.

RESULTS

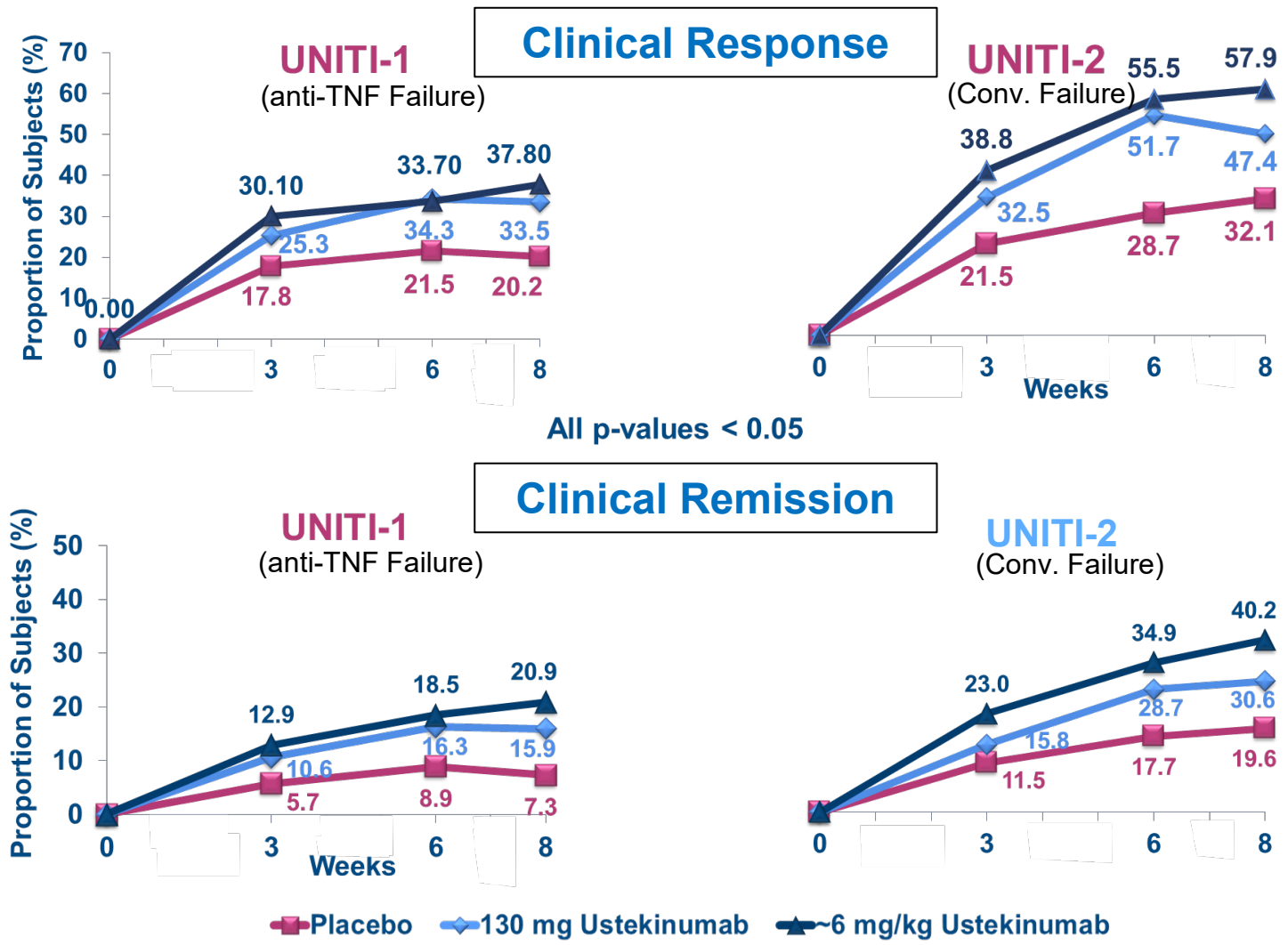
At week 12, the percentage of patients with a 90% or greater reduction in the PASI score was 77% (64 of 83 patients) for risankizumab (90-mg and 180-mg groups, pooled), as compared with 40% (16 of 40 patients) for ustekinumab (P<0.001); the percentage of patients with a 100% reduction in the PASI score was 45% in the pooled 90-mg and 180-mg risankizumab groups, as compared with 18% in the ustekinumab group. Efficacy was generally maintained up to 20 weeks after the final dose of 90 or 180 mg of risankizumab. In the 18-mg and 90-mg risankizumab groups and the ustekinumab group, 5 patients (12%), 6 patients (15%), and 3 patients (8%), respectively, had serious adverse events, including two basal-cell carcinomas and one major cardiovascular adverse event; there were no serious adverse events in the 180-mg risankizumab group.

CONCLUSIONS

In this phase 2 trial, selective blockade of interleukin-23 with risankizumab was associated with clinical responses superior to those associated with ustekinumab. This trial was not large enough or of long enough duration to draw conclusions about safety. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT02054481.)

Griffiths CE. et al. N Eng J Med. 2010;362(2):118-28
Lebwohl M et al. N Eng J Med. 2015;373(14):1318-28.
Papp KA, et al. N Eng J Med. 2017;376(16):1551-1560.

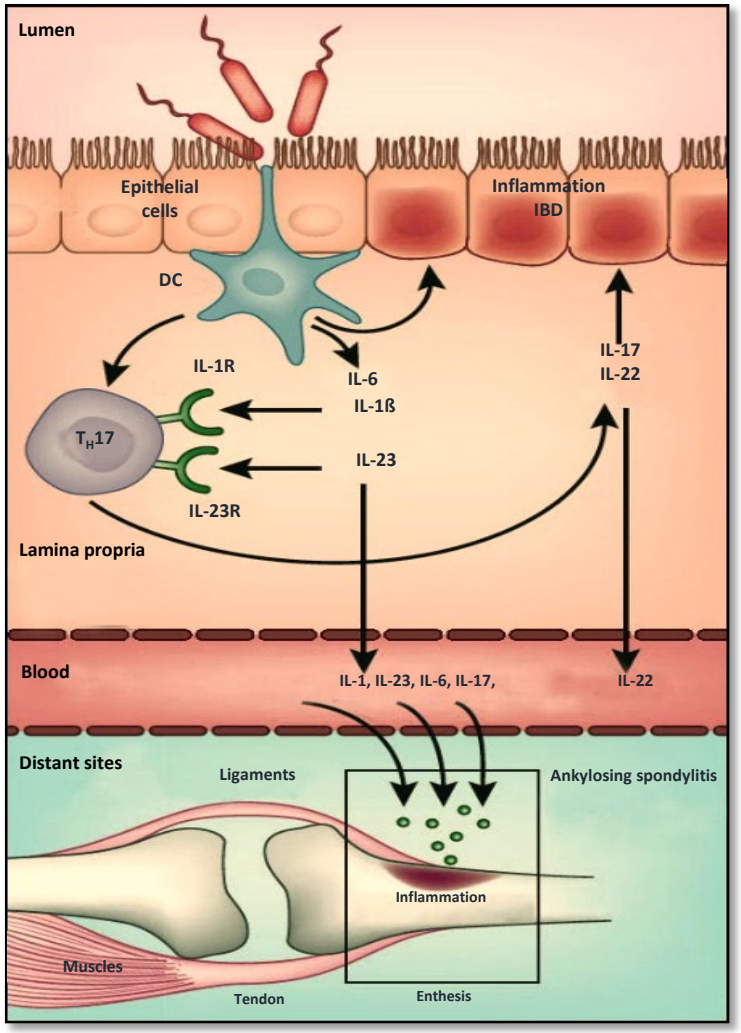
Ustekinumab Clinical Response and Remission Through Week 8



Feagan et al New Eng J Med 2016.

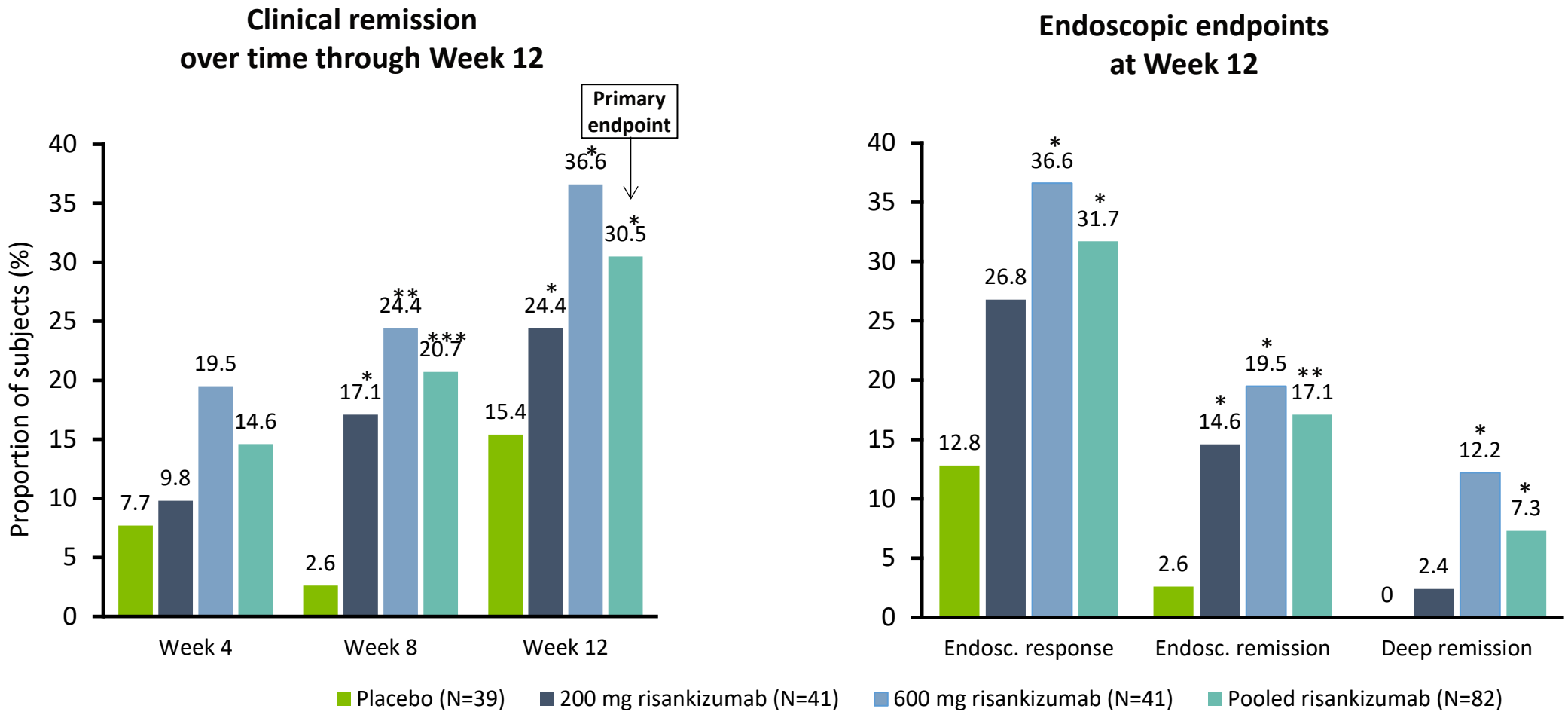
Why is Blockade of IL-23 Safe?

- IL-23 is a key cytokine that is triggered when the microbiome barrier is disrupted
  - **IL-23 producing cells are 'sentinels'** that become activated when microbiome is disrupted
- IL-23 sensitivity associated with IBD, psoriasis, and enthesopathy (PSA,) AS
  - IL-23R SNPs
- IL-23 overproduction associated with IBD pathology
- Knockout mouse is immune competent!



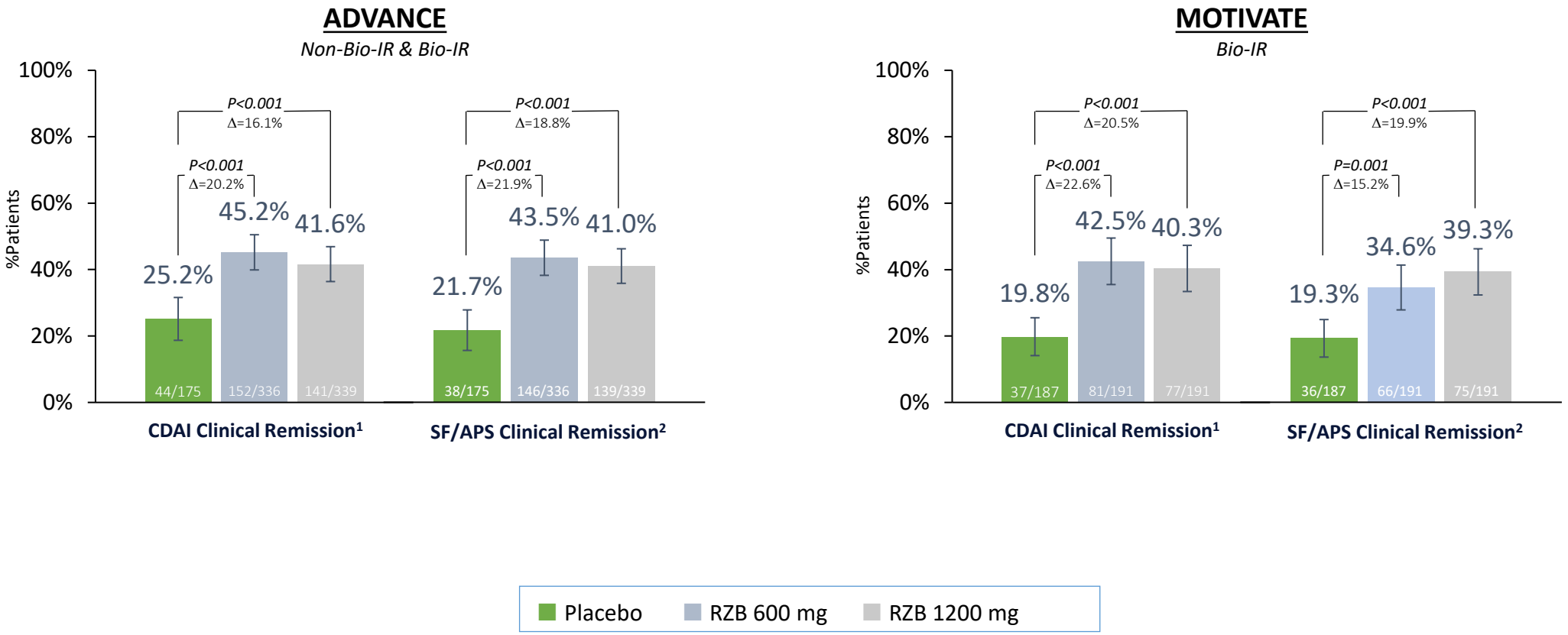
Adapted from: Cua DJ and Sherlock JP, Nat Med. 2011;17(9):1055–6

Risankizumab for CD: Is anti-P19 the Answer?



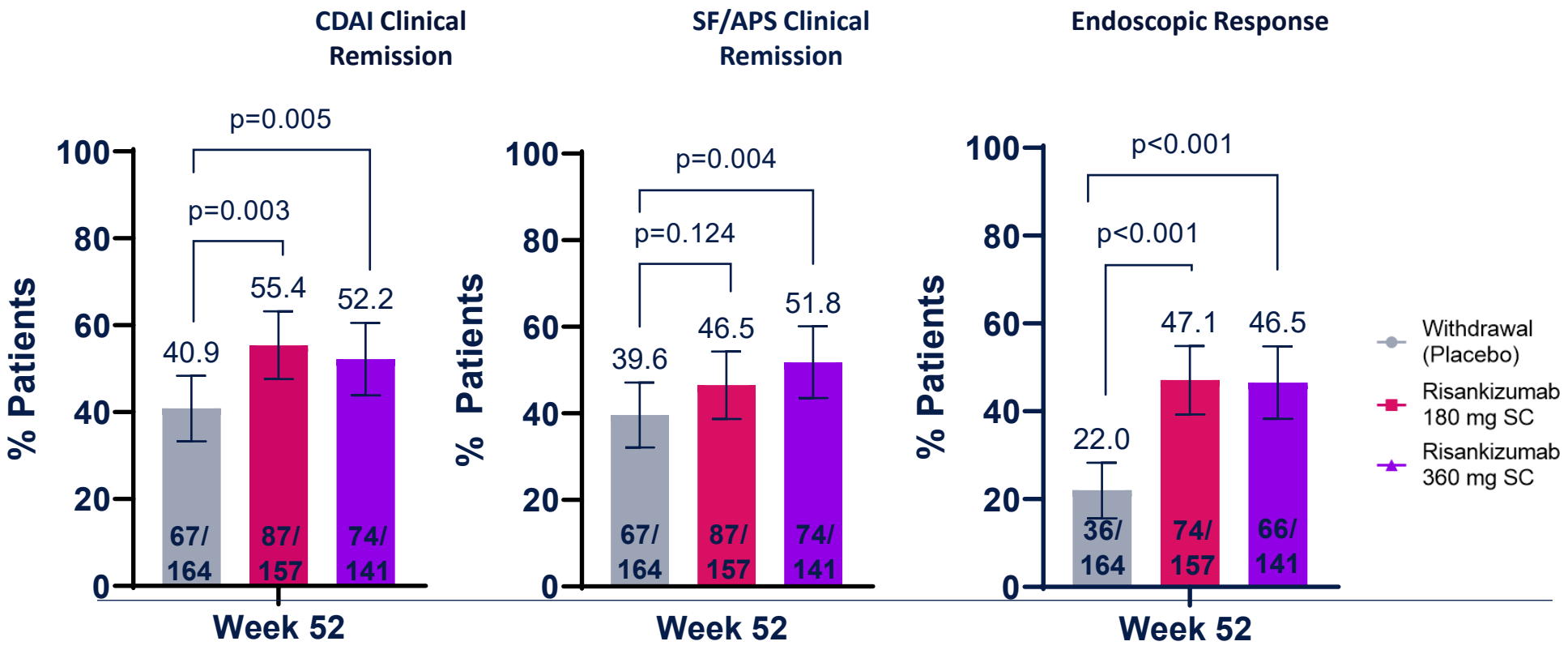
Feagan B, et al. Lancet 2017;389:1699–1709

Risankizumab Induction: Clinical Remission Week 12

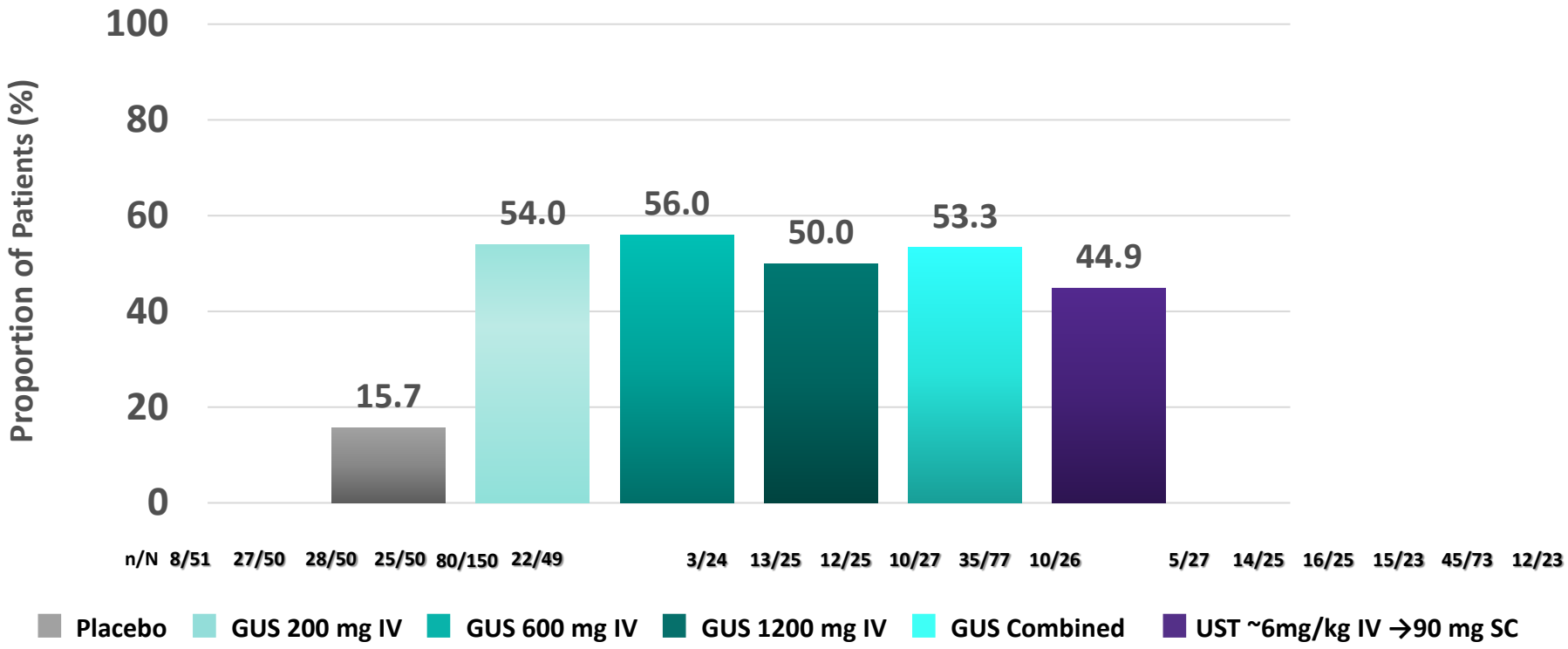


Ferrante et al UEGW 2021

Risankizumab for Maintenance
FORTIFY Co-Primary Endpoints- Week 52



GALAXI: Remission at Week 12



Clinical remission defined as CDAI score <150

Janus Kinase Inhibitors

The ORAL Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., Sujatha Menon, Ph.D., Yanhui Sun, Ph.D., Cunshan Wang, Ph.D., Andrea B. Shapiro, M.D., Keith S. Kanik, M.D., and Carol A. Connell, R.N., Ph.D., for the ORAL Surveillance Investigators*

From the Division of Rheumatology, Mayo Clinic, Rochester, MN (S.R.Y.); the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (D.L.B.); the Division of Rheumatology, University of Nebraska Medical Center, Omaha (T.R.M.); the Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill (G.G.K.); Metroplex Clinical Research Center and University of Texas Southwestern Medical Center, Dallas (R.F.); Pfizer, Madrid (J.L.R.); Pfizer, New York (R.G.); Pfizer, Groton, CT (S.M., C.W., K.S.K., C.A.C.); Pfizer, Shanghai, China (Y.S.); and Pfizer, Peapack, NJ (A.B.S.). Dr. Ytterberg can be contacted at ytterberg.steven@mayo.edu or at Mayo Clinic, 200 First St. SW, Rochester, MN 55905.

*A list of the ORAL Surveillance investigators is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2022;386:316-26.
DOI: 10.1056/NEJMoa2109927

ABSTRACT

BACKGROUND

Increases in lipid levels and cancers with tofacitinib prompted a trial of major adverse cardiovascular events (MACE) and cancers in patients with rheumatoid arthritis receiving tofacitinib as compared with a tumor necrosis factor (TNF) inhibitor.

METHODS

We conducted a randomized, open-label, noninferiority, postauthorization, safety end-point trial involving patients with active rheumatoid arthritis despite methotrexate treatment who were 50 years of age or older and had at least one additional cardiovascular risk factor. Patients were randomly assigned in a 1:1:1 ratio to receive tofacitinib at a dose of 5 mg or 10 mg twice daily or a TNF inhibitor. The coprimary end points were adjudicated MACE and cancers, excluding nonmelanoma skin cancer. The noninferiority of tofacitinib would be shown if the upper boundary of the two-sided 95% confidence interval for the hazard ratio was less than 1.8 for the combined tofacitinib doses as compared with a TNF inhibitor.

RESULTS

A total of 1455 patients received tofacitinib at a dose of 5 mg twice daily, 1456 received tofacitinib at a dose of 10 mg twice daily, and 1451 received a TNF inhibitor. During a median follow-up of 4.0 years, the incidences of MACE and cancer were higher with the combined tofacitinib doses (3.4% [98 patients] and 4.2% [122 patients], respectively) than with a TNF inhibitor (2.5% [37 patients] and 2.9% [42 patients]). The hazard ratios were 1.33 (95% confidence interval [CI], 0.91 to 1.94) for MACE and 1.48 (95% CI, 1.04 to 2.09) for cancers; the noninferiority of tofacitinib was not shown. The incidences of adjudicated opportunistic infections (including herpes zoster and tuberculosis), all herpes zoster (nonserious and serious), and adjudicated nonmelanoma skin cancer were higher with tofacitinib than with a TNF inhibitor. Efficacy was similar in all three groups, with improvements from month 2 that were sustained through trial completion.

CONCLUSIONS

In this trial comparing the combined tofacitinib doses with a TNF inhibitor in a cardiovascular risk–enriched population, risks of MACE and cancers were higher with tofacitinib and did not meet noninferiority criteria. Several adverse events were more common with tofacitinib. (Funded by Pfizer; ORAL Surveillance ClinicalTrials.gov number, NCT02092467.)

Serious Infections

incr. risk of serious infection leading to hospitalization or death; pulmonary and extrapulmonary TB, invasive fungal infections, and other opportunistic infections observed; most infections occur in combo w/ immunosuppressants; screen for latent TB infection before and during tofacitinib tx; initiate anti-TB tx before tofacitinib tx; weigh risk/benefit in pts w/ chronic or recurrent infection; monitor closely for infection s/sx during and after tx, incl. TB development in pts w/ negative TB test; D/C tofacitinib if serious infection develops

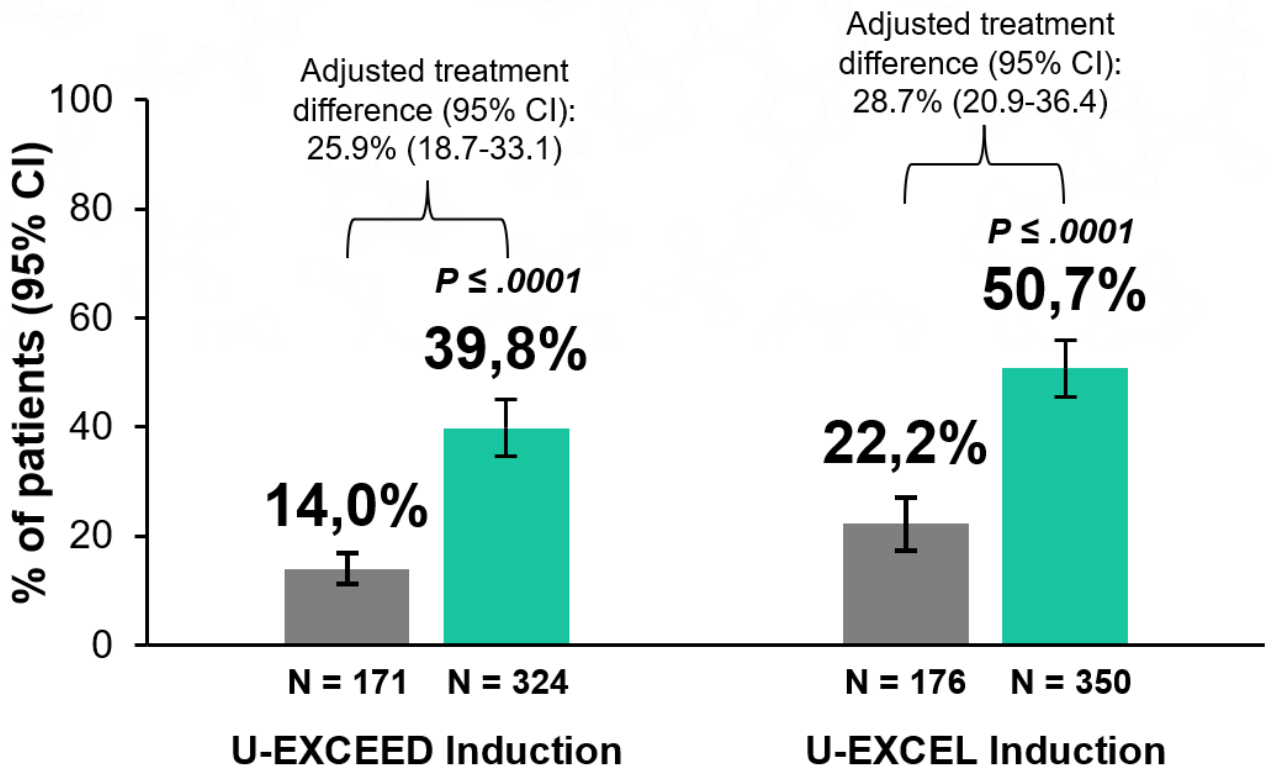
Malignancies

lymphoma and other malignancies observed; incr. rate of EBV-assoc. post-transplant lymphoproliferative dz observed in renal transplant pts receiving concomitant immunosuppressive meds

Upadacitinib: Clinical Remission (SF/APS) at Week 12

Co-primary endpoint

Daily SF ≤ 2.8 & daily APS ≤ 1 & not worse than BL



- Disease duration : 6-10 years
- CS : 35% and taper as of week 4
- Daily SF / AP : 6 / 2
- U-EXCEED : 100% BioIR (≥2 60%)
- U-EXCEL : 45% BioR (≥2 30%)

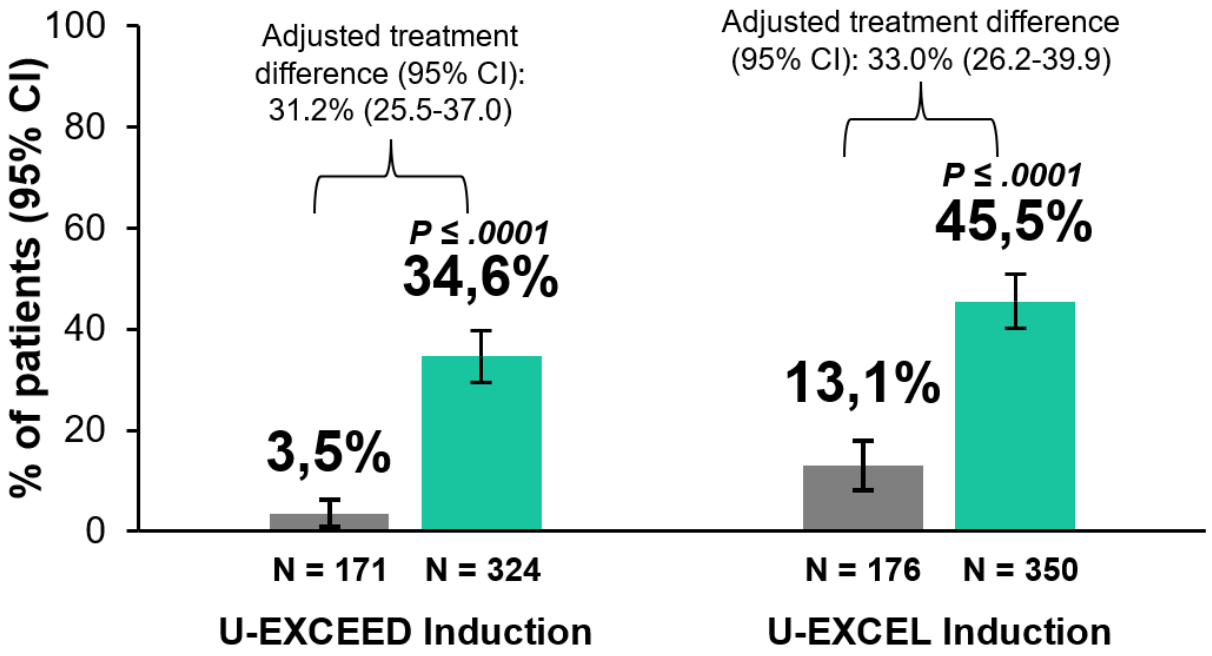
Placebo UPA 45 mg

APS, abdominal pain score; CI, confidence interval; COVID-19, coronavirus disease 2019; NRI-C, nonresponder imputation–COVID-19; SF, stool frequency; UPA, upadacitinib; wk, week. 1. Colombel JF, et al. Gastroenterology. 2022;162(7):S-1394. 2. Loftus EV Jr, et al. United European Gastroenterol J. 2022;10(S8):103-104. 3. Panes J, et al. Oral presentation at: the American College of Gastroenterology Annual Scientific Meeting; October 21-26, 2022; Charlotte, NC.

Upadacitinib :Endoscopic Response at week 12

Co-primary endpoint

Decrease in SES-CD of > 50%

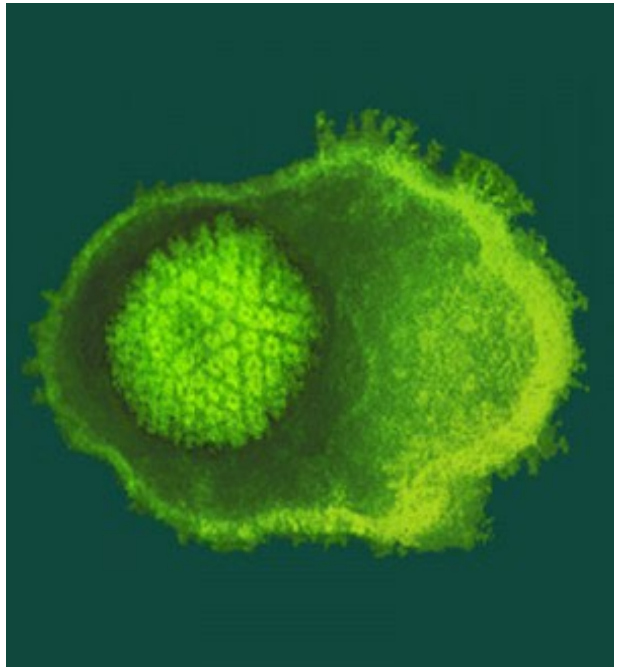


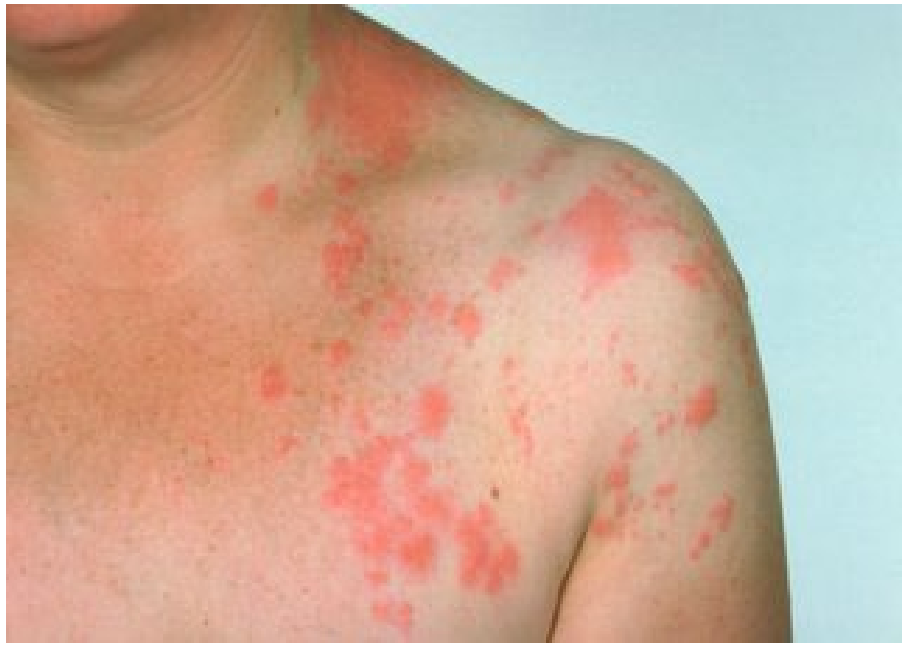
- **Disease duration : 6-10 years**
- **CS : 35%**
- **SES-CD : 14-15**
- **U-EXCEED : 100% BioIR (≥2 60%)**
- **U-EXCEL : 45% BioR (≥2 60%)**

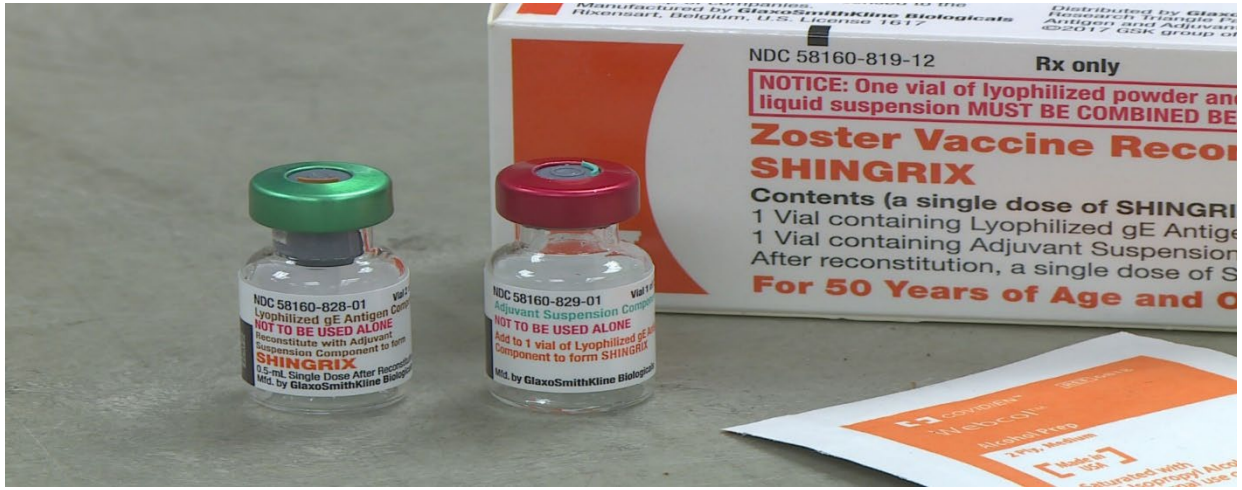
Placebo UPA 45 mg

APS, abdominal pain score; CI, confidence interval; COVID-19, coronavirus disease 2019; NRI-C, nonresponder imputation–COVID-19; SF, stool frequency; UPA, upadacitinib; wk, week. 1. Colombel JF, et al. Gastroenterology. 2022;162(7):S-1394. 2. Loftus EV Jr, et al. United European Gastroenterol J. 2022;10(S8):103-104. 3. Panes J, et al. Oral presentation at: the American College of Gastroenterology Annual Scientific Meeting; October 21-26, 2022; Charlotte, NC.

Varicella-Zoster Infection

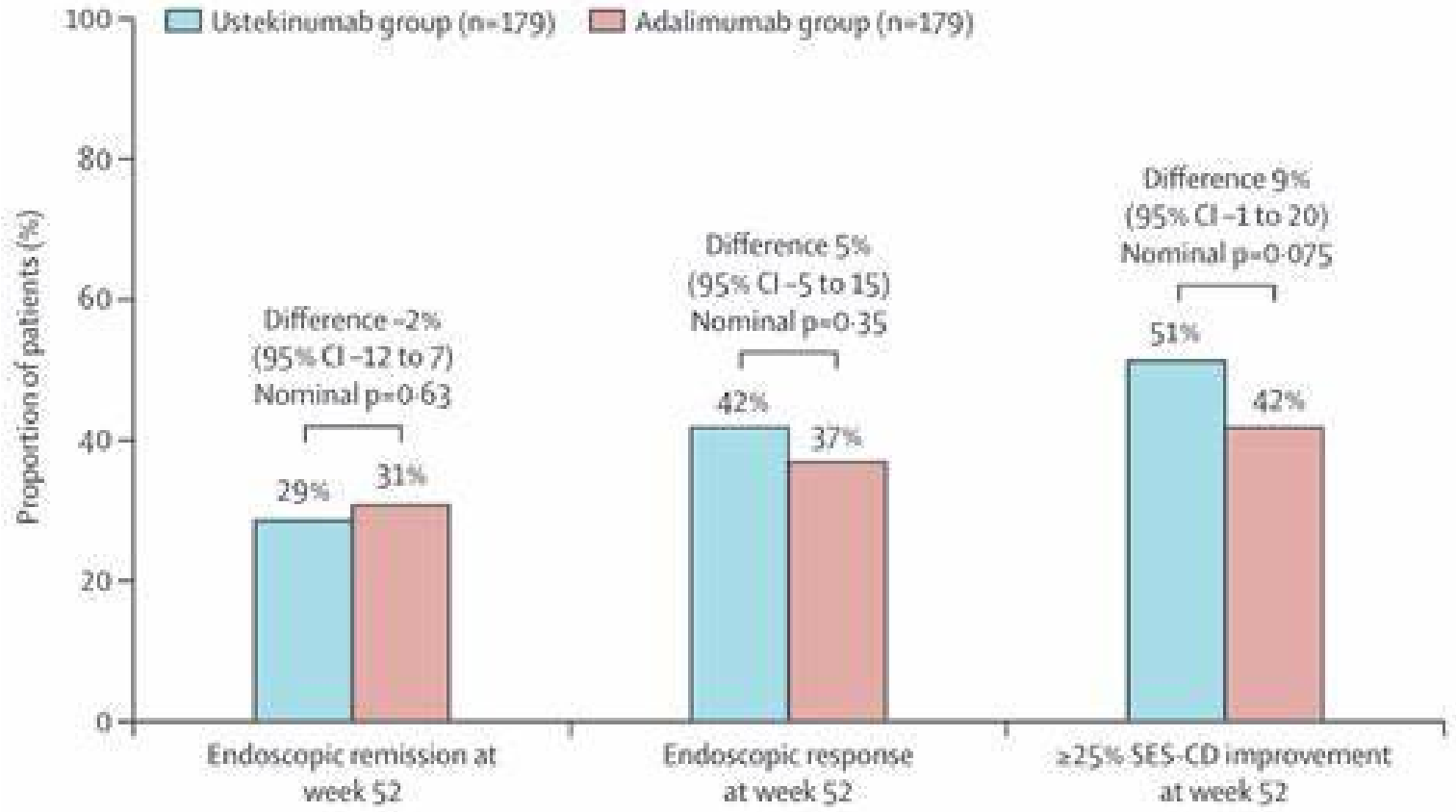






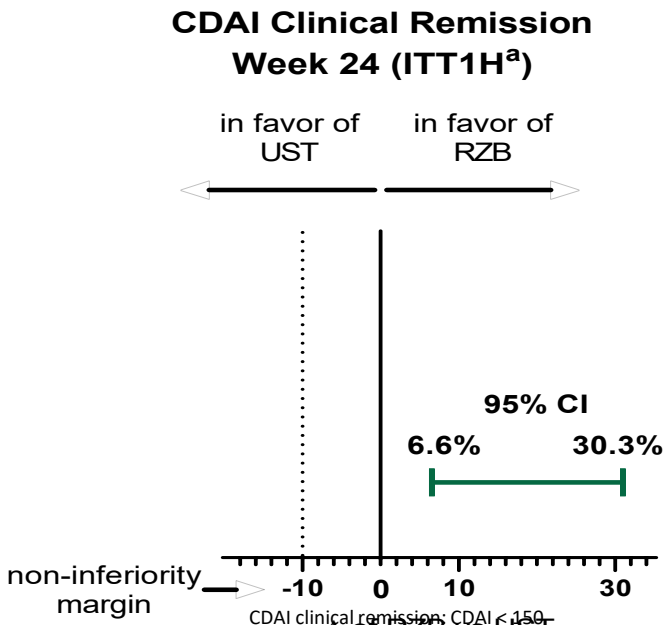
We Need More Comparative Effectiveness Studies!

SEAVUE ADA vs USTE



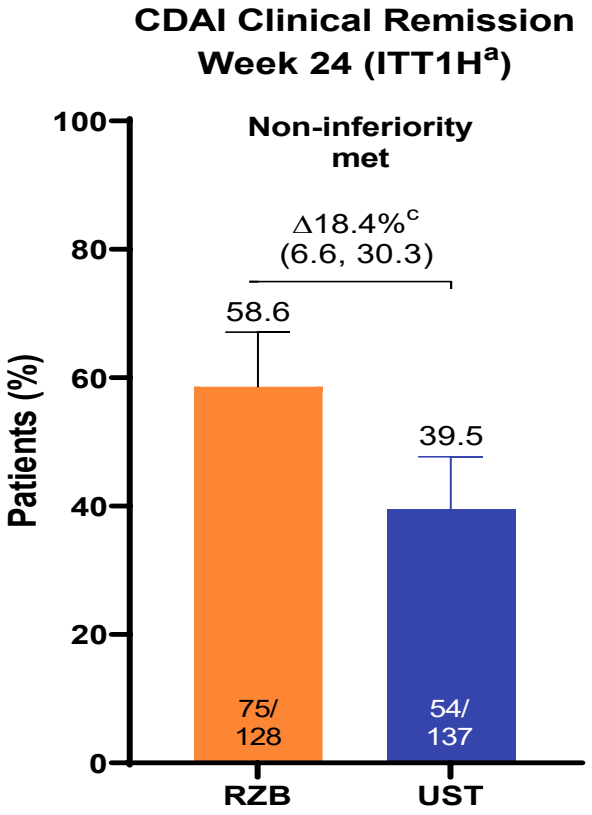
Sands B et al Lancet 2022

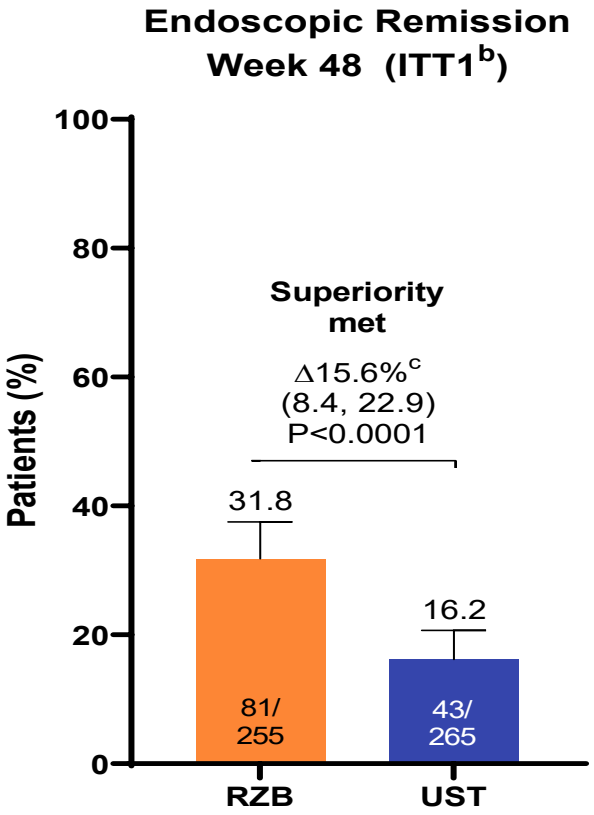
SEQUENCE: Risankizumab versus Ustekinumab: Week 24 and 48 Endpoints



CDAI clinical remission: CDAI < 150

Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore > 1 in any individual variable, as scored by a central reviewer





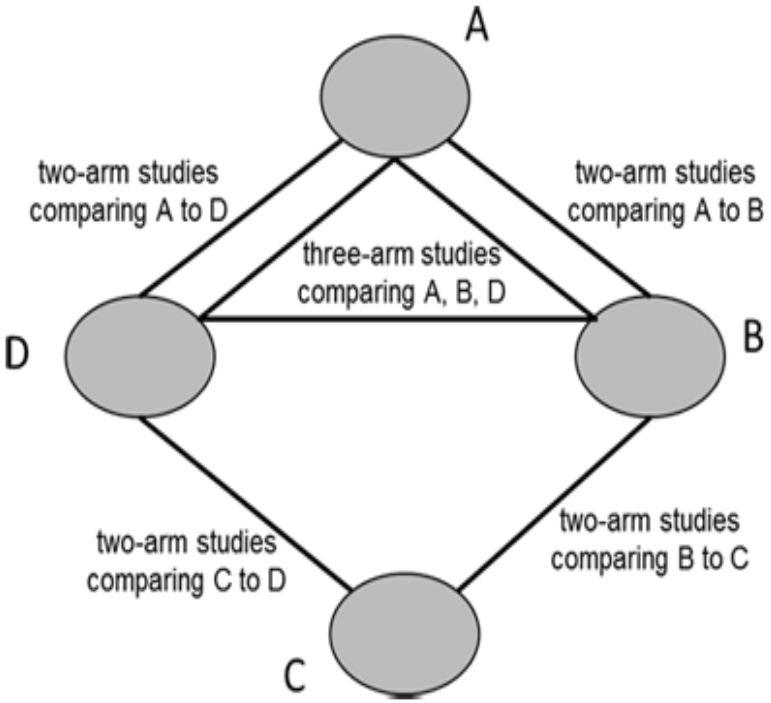
Nominal *P* <0.01 from a post hoc analysis testing for superiority

RISN-CA-00378-FM v1 October 2023

Peyrin-Biroulet, L et al. UEGW 2023

Network Meta-analysis

- compare three or more interventions across a network of studies.
- generates relative effect estimates between interventions with a ranking and hierarchy of interventions.
- relies on the assumption that included trials are highly similar

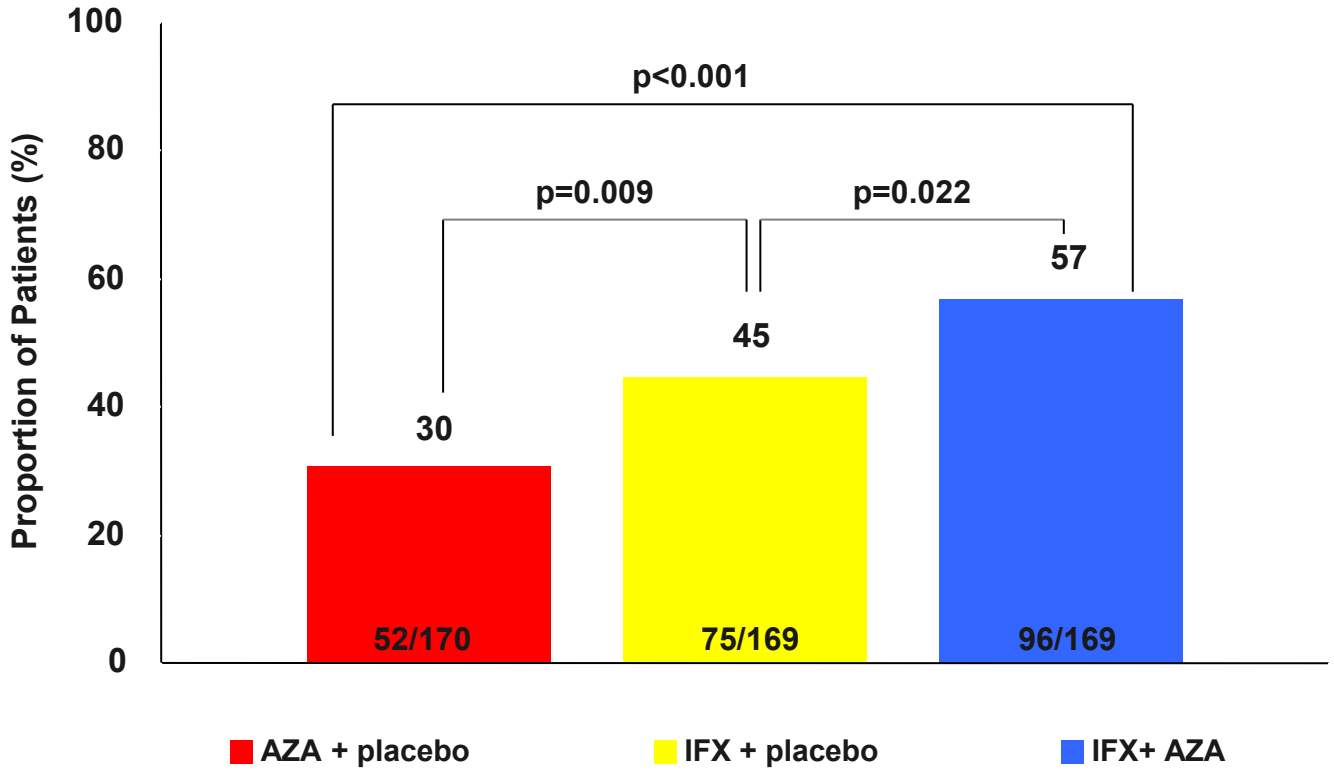


Chaimani A et al. Chapter 11 Cochrane training manual 2020

How Do We Obtain Transformational Efficacy?

There is a well described path forward…

SONIC



Colombel JF. et al. N Engl J Med. 2010 Apr 15;362(15):1383-95.

VEGA: Guselkumab + Golimumab

STUDY

- Phase 2a, randomized, double-blind, placebo-controlled, active-comparator-controlled, parallel-group, proof-of-concept, multicentre study

PURPOSE

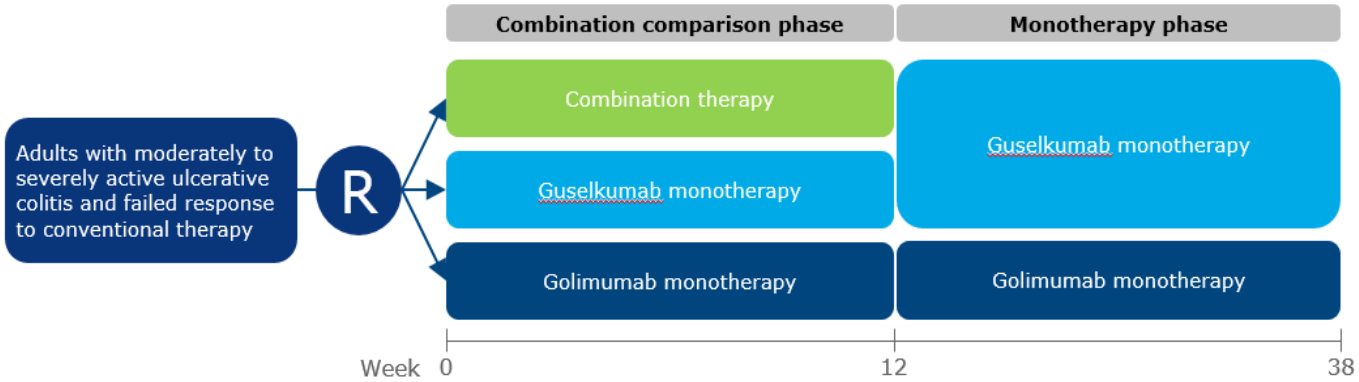
- To evaluate the safety and efficacy of combination therapy with guselkumab and golimumab in patients with moderately to severely active ulcerative colitis

PRIMARY ENDPOINT

- Clinical response at Week 12 defined by Mayo score

MAJOR SECONDARY ENDPOINTS

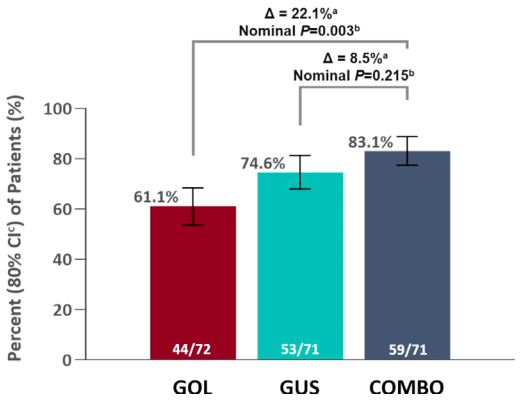
- Clinical remission at Week 12 defined by Mayo score



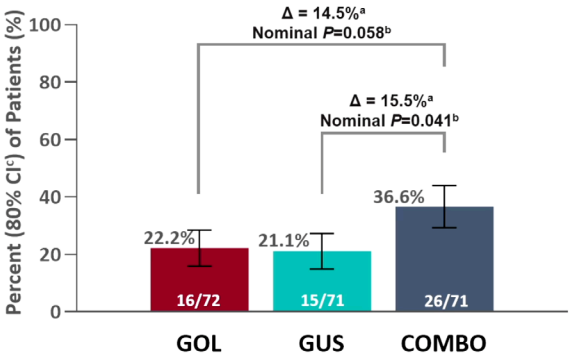
Feagan B et al. Lancet Gastroenterology and Hepatology 2023. In press

VEGA Clinical Response and Remission at Week 12

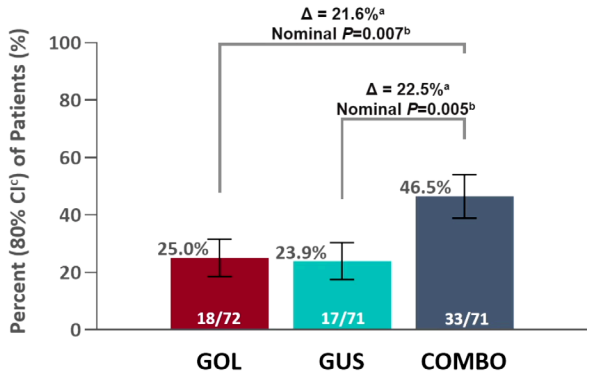
Clinical Response
(decrease from baseline in the Mayo score ≥30% and ≥3 points with either a decrease in rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1)



Clinical Remission
(Mayo score ≤2 with no individual subscore >1



Clinical Remission
(modified Mayo score: Mayo stool frequency subscore of 0 or 1 and not increased from baseline, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy)



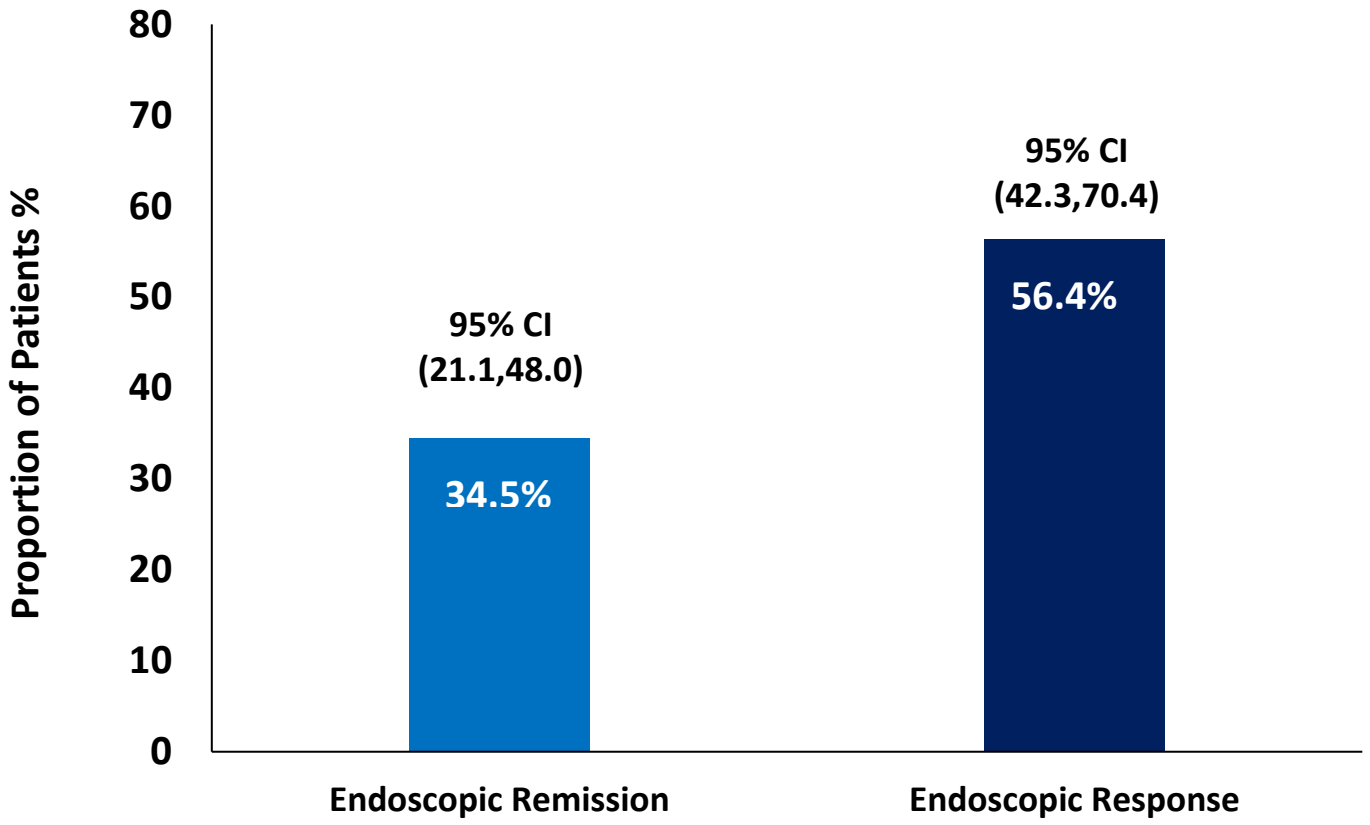
- ***A greater proportion of patients in the combination group achieved clinical response and remission at week 12***

[a]The adjusted treatment difference between the combination therapy vs the monotherapy groups were based on the Wald statistic with CMH weight; [b]The p-value was based on the CMH chi-square test, stratified by corticosteroid use at baseline (yes/no); [c]The 80% confidence intervals for response rates were based on the Wald statistic. GUS: guselkumab; GOL: golimumab

ECCO 2022 data may include drugs, doses and indications not approved by Health Canada

Feagan B. et al. Lancet Gastroenterology and Hepatology.In press

Explorer -Triple Combination Therapy with Vedolizumab, Adalimumab and MTX in CD



Week 26 (n=55)

Summary: Differences Between Agents

	Anti-TNF	Vedolizumab	JAKs	Ustekinumab\23s
PROS	• IFX: fast onset of action • ADA: Convenient (SQ) • TDM++ based dose adjustments • Treats EIMs • Excellent safety record in pregnancy • No increased risk of solid malignancies	• Gut-specific • Excellent safety profile • Low immunogenicity • Live vaccines	• Oral • Rapid onset • High endoscopic response • No immunogenicity • Stable pharmacokinetics	• Excellent safety profile • High endoscopic response rates for anti-IL-23s • Convenient (SQ q8w) • Low immunogenicity • Treats associated psoriasis)
CONS	• Infections • Skin CA? • High immunogenicity – often needs IMM-↓ safety • Need for combined therapy	• Thought to have slower onset of action (VDZ faster ADA in VARSITY for UC) • EIM?	• Not approved for biologic-naïve • DVT/PE risk to be defined • Herpes zoster • Cytopenias • Concerns regarding pregnancy	• EIMs?

Medical Therapies in the Treatment of CD: Conclusions

- For most patients TNF antagonists are no longer the initial treatment of choice in CD
- Safety is important to patients – two classes of agents are completely safe (vedolizumab/IL-12-23s)
- Newer agents are not TNF antagonists with respect to dose-response optimization or immunogenicity
- IL-23 antagonists and upadacitinib appear to have greater efficacy than other agents for endoscopic outcomes
- Efficacy ceiling is an enormous problem –combination therapy is the most promising solution combination therapy