Novel Pathways and Upcoming IBD Therapies

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Brian G. Feagan MD

Professor of Medicine, Epidemiology and Biostatistics

Western University

Senior Scientific Director, Alimentiv Inc.

London, Ontario, Canada

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Disclosures

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Consultant	Abbott/AbbVie, Akebia Therapeutics, Allergan, Amgen, Applied Molecular Transport Inc., Aptevo Therapeutics, Astra Zeneca, Atlantic Pharma, Avir Pharma, Biogen Idec, BioMx Israel, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, Galapagos, GiCare Pharma, Gilead, Gossamer Pharma, GSK, Inception IBD Inc, JnJ/Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nestles, Nextbiotix, Novonordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Progenity, Protagonist, Receptos, Salix Pharma, Shire, Sienna Biologics, Sigmoid Pharma, Sterna Biologicals, Synergy Pharma Inc., Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, Vivelix Pharma, VHsquared Ltd., Zyngenia
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Topic to be Discussed:
Horizon Agents

- More effective therapy for fistulizing\fibrostenosing CD
- Il-23 antagonists-Quo vadis?
- mRNA silencing

Fibrostenosing/Fistulizing CD:
A Critical Problem!

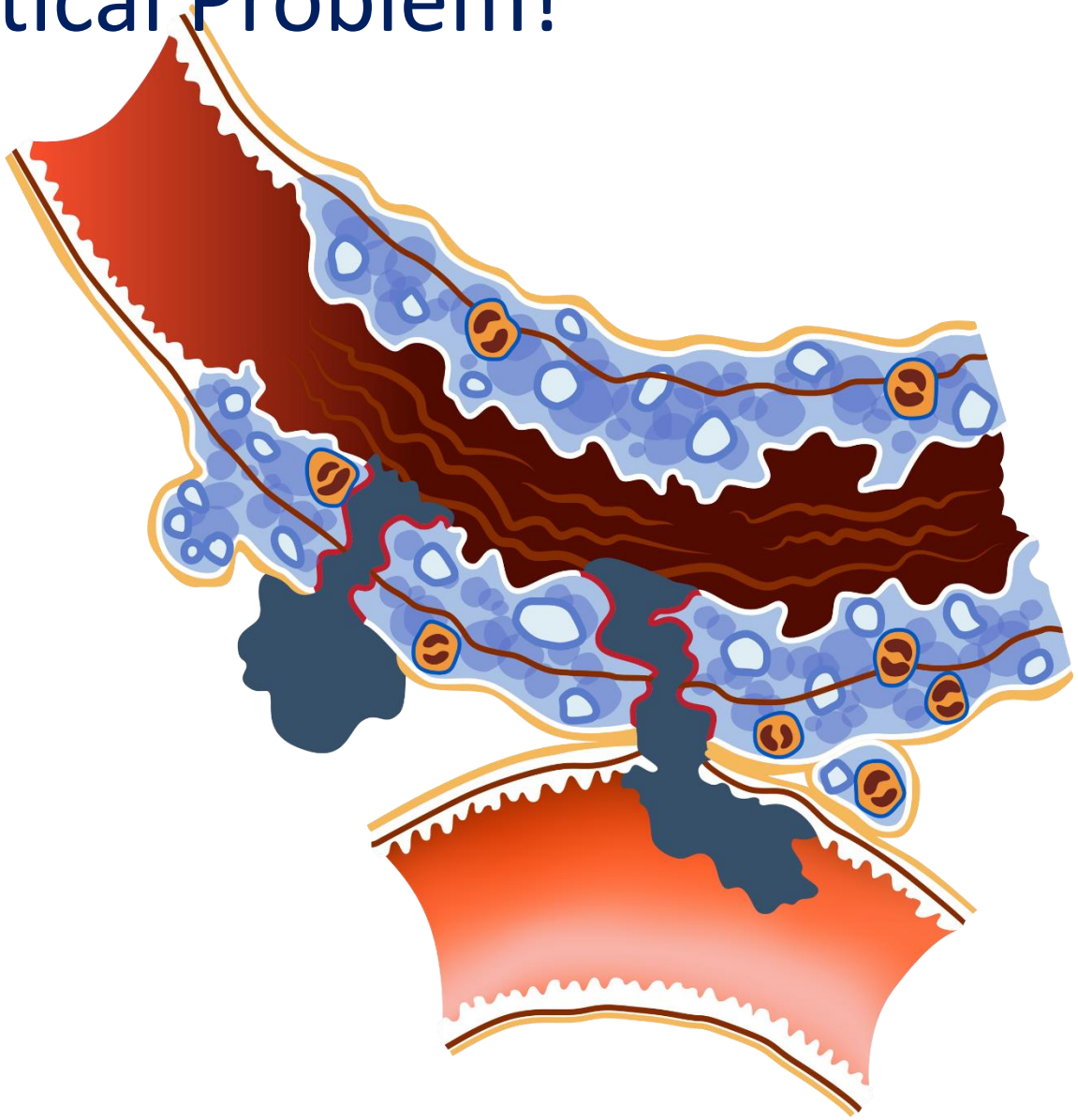

Figure adapted from Rubin E, Farber JL. Pathology 4th ed. Philadelphia. Lipponcott Wilkins, 2005.

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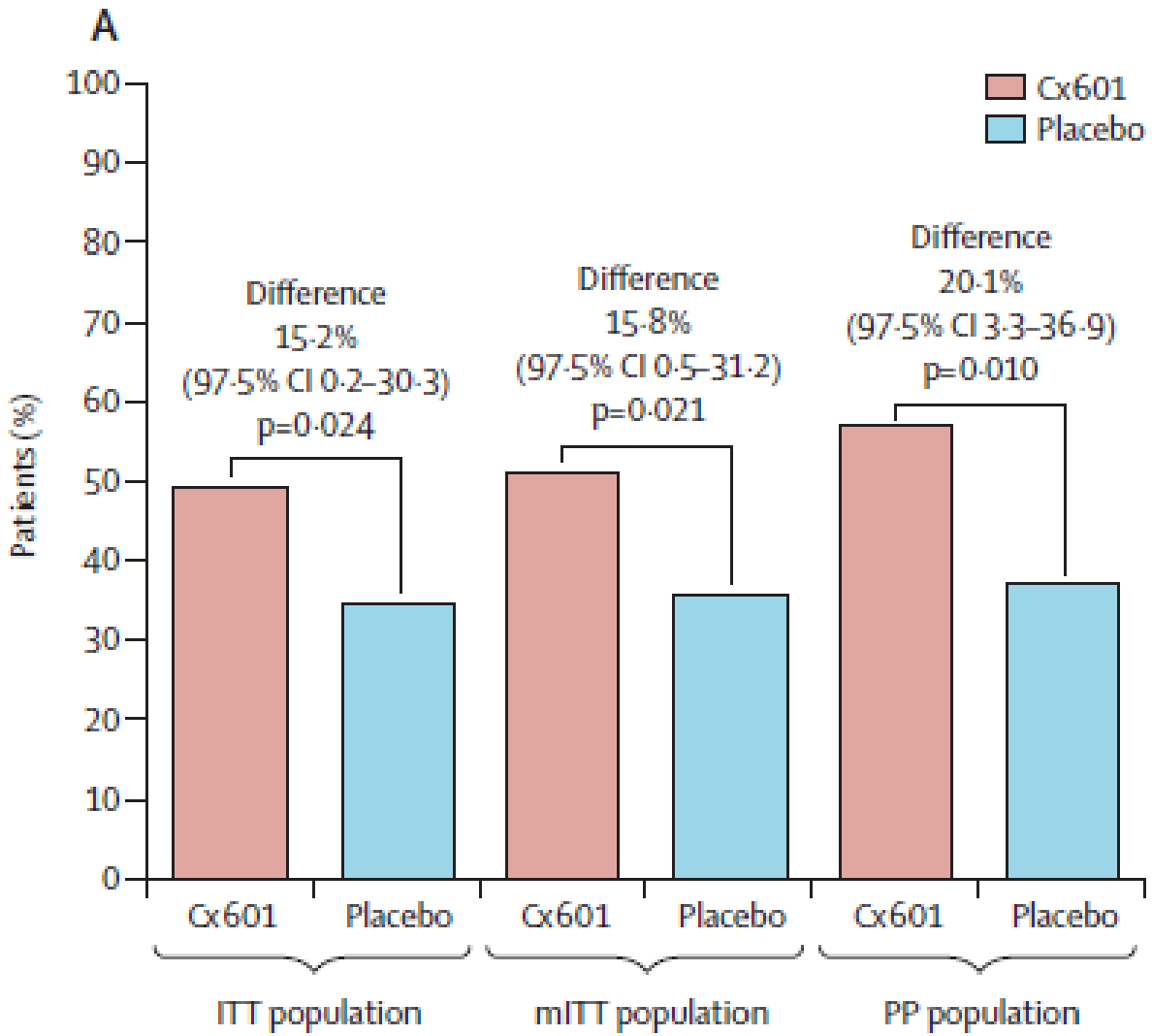
Allogeneic Stem Cells for Complex Perianal Fistula in CD: Remission at Week 24



Panes J. et al. The Lancet. 2016 Sep 24;388(10051):1281-90

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Allogeneic Stem Cells for Complex Perianal Fistula in CD: Current Status

- Approved by EMA
- FDA required a second Phase 3 RCT –ADMIRE CD II
- Large sample size n=554 – difficult to recruit but has been completed at large referral centers
- Likely to be costly – difficult to access

Panes J. et al. The Lancet. 2016 Sep 24;388(10051):1281-90

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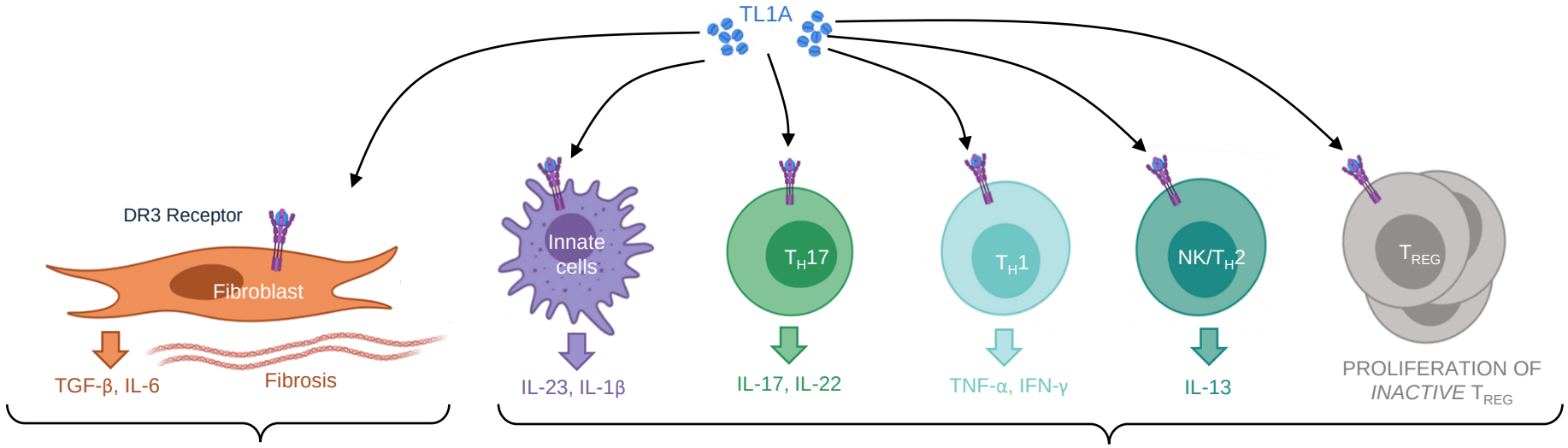
A Medical Option? TL1A in the Pathophysiology of IBD



FIBROSIS

- Directly activates fibroblasts
- Leads to collagen disposition
- Fibrosis independent of inflammation

INFLAMMATION

- Broad pro-inflammatory effect
- Early response cytokine that set the stage for inflammation
- Stimulates innate and adaptive immune response

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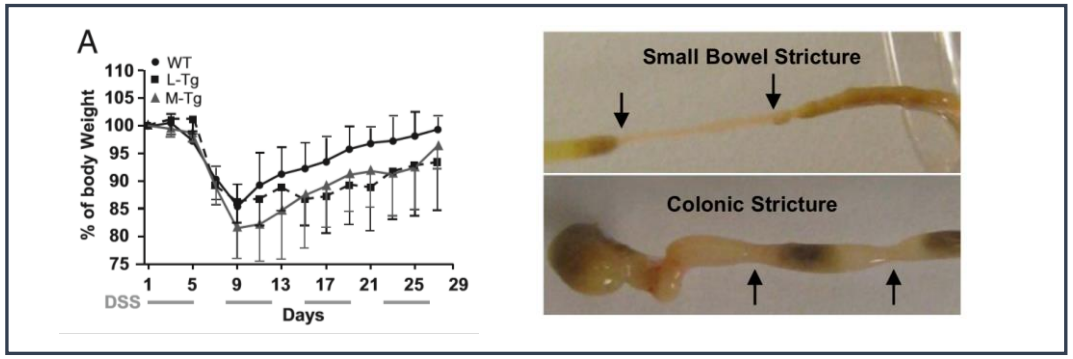
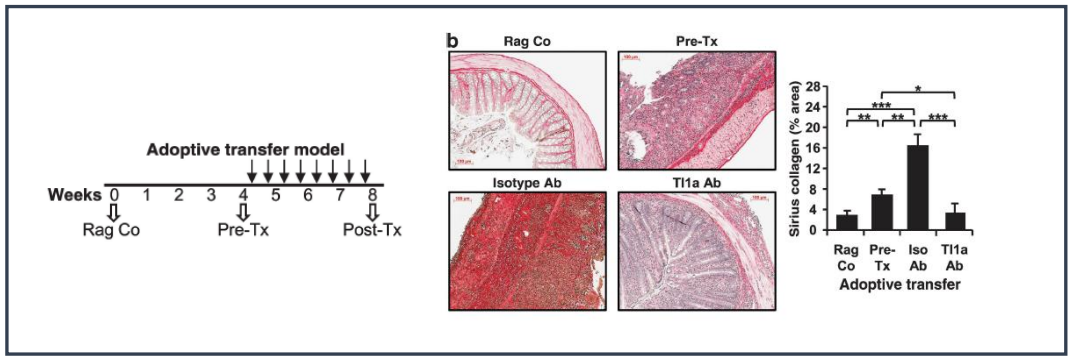
TL1A Signaling is a Primary Driver of Fibrosis in Mouse Models of IBD



- TL1A transgenic mouse models resemble a complicated form of severe human CD
- Sustained TL1A overexpression causes stricturing disease that is caused by increased collagen deposition



- TL1A antibody treatment reverses established fibrosis in murine colitis
- This was observed in two different mouse models of chronic colitis in a study conducted by Cedars-Sinai

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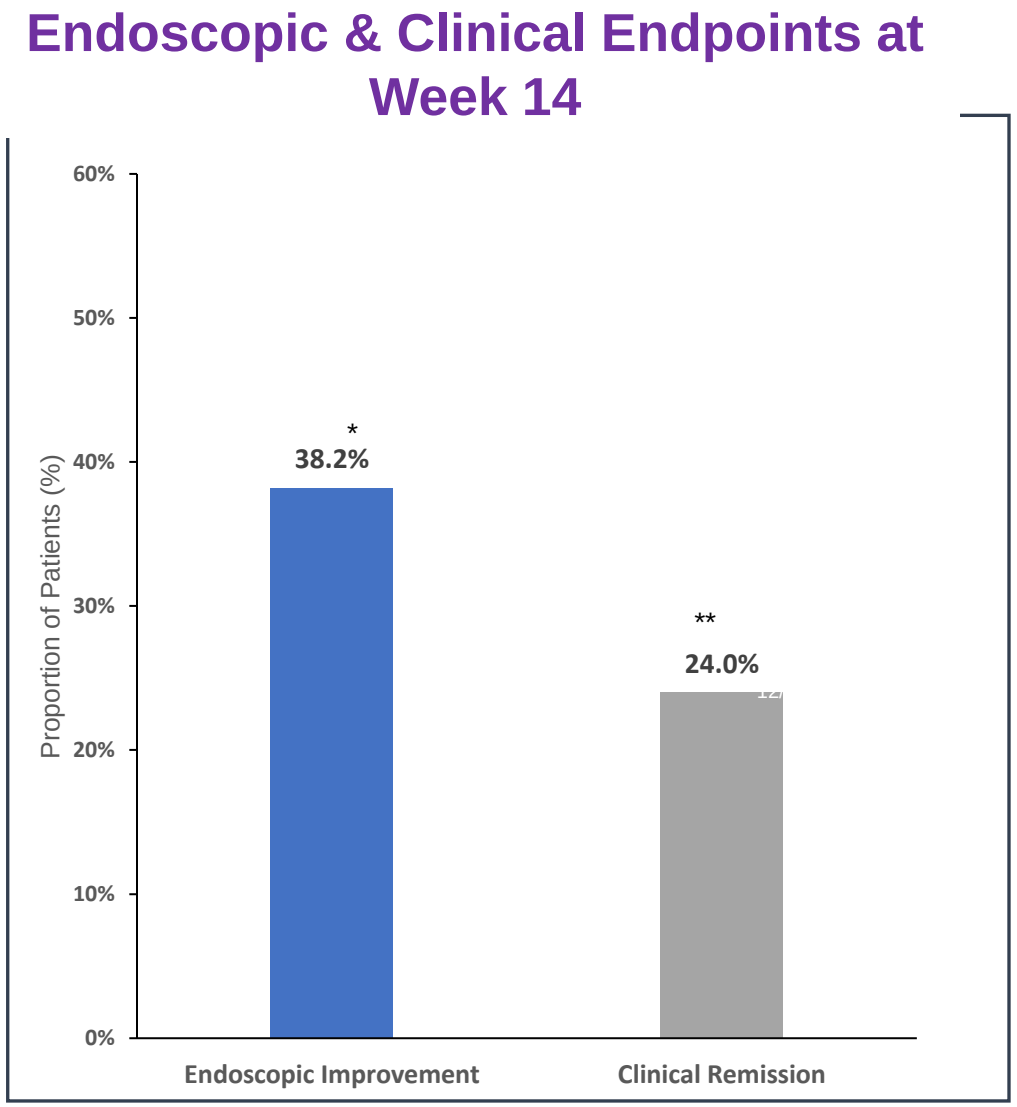
TL1A Antagonist Therapy for UC Induction



- 14 week open-label study in moderately to severely active ulcerative colitis, N=50
- proof of concept achieved
- No clinically meaningful safety signa observed

Adapted from ECCO'20 Vienna Congress Presentation – Speaker: Dr. Silvio Danese. Danese et al. Safety, Tolerability and efficacy of anti-TL1A antibody PF-06480605 in treatment of ulcerative colitis: the open-label, multicentre, Phase 2a TUSCANY study.

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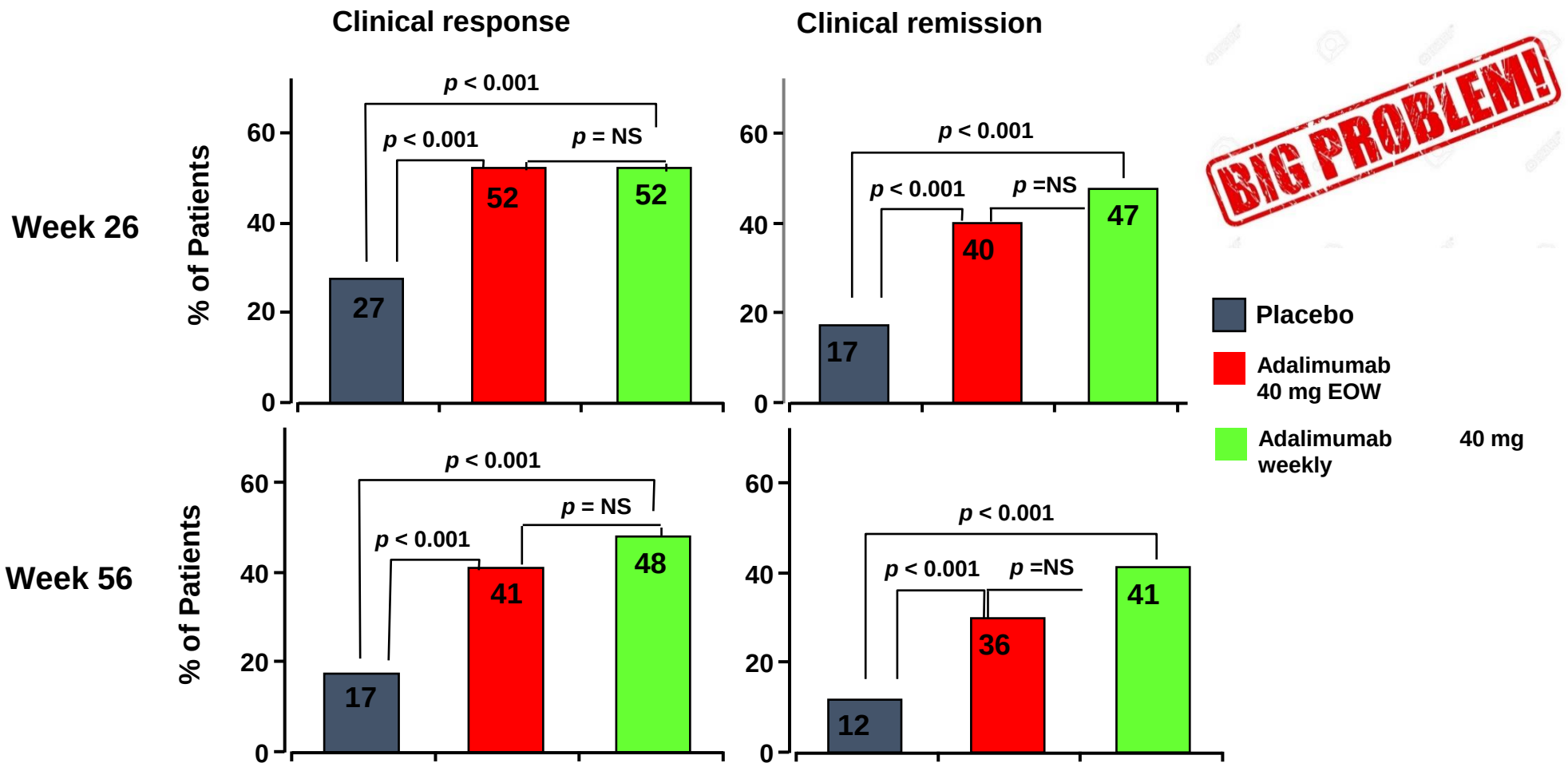
Topic to be Discussed

Horizon Agents

- More effective therapy for fistulizing/fibrostenosing CD
- Il-23 antagonists- Quo vadis?
- mRNA silencing

Greater Efficacy is Needed:
Positive Yet Suboptimal Results with TNF Antagonists



Colombel JF. et al. Gastroenterology 2007

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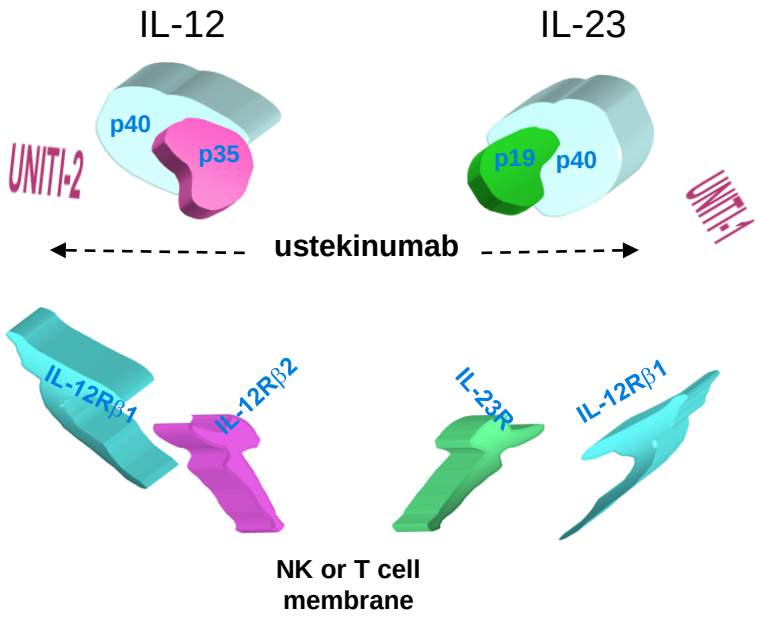
Anti-p40 Ustekinumab: Background



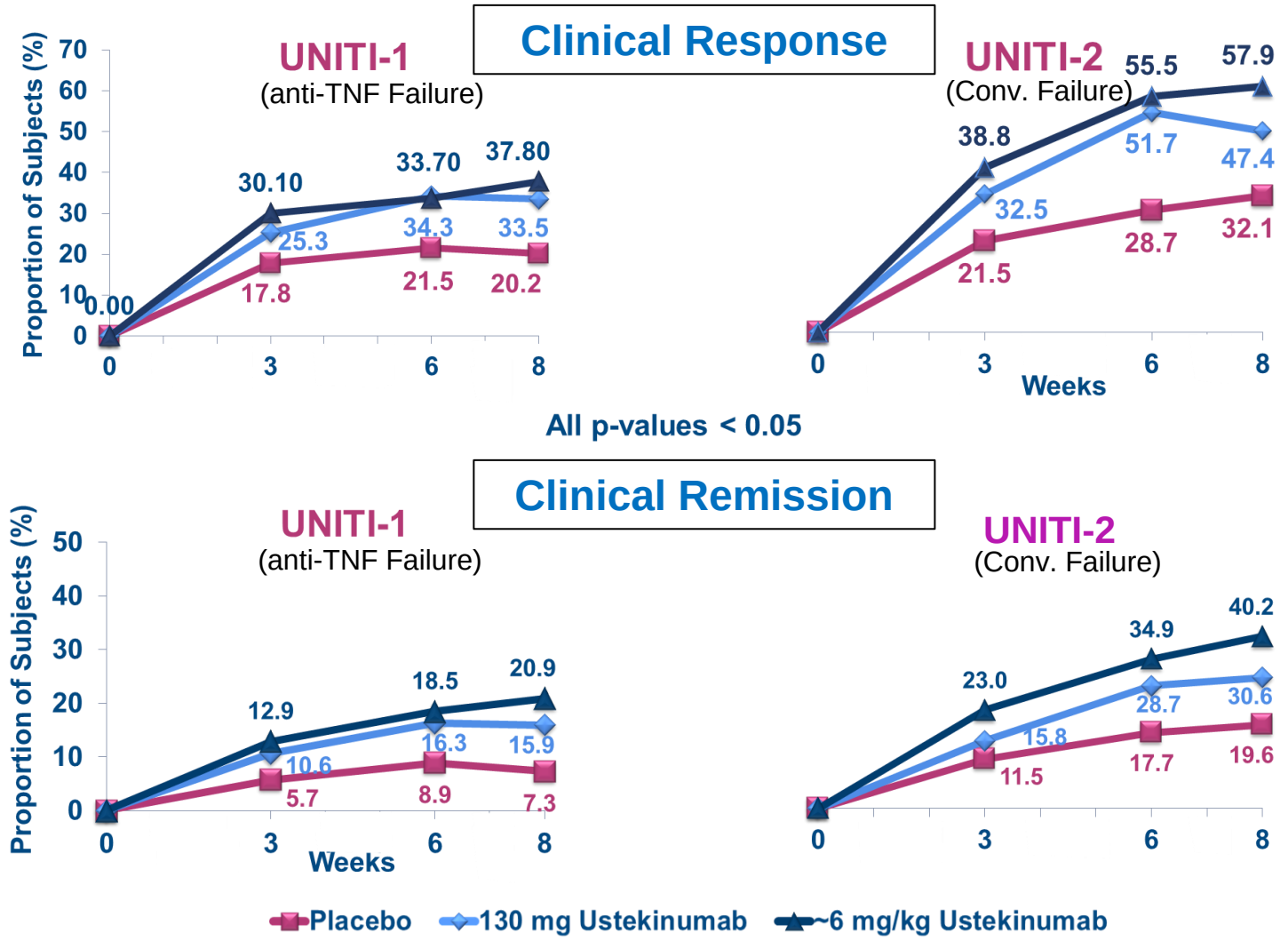
No IL-12 or IL-23 intracellular signal

- 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.

Ustekinumab Clinical Response and Remission Through Week 8



Feagan et al New Eng J Med 2016.

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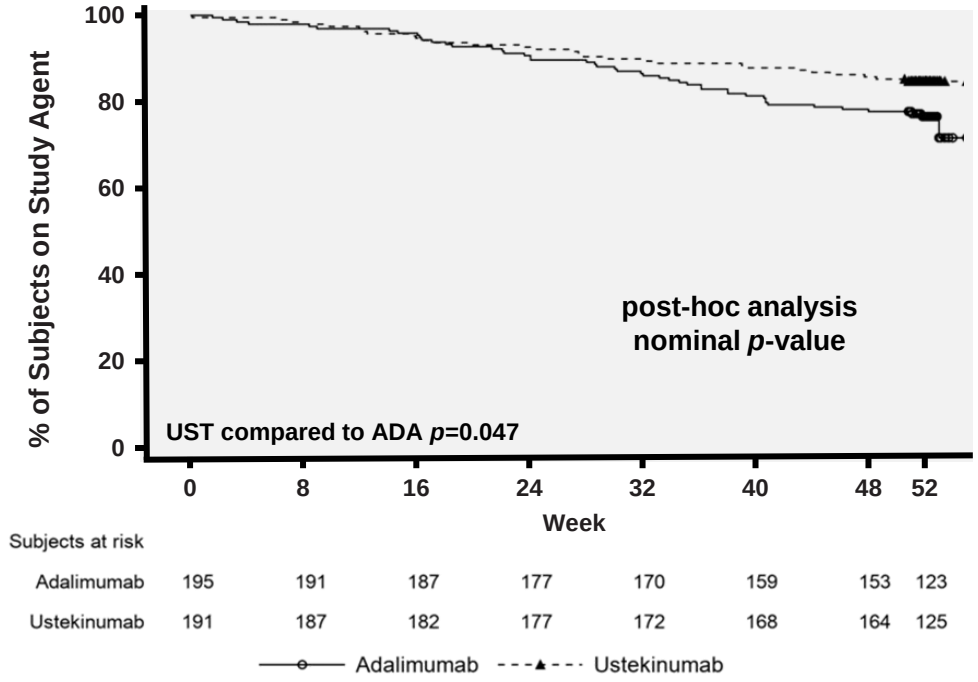
UST vs ADA in Bio-Naïve CD Patients

Treatment Disposition through Week 52

	ADA	UST
Number of patients	195	191
Completed study through Week 52, n (%)	149 (76.4%)	162 (84.8%)
Lack of efficacy, n (%)	10 (5.1%)	4 (2.1%)
Withdrew consent, n (%)	10 (5.1%)	11 (5.8%)
Adverse event, n	21	11
Worsening of Crohn's disease, n (%)	8 (4.1%)	5 (2.6%)
Other, n (%)	13 (6.7%)	6 (3.1%)
Lost to follow-up, n (%)	2 (1.0%)	2 (1.0%)
Pregnancy, n (%)	1 (0.5%)	1 (0.5%)
Death, n (%)	0	0
Other, n (%)	2 (1.0%)	0
COVID-19 related, n (%)	2 (1.0%)	0

Time to Treatment Discontinuation



Irving P et al ECCO 2021

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Transformational Efficacy in Psoriasis Therapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Ustekinumab and Etanerc
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. 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 and Alan Menter, M.D., for the ACCEPT Study Group*

ABSTRACT

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

METHODS
We randomly assigned 903 patients with moderate-to-severe psoriasis to r subcutaneous injections of either 45 or 90 mg of ustekinumab (at weeks 0 and high-dose etanercept (50 mg twice weekly for 12 weeks). The primary end point the proportion of patients with at least 75% improvement in the psoriasis area severity index (PASI) at week 12; a secondary end point was the proportion cleared or minimal disease on the basis of the physician's global assessmen sessors were unaware of the treatment assignments. The efficacy and safety 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 received 45 mg of ustekinumab and 73.8% of patients who received 90 mg, as pared with 56.8% of those who received etanercept (P=0.01 and P<0.001, respe ly). Similarly, 65.1% of patients who received 45 mg of ustekinumab and 70.(patients who received 90 mg of ustekinumab had cleared or minimal disea cording to the physician's global assessment, as compared with 49.0% of those received etanercept (P<0.001 for both comparisons). Among patients who di have a response to etanercept, 48.9% had at least 75% improvement in the within 12 weeks after crossover to ustekinumab. One or more adverse events occ through week 12 in 66.0% of patients who received 45 mg of ustekinumab and (of patients who received 90 mg of ustekinumab and in 70.0% who received et cept; 1.9%, 1.2%, and 1.2%, respectively, had serious adverse events. Safety pat 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 dose etanercept over a 12-week period in patients with psoriasis. (ClinicalTrial number, NCT00454584.)

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.
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N ENGL J MED 362;2 NEJM.ORG JANUARY 14, 2010

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

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 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.

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1318

N ENGL J MED 373;14 NEJM.ORG OCTOBER 1, 2015

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.

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.)

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 1C8, Canada, or at kapapp@probity-medical.com.

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N ENGL J MED 376;16 NEJM.ORG APRIL 20, 2017

1551

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.

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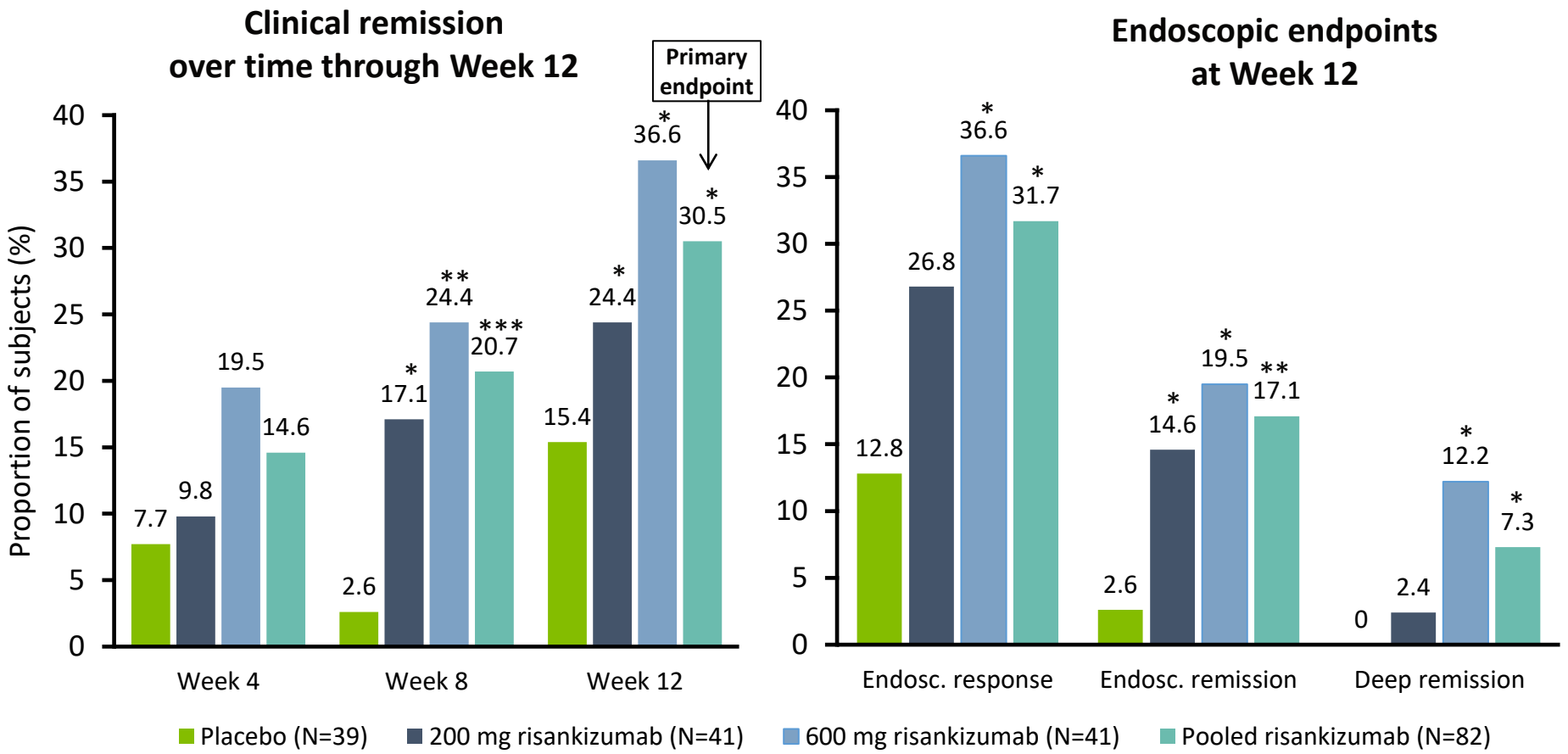
Risankizumab for CD:
Is anti-P19 the Answer?



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

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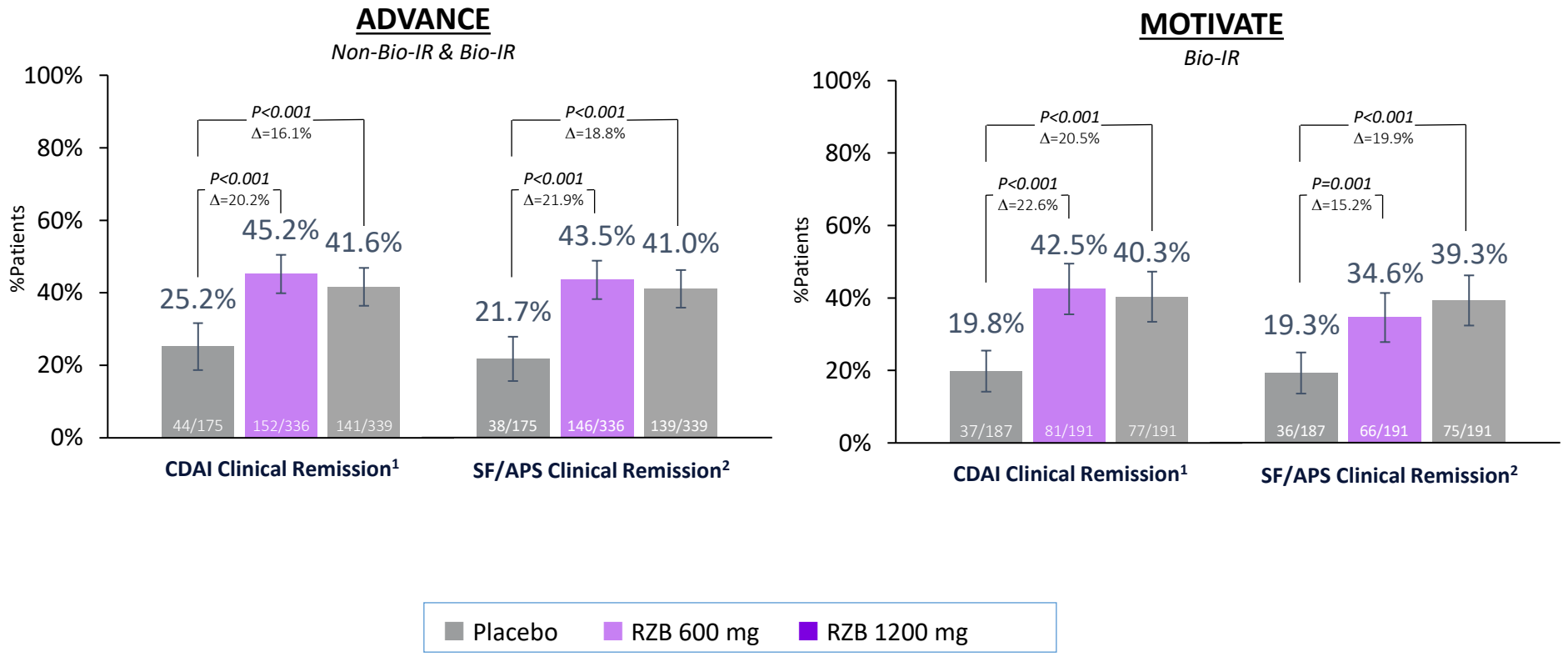
Risankizumab Induction:
Clinical Remission Week 12



Ferrante et al UEGW 2021

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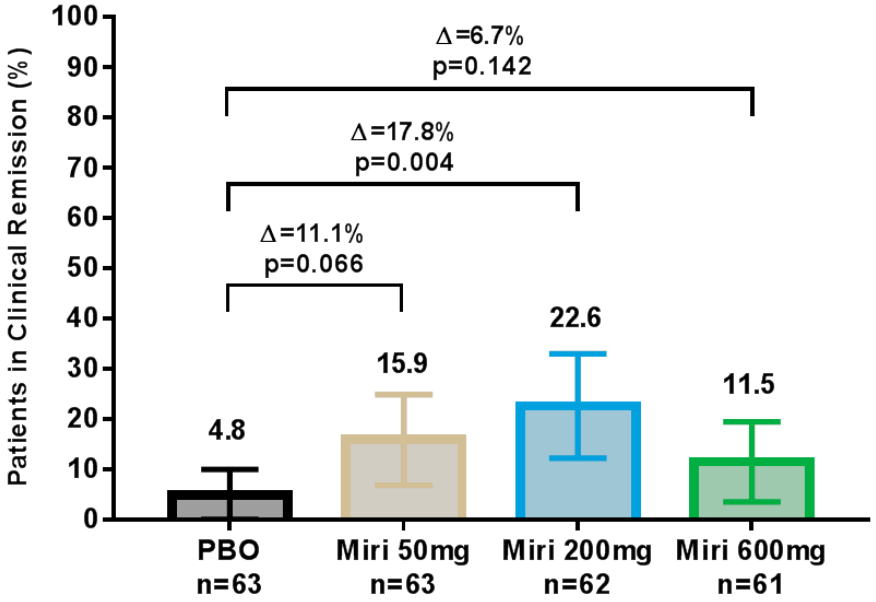
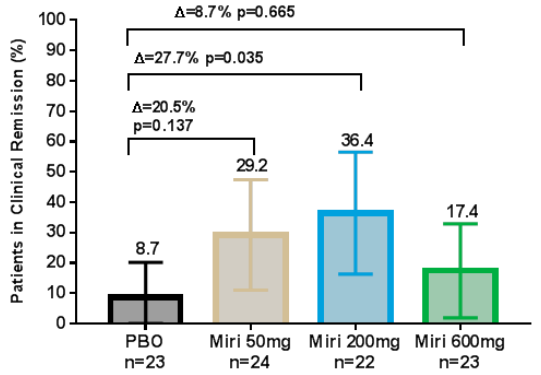
Mirikizumab for UC Clinical Remission Week12

Clinical Remission

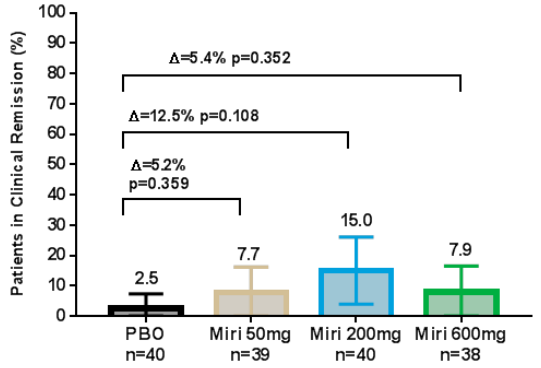
Rectal bleeding Mayo subscore of 0, stool frequency Mayo subscore of 0 or 1 (with ≥1 point decrease from baseline) and Mayo endoscopic subscore of 0 or 1



Biologic Naïve



Biologic Experienced



NRI: all patients who discontinued from the study at any time prior to week 12 for any reason or failed to have an adequate week 12 efficacy assessment were considered non-responders at week 12.

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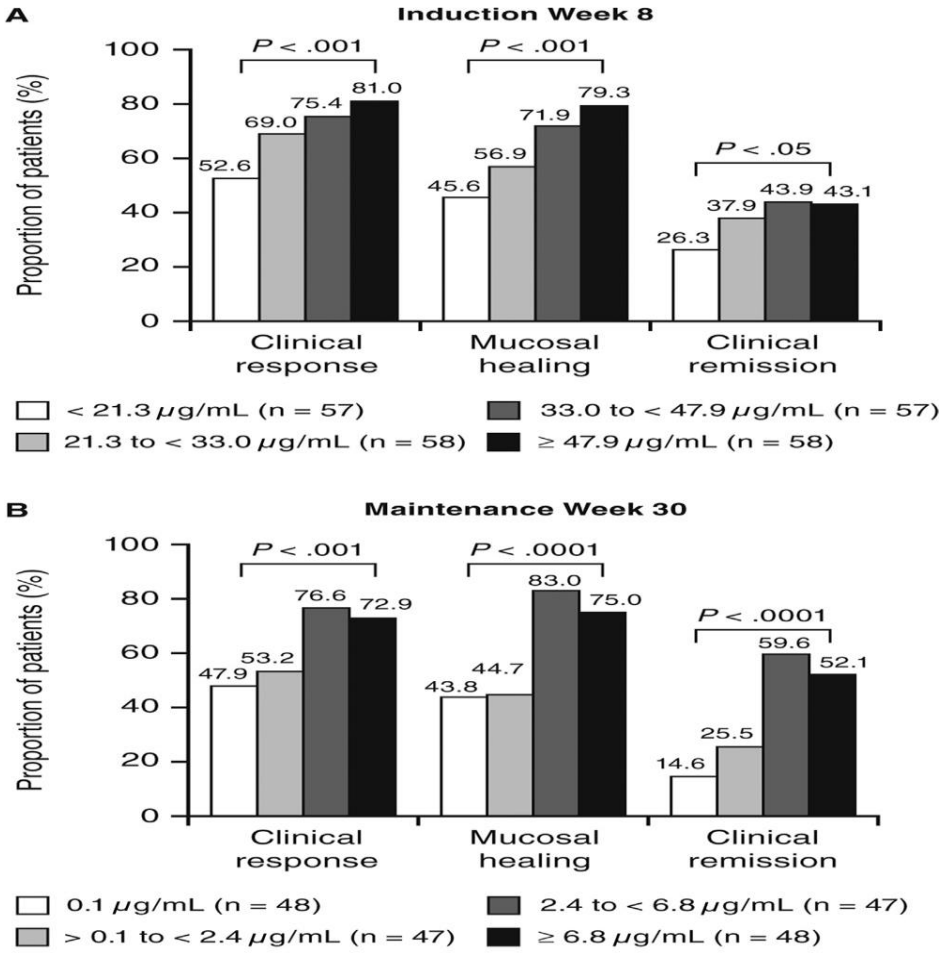
One disturbing thought…….

Is proactive TDM dead?

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

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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.

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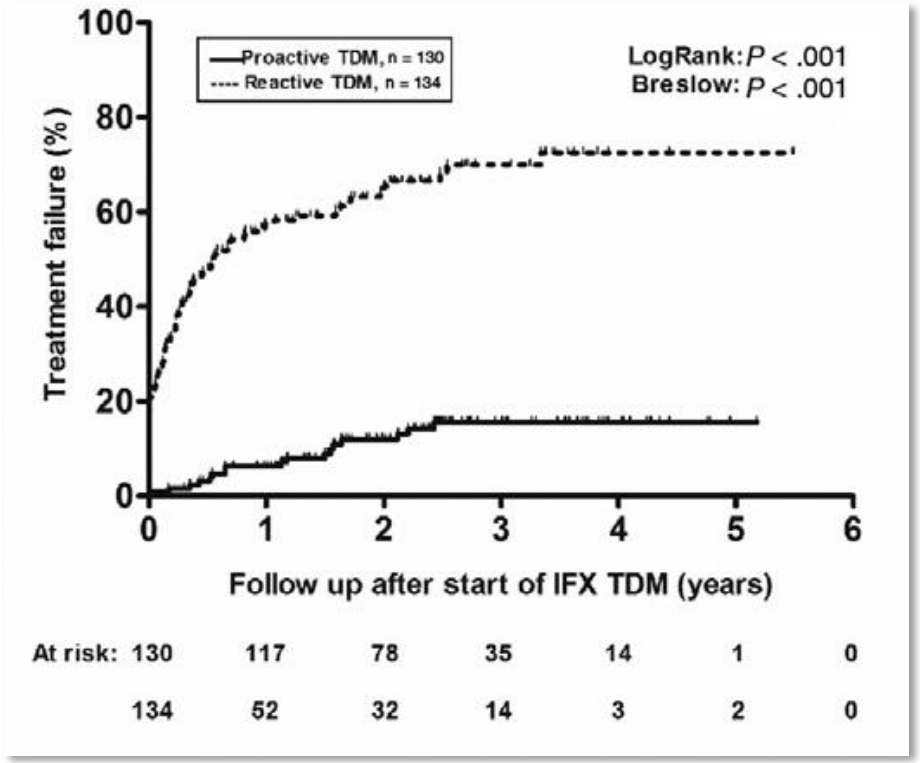
Proactive vs. Reactive TDM

Retrospective Study

- 264 IBD patients
  - 130 Proactive TDM
  - 134 Reactive TDM

- Treatment failure defined as drug discontinuation for loss of response or serious adverse event or need for surgery.



- **<u>Proactive TDM 1-2x/ year</u>**

Papamichael K, *et al. Clin Gastroenterol Hepatol* 2017;15(10):1580-1588

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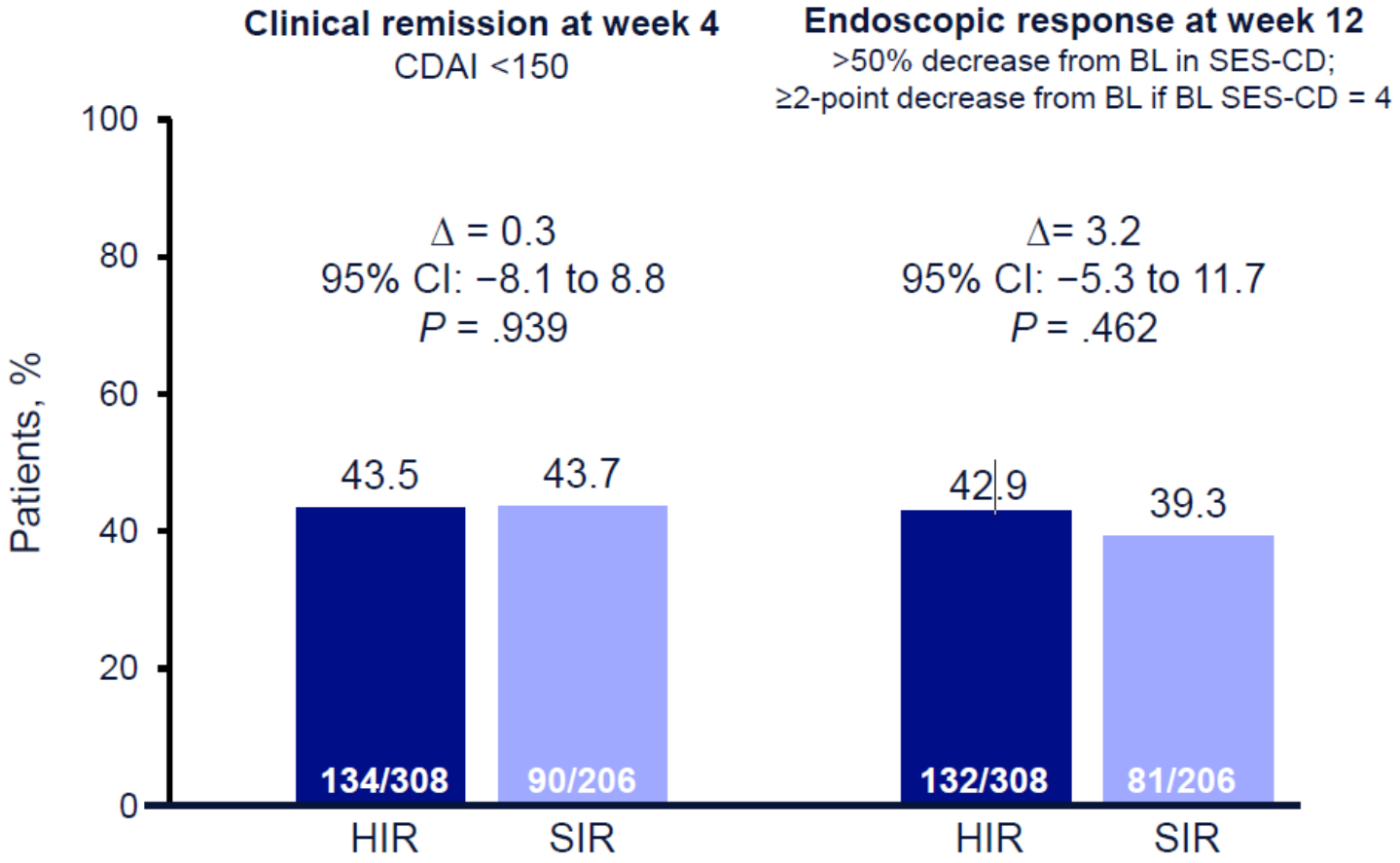
Clinical Remission at Week 4 and Endoscopic Response at Week 12

SERENE CD



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

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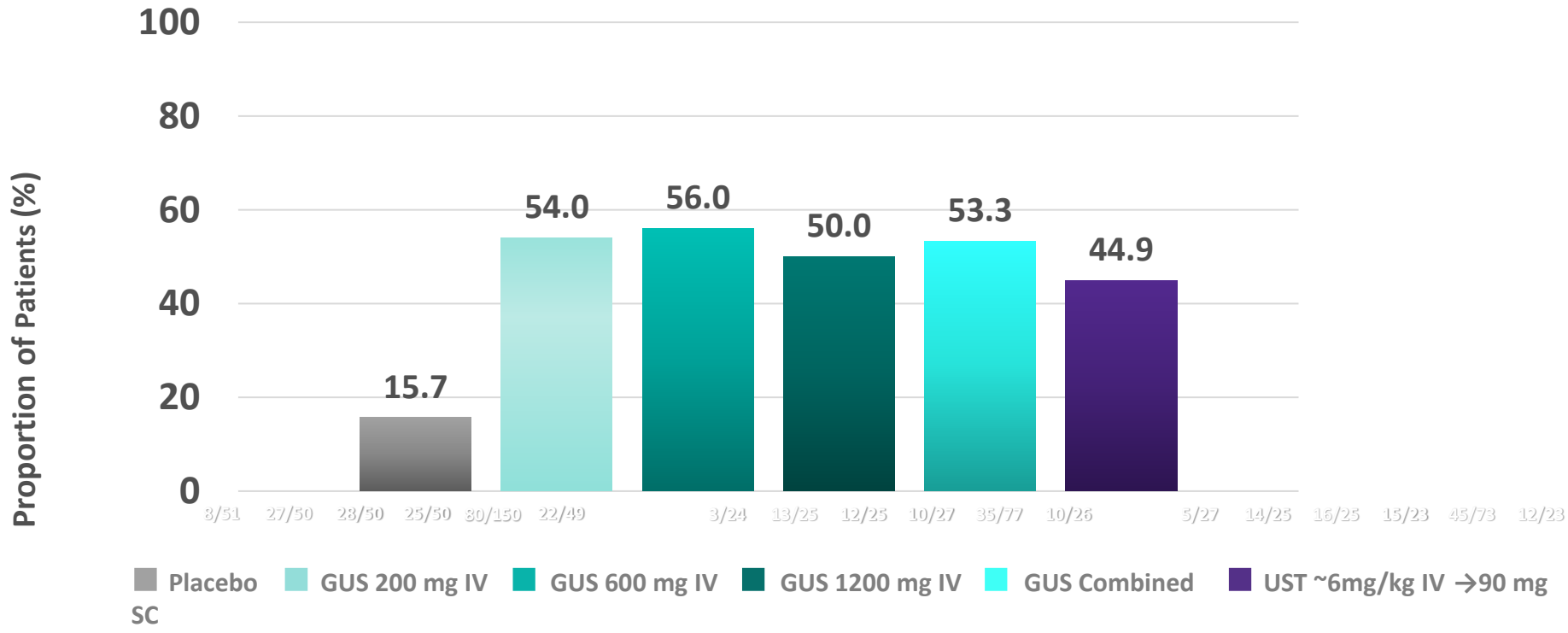
GALAXI: Remission at Week 12



Clinical remission defined as CDAI score <150

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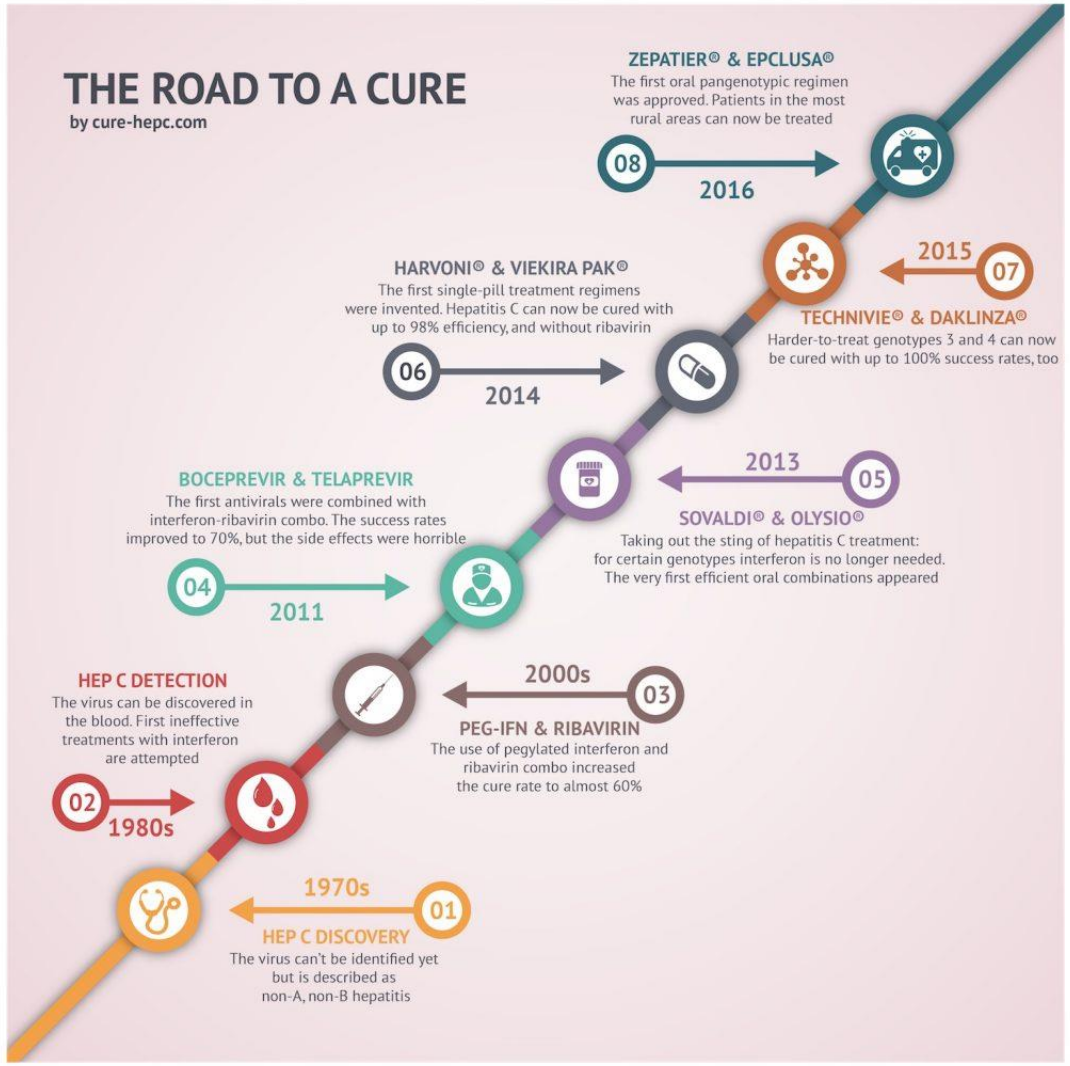
How Do We Obtain Transformational Efficacy?

…… there is a well described path forward:

Consider HCV treatment



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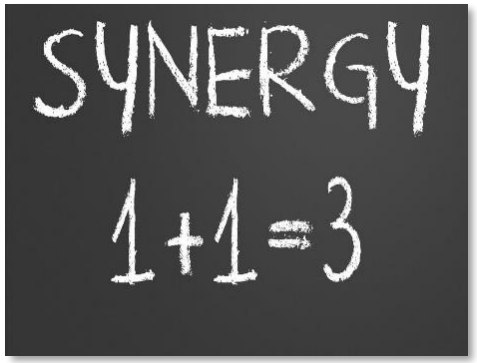
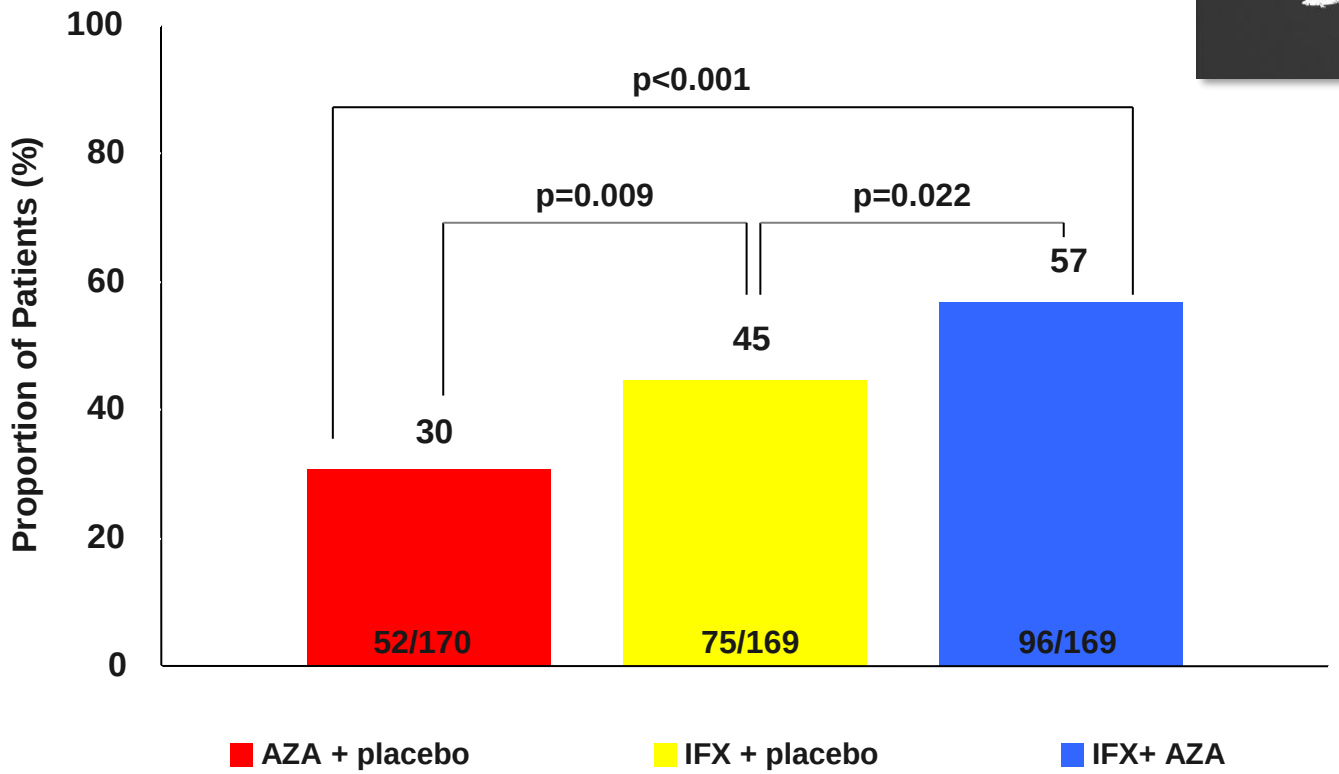
SONIC Provides a Clue!





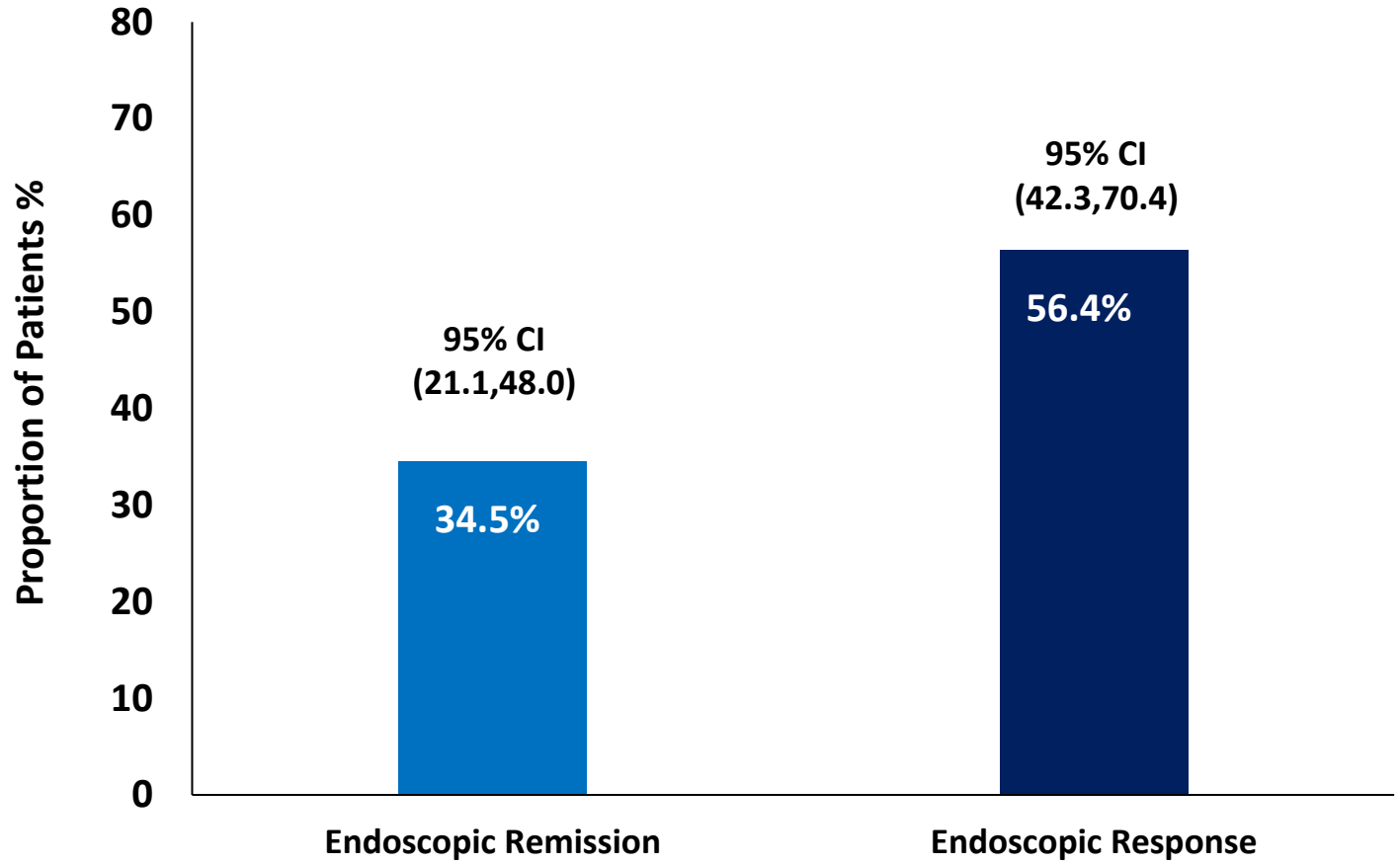
Colombel JF. et al. N Engl J Med. 2010 Apr 15;362(15):1383-95.

Vedolizumab/Adalimumab/MTX Combination

Triple Combination Therapy in High Risk Crohn's Disease

- Open-label, phase 4 study
- Efficacy and safety of triple combination therapy with vedolizumab IV, adalimumab SC, and oral methotrexate in early treatment of patients with moderate to severe CD at moderate-high risk for developing complications
- CD must have been diagnosed within the previous 24 months and patients must be naïve to biologics

Triple Combination Therapy:
Week 26 (n=55)



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Combination Therapy VEGA:
Guselkumab + Golimumab in UC

STUDY

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

PURPOSE

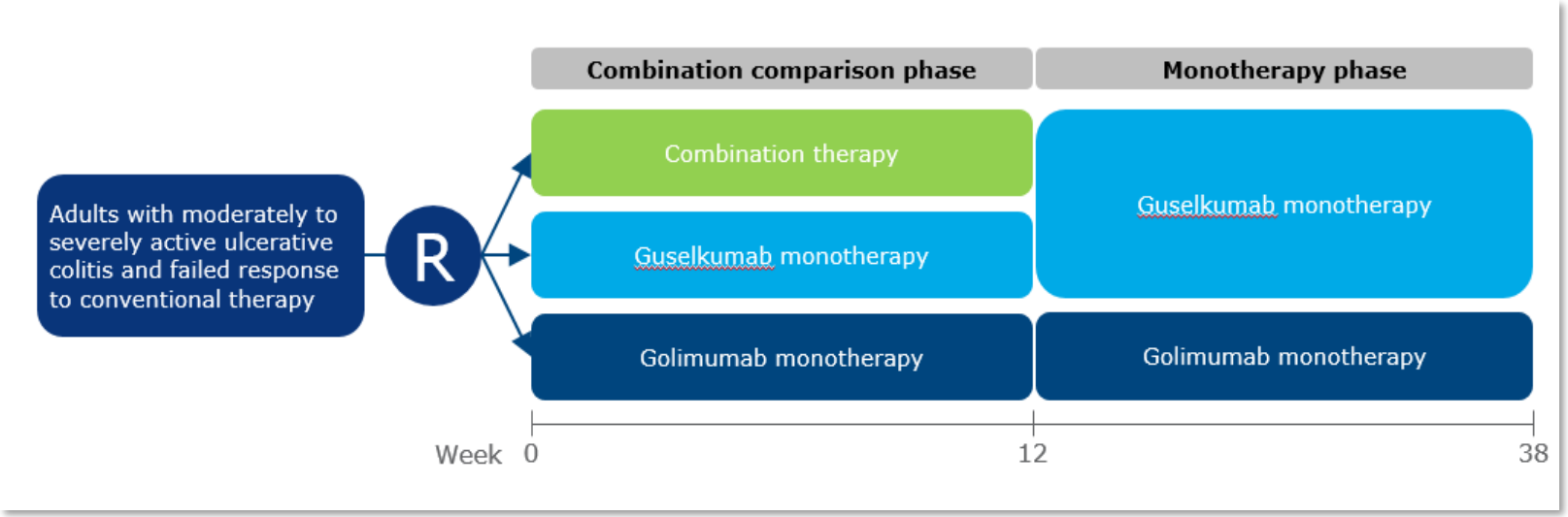
- To evaluate the safety and efficacy of combination therapy with guselkumab and golimumab in patients with moderately to severely active ulcerative colitis

PRIMARY ENDPOINT

- Clinical response at Week 12 defined by Mayo score

MAJOR SECONDARY ENDPOINTS

- Clinical remission at Week 12 defined by Mayo score



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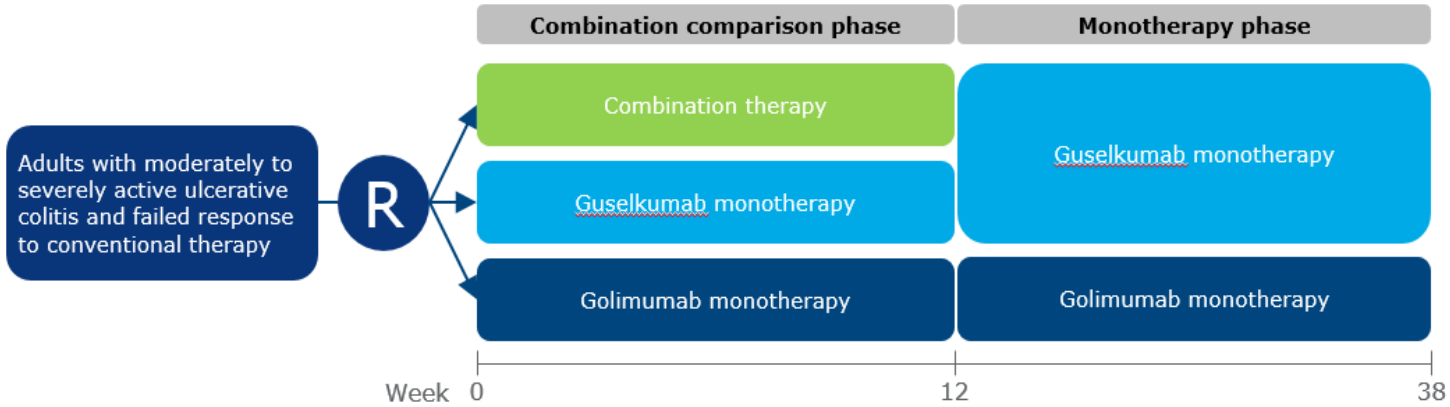

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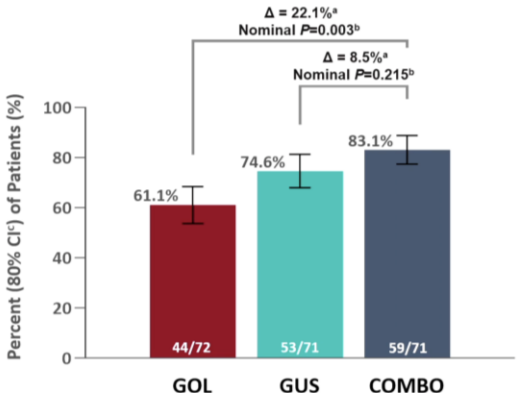
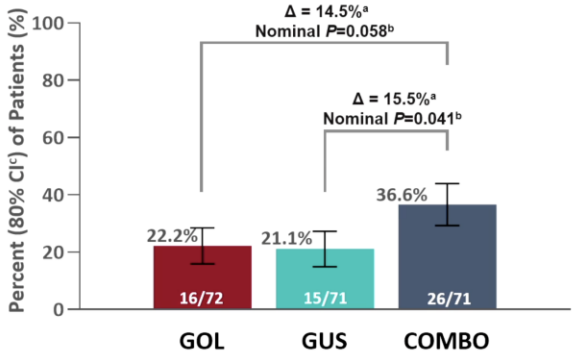
Clinical Response and Remission at Week 12

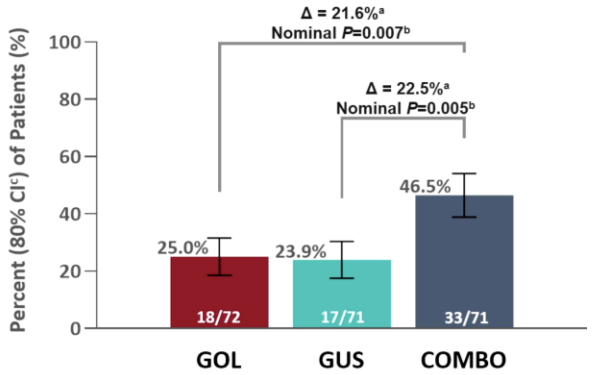
Clinical Response
(decrease from baseline in the Mayo score ≥30% and ≥3 points with either a decrease in rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1)

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

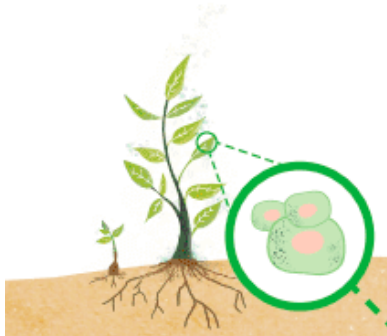
Sands BE, Feagan BG, Sandborn WJ, et al. Efficacy and safety of combination induction therapy with guselkumab and golimumab in participants with moderately-to-severely active Ulcerative Colitis: Results through week 12 of a phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept study (OP36). J Crohn's Colitis 2022;16(S1);i042.

Topic to be Discussed:
Horizon Agents

- More effective therapy for fistulizing\fibrostenosing CD
- Il-23 antagonists- Quo vadis?
- mRNA silencing

UNDERSTANDING RNAi

RNAi, or "RNA Interference," is a natural process that occurs in the cells of plants, animals, and people.



All living things – like this plant – are made up of **cells**, the basic units of life.

Inside the nucleus of each cell is a detailed genetic blueprint, encoded in **DNA**...

... which is transcribed (copied) into **messenger RNA (mRNA)** ...

...which gets translated by the cell's machinery to make a specific **protein**.

Cytoplasm

Nucleus

DNA

mRNA

Protein

Proteins are the building blocks of tissues and they carry out many essential biological functions. In some cases, decreasing the production of specific proteins can be beneficial. RNAi is a natural process that works like a "dimmer switch" to dial down the level of a protein. It likely evolved to protect cells from viruses.

HOW DOES RNAi WORK?

1. It begins when a form of RNA made of two strands (**double-stranded RNA, or dsRNA**) is introduced into the cell, for example by a virus, or produced in the cell.
2. When a cell "sees" dsRNA, it activates structures that work like scissors to **cut it up**.
3. Next, **other structures attach** to these small pieces of RNA and turn them back into single-stranded RNA.
4. These structures then bind to **mRNA with a matching code**.
5. As a result, **production of the protein** encoded by that mRNA is prevented.

Protein

When we know the gene that encodes a certain protein, we can use RNAi to target that protein and dial it down in a highly specific way. In agriculture, for example, this can potentially impact the production of proteins responsible for the development of a disease or essential for a pest's survival, thus protecting plants from such disease or pest infestations.

CropLife

Obefazimod Induction Therapy for UC

- Oral , small molecule agonist that stimulates sRNA production
- Inhibits pro-inflammatory cytokine production
- Excellent safety profile in HIV therapy studies
- Previous positive 2a POC
- Phase 2 study in UC

Vermiere S. et al. Lancet Gastro Hepatology. Sept 2022

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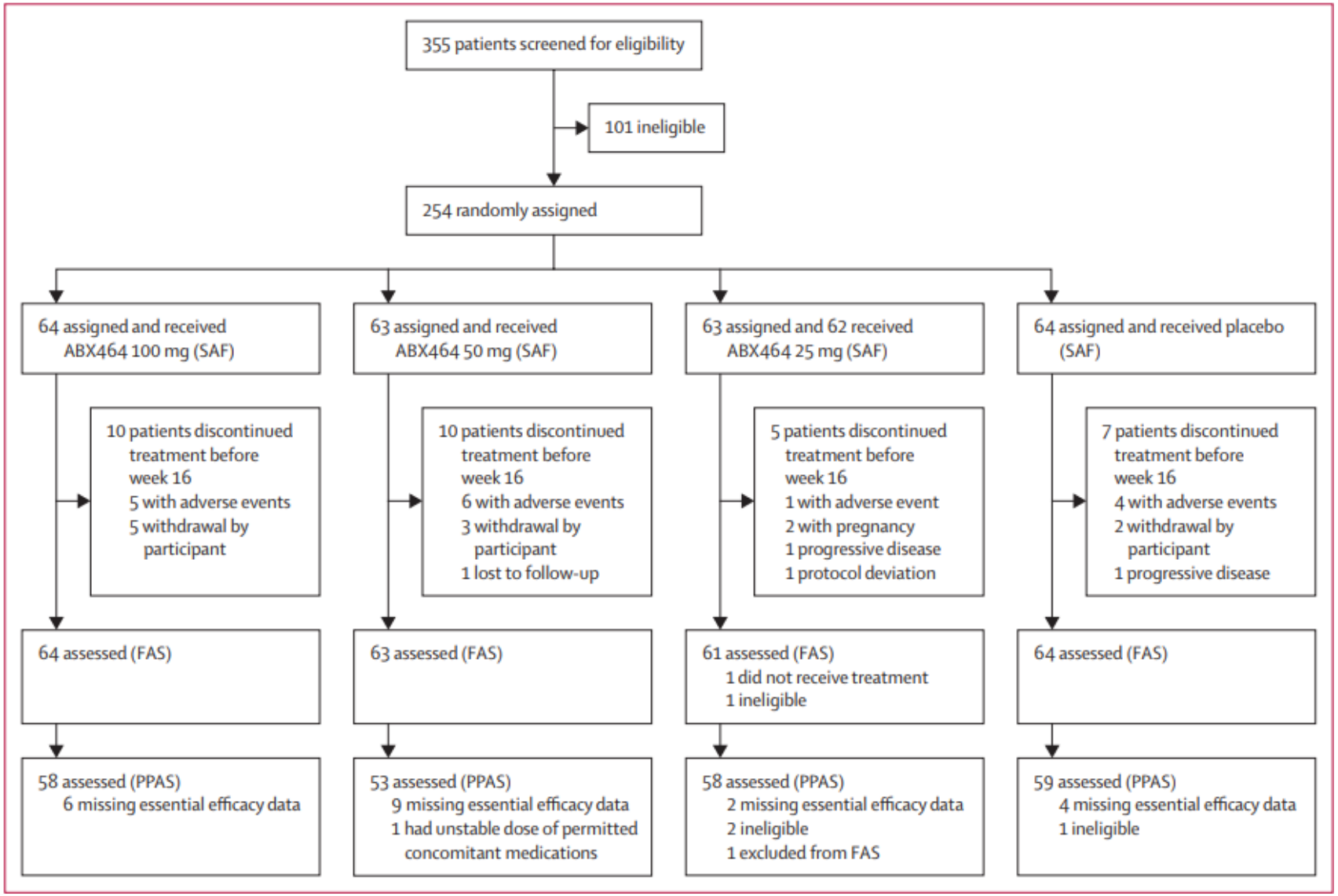
Obefazimod Induction Therapy for UC



Vermiere S. et al. Lancet Gastro Hepatology. Sept 2022

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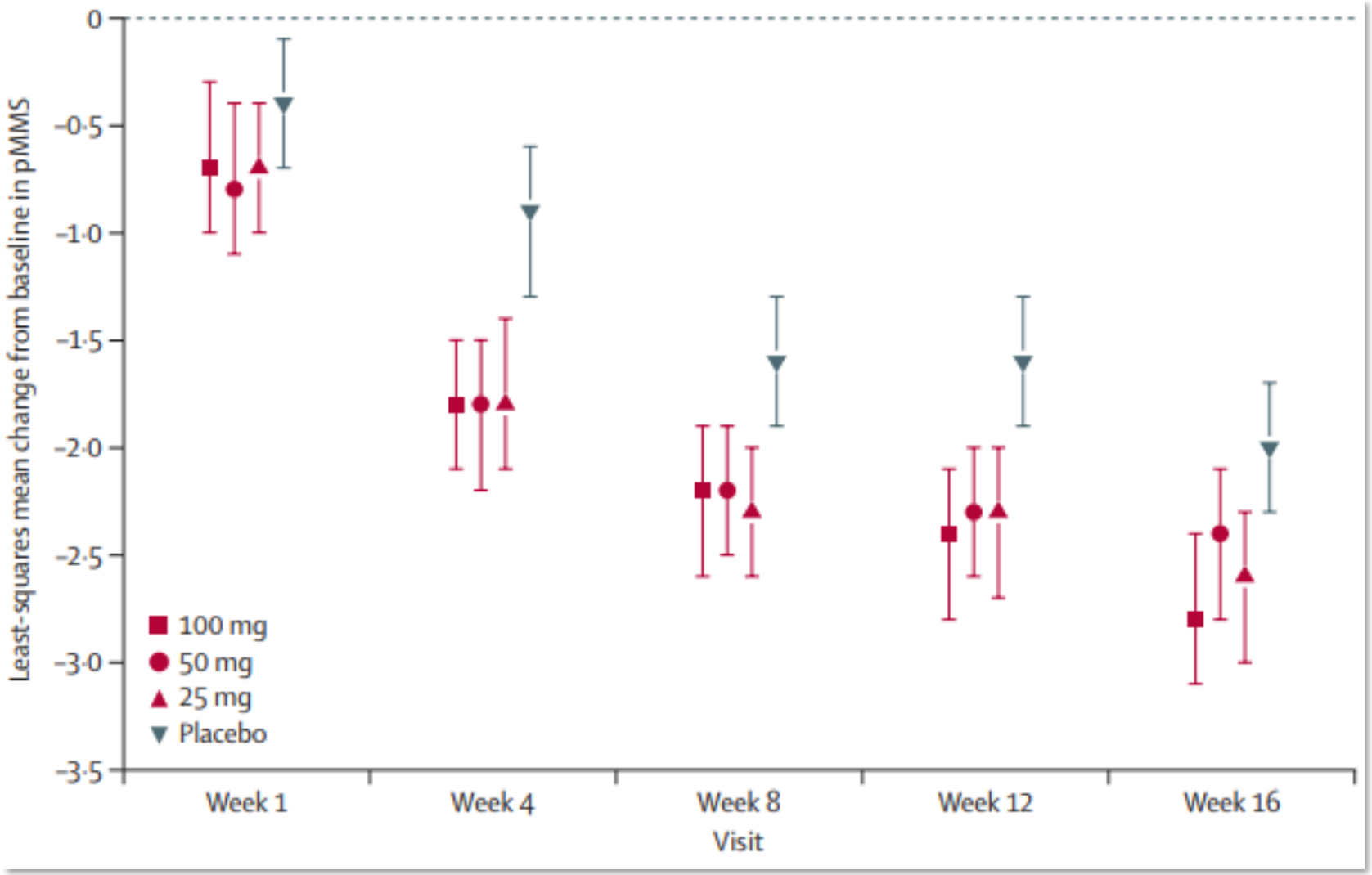

Vermiere S. et al. Lancet Gastro Hepatology. Sept 2022

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Conclusions

- Multiple new agents/approaches are on the horizon
- Cell therapy, TL1A monoclonals, Il-23 combination therapy and MRNA silencing are potential solutions
- Future is bright!
- (yet) Phase 3 looms!

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Novel Pathways and Upcoming IBD Therapies

1st Gulf Coast Symposium

Omni Royal Hotel New Orleans, Louisiana

October 15, 2022

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