Emerging Therapies 2024: What, Where, Why and When

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Disclosures

Grant/Research Support	
Consultant	AbbVie, Abivax, Adiso, AgomAB Therapeutics, Akros, Alira Health, Ally Bridge Group, AnaptysBio, Apini Therapeutics, Argenx, Avoro Capital Advisors, Belmore Law, BioFactura, BioJamp, Biora Therapeutics, Blackbird Laboratories, Boehringer-Ingelheim, Boxer Capital, Celsius Therapeutics, Celgene/BMS, Celltrion, Clarivate, Connect BioPharma, Disc Medicine, Duality, EcoR1, Eli Lilly, Ensho Therapeutics, Evida, Enveda, Faes Farma,First Wave, Forbion, Galapagos, Galen Atlantica, Genentech/Roche, General Atlantic, Genesis Therapeutics, Gilead, Gossamer Pharma, GSK, Imhotex, ImmiDomics, Immunic Therapeutics, Intercept, Janssen, Japan Tobacco Inc., Klick Health, LifeMine Therapeutics, Mage Biologics, Merck, Mestag, Mirador Therapeutics, Mobius, Monte Rosa Tx, Morphic Therapeutics, Nexys Therapeutics, Nighthawk Therapeutics, Nimbus Therapeutics, Novartis, OncoC4, OrbiMed, Orphagen, Pendopharm, Pfizer, Protagonist,32 Bio, REDX, Roche, Roivant/Televant, Sanofi, Sobi, Sorriso, Spyre Therapeutics, Surrozen Inc., Sun Pharma, Synedgen, Takeda, Teva, Triastek, Trex Bio, TR1X Inc. TVM Lifesciences, Ventyx Biosciences, Versant Ventures, Vida Ventures, Zagbio
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Expert Testimony	Belmore Law
Other Relationship/Affiliation	Senior Scientific Director, Alimentiv Inc.

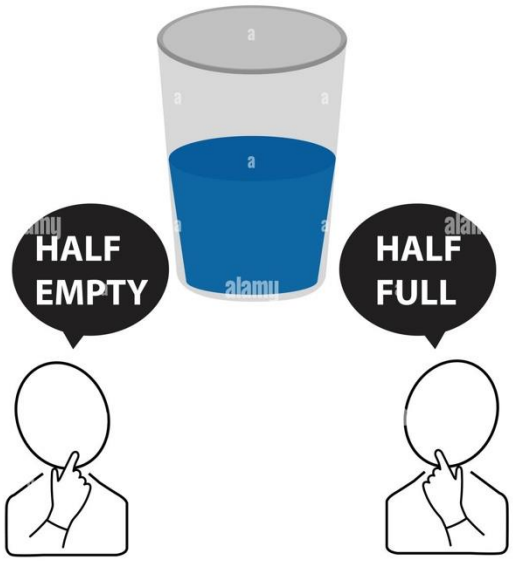
My Crystal Ball – A Disclaimer!

Topics to Be Discussed

- The Present -2024 a glass half full!
- Where are we headed?
  - Horizon agents
  - Combination therapy
  - Horizon indications/strategies
- Summary

IBD 2024- A glass half full!

- The introduction of multiple new treatments in the past 25 years has not resulted in consistently high rates of remission.
- Personalized medicine has not evolved as a management strategy for IBD
- We still do not understand the cause(s)



- Two emergent MOAs, anti-integrin therapy (vedolizumab) and IL-12/23 are extraordinarily safe.
- Several new MOAs have been validated
- Surgical rates have fallen dramatically in both UC and CD.

Topics to Be Discussed

- The Present = 2024 – A glass half full!
- Where are we headed?
  - Horizon agents
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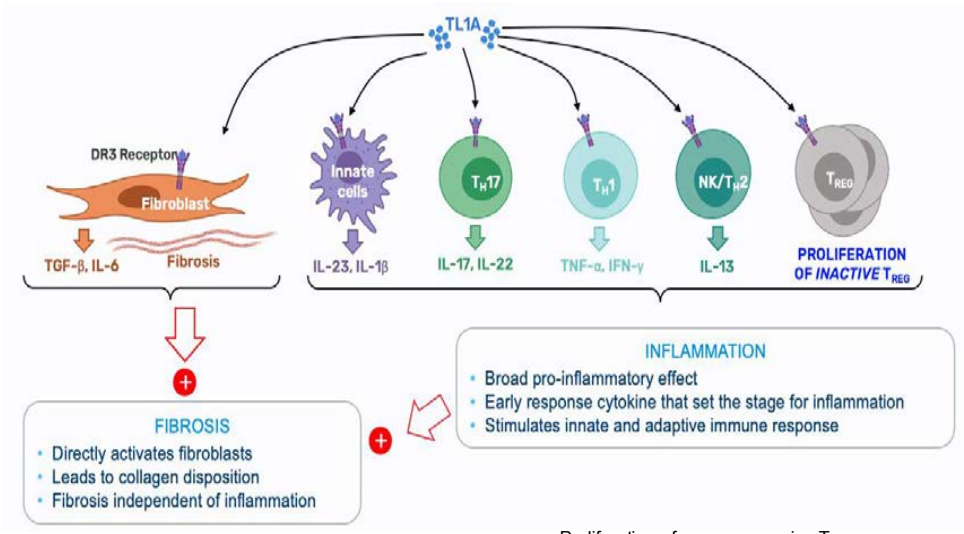
  - Horizon indications/strategies
- Summary

Horizon Agents: TL1A monoclonals

- TNF-like cytokine 1A, member of the TNF superfamily
- Variants in the TL1A-encoding gene (TNFSF15) are associated with increased IBD risk
- Expressed in antigen presenting cells, lymphocytes, and endothelial cells
- Transgenic mice develop colitis and intestinal fibrosis
- Murine anti-TL1A antibody alleviates inflammation and fibrosis

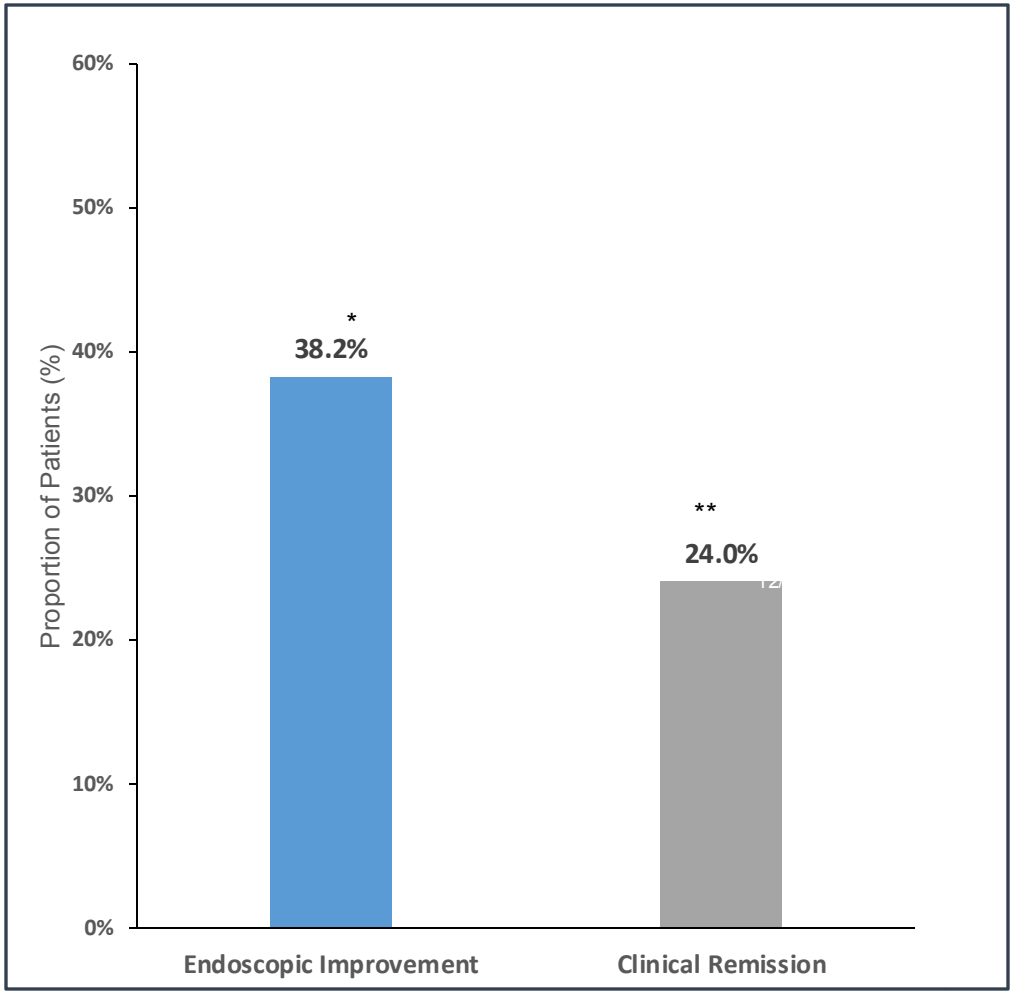


Proliferation of non-suppressive Tregs

[1]Ruuls et al. Immunity 2001
[2] Yue et al. J Biol Chem 1999.
[3]Furfaro et al. Curr Drug Targets 2021.
[4]Xu et al. Front Immunol 2022.

TL1A Antagonist as Induction Therapy for UC

Endoscopic & Clinical Endpoints at Week 14



- 14 week open-label study in moderately to severely active ulcerative colitis, N=50
- propensity matched artificial control
- 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.

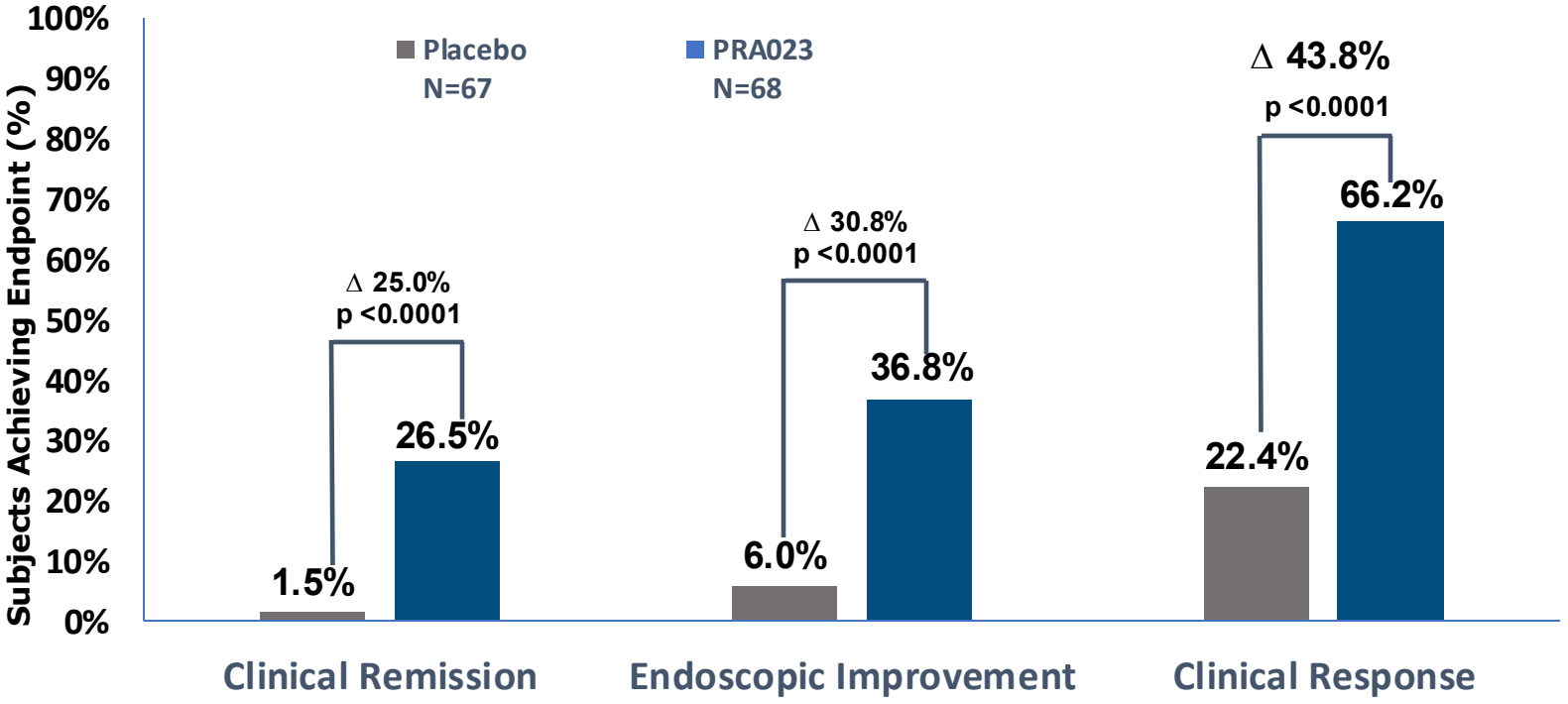
Primary and Secondary Endpoints at Week 12 Tulisokibart vs. Placebo

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 2 Trial of Anti-TL1A Monoclonal Antibody Tulisokibart for Ulcerative Colitis

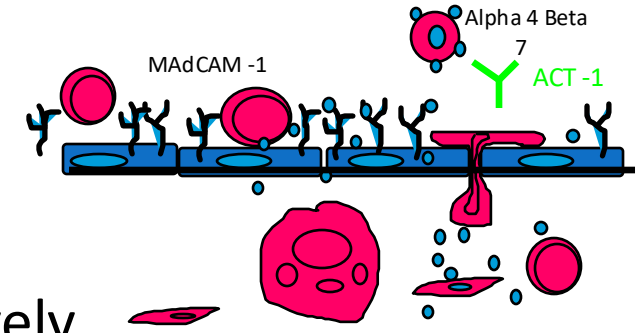
Bruce E. Sands, M.D., Brian G. Feagan, M.D., Laurent Peyrin-Biroulet, M.D., Ph.D., Silvio Danese, M.D., David T. Rubin, M.D., Olivier Laurent, Ph.D., Allison Luo, M.D., Deanna D. Nguyen, M.D., Jiandong Lu, Ph.D., Mark Yen, M.D., Jaroslaw Leszczyszyn, M.D., Ph.D., Radosław Kempiński, M.D., Ph.D., Dermot P.B. McGovern, M.D., Ph.D., Christopher Ma, M.D., Timothy E. Ritter, M.D., and Stephan Targan, M.D., for the ARTEMIS-UC Study Group*



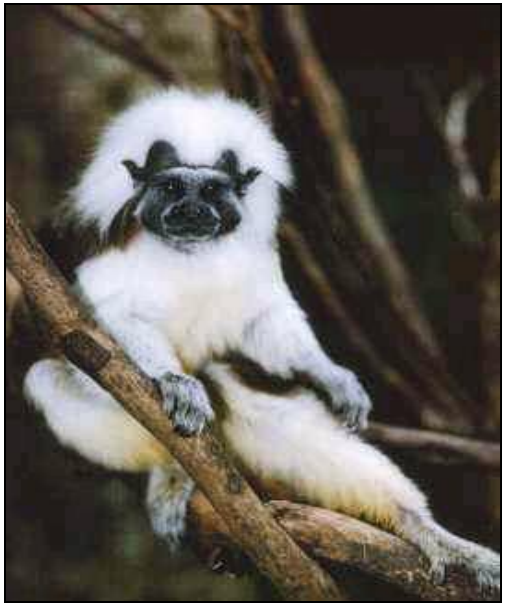
Clinical remission per mMS is defined as endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and stool frequency subscore of 0 or 1 and not greater than Baseline; Endoscopic improvement is defined as endoscopy subscore ≤ 1 with no friability; Clinical response per mMS is defined as reduction from Baseline ≥ 2 points and ≥ 30% in 3-component Modified Mayo Score, accompanied by a reduction ≥ 1 in rectal bleeding subscore or absolute rectal bleeding subscore ≤ 1. | P-values for testing the treatment difference are based on Cochran-Mantel-Haenszel test adjusted for prior biologic exposure status and CDx status. All endpoints are statistically significant according to multiplicity controlled 2-sided alpha of 0.05.

Sands BE. Et al. New Eng J Med. 2024;391(12):1119-29

Oral Alpha 4 Beta7 Blockade: 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

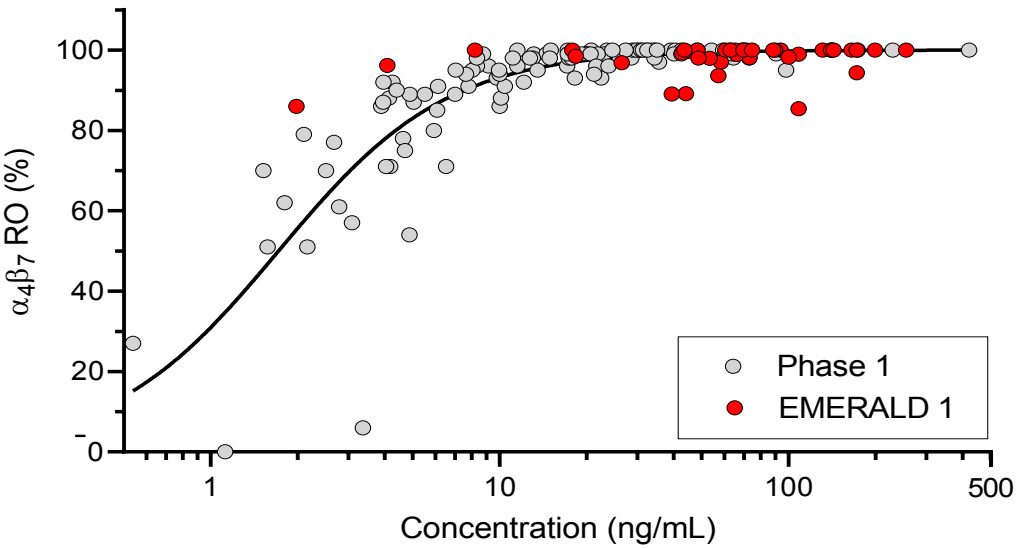
Oral Alpha4 Beta7 Antagonists

- Unique MOA
- Vedolizumab highly effective and safe in UC
- Multiple new indications (pouchitis, post-operative CD, GVH)
- Potential in combination therapy = the “polypill”

Morphic Data: Patient a4β7 Receptor Occupancy (RO) Consistent with Healthy Volunteer RO

a4β7 selectivity over a4β1 consistent with Phase 1 results

- a4β7 RO achieved early and sustained saturating levels
- a4β1 RO remained at low levels
- No lymphocytosis or changes to circulating naïve T-cells were observed
- a4β1 projected RO was below the limit of quantitation



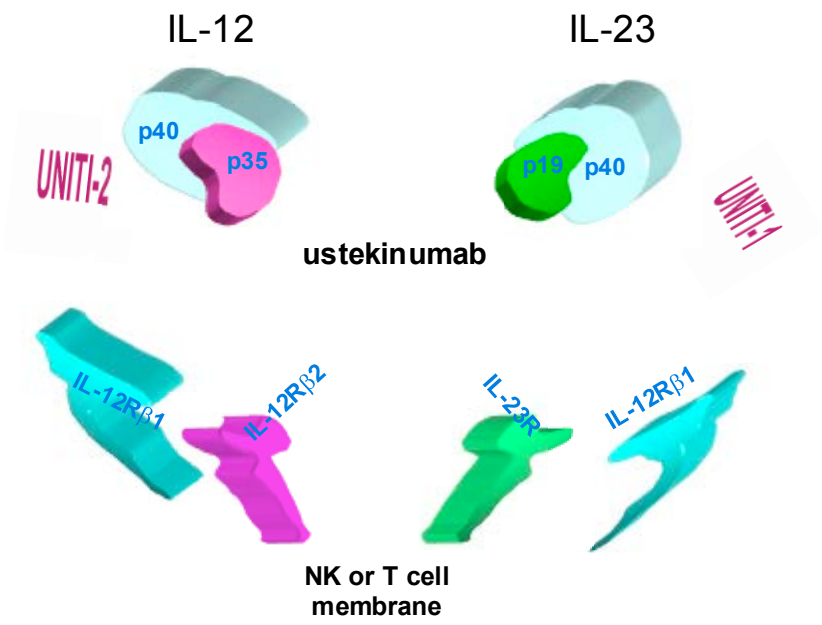
RO: Receptor Occupancy; BLQ, Below Limit of Quantification

Primary Endpoint Met with High Statistical Significance Consistent Effects Observed Among All Exploratory Measures

Endpoint @ Week 12	Overall (N=35)
Change in RHI, Mean (SD)	**-6.4 (11.18)** ***p=0.0019***
RHI remission, n (%)	8 (22.9%)
Clinical response (mMCS)[1], n (%)	16 (45.7%)
Clinical remission (mMCS)[2], n (%)	9 (25.7%)
Endoscopic Response/Improvement[3], n (%)	9 (25.7%)
Change from baseline to Week 12 in the Modified MCS, Mean (SD)	-2.3 (2.14)

1. Clinical response (mMCS): decrease from baseline in the mMCS ≥2 points and ≥30% from baseline, plus a decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore ≤1
2. Clinical remission (mMCS): rectal bleeding subscore of 0; a stool frequency subscore of ≤1; and an MES of ≤1 without friability
3. Endoscopic response / improvement: MES ≤1

Anti-p40 Ustekinumab: Background for Oral Il-23



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.

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 poin 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 safet 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 patient 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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118 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.

N Engl J Med 2015;373:1318-28.
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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 1CE, Canada, or at kapapp@probity medical.com.

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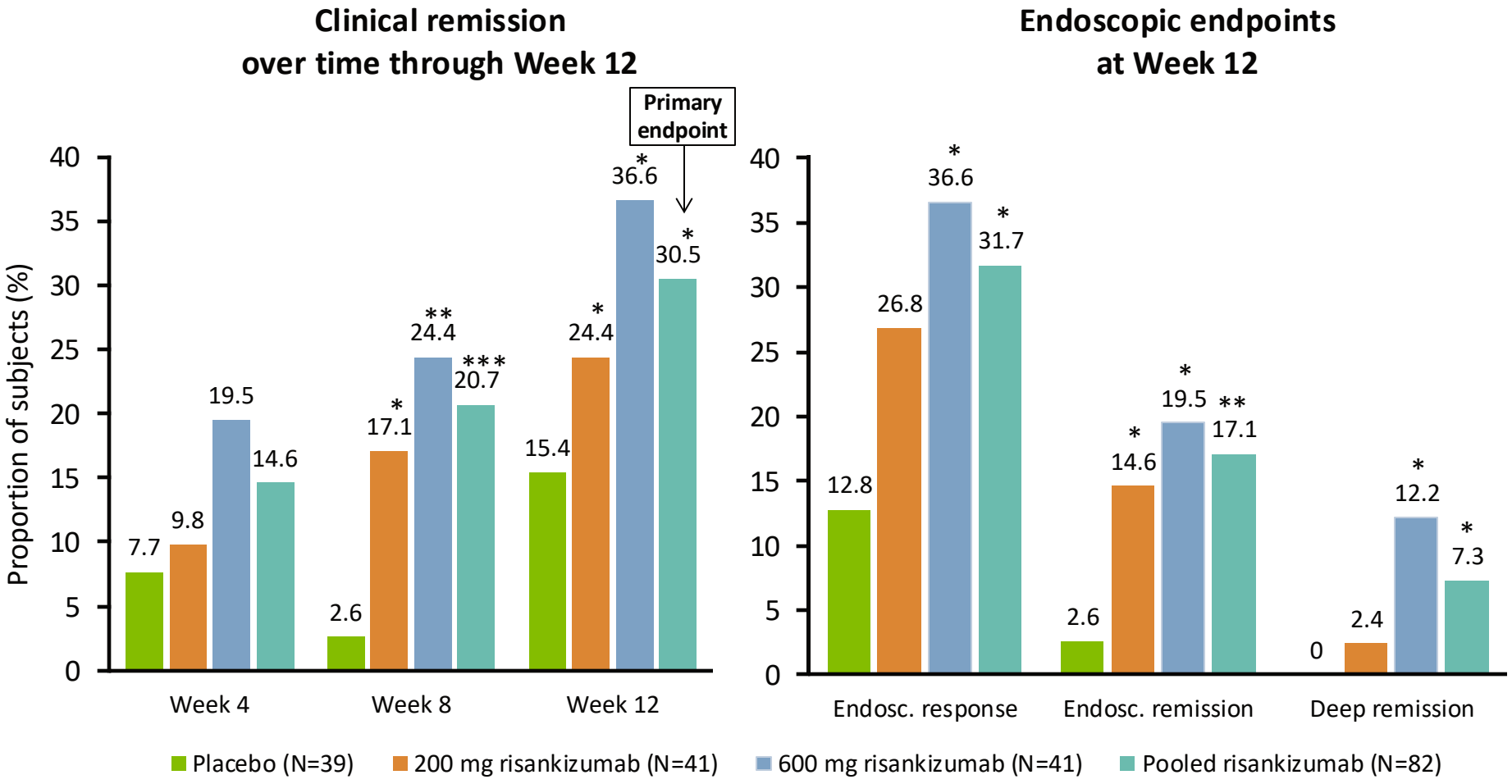
N ENGL J MED 376;16 NEJM.ORG APRIL 20, 2017 1551

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.

Risankizumab for CD: Is anti-P19 the Answer?



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

Oral IL-23 Peptide Therapy for Psoriasis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An Oral Interleukin-23–Receptor Antagonist Peptide for Plaque Psoriasis

Robert Bissonnette, M.D., Andreas Pinter, M.D., Laura K. Ferris, M.D., Ph.D., Sascha Gerdes, M.D., Phoebe Rich, M.D., Ronald Vender, M.D., Megan Miller, M.P.H., Yaung-Kaung Shen, Ph.D., Arun Kannan, Ph.D., Shu Li, Ph.D., Cynthia DeKlotz, M.D., and Kim Papp, M.D., Ph.D.

ABSTRACT

BACKGROUND

The use of monoclonal antibodies has changed the treatment of several immune-mediated inflammatory diseases, including psoriasis. However, these large proteins must be administered by injection. JNJ-77242113 is a novel, orally administered interleukin-23–receptor antagonist peptide that selectively blocks interleukin-23 signaling and downstream cytokine production.

METHODS

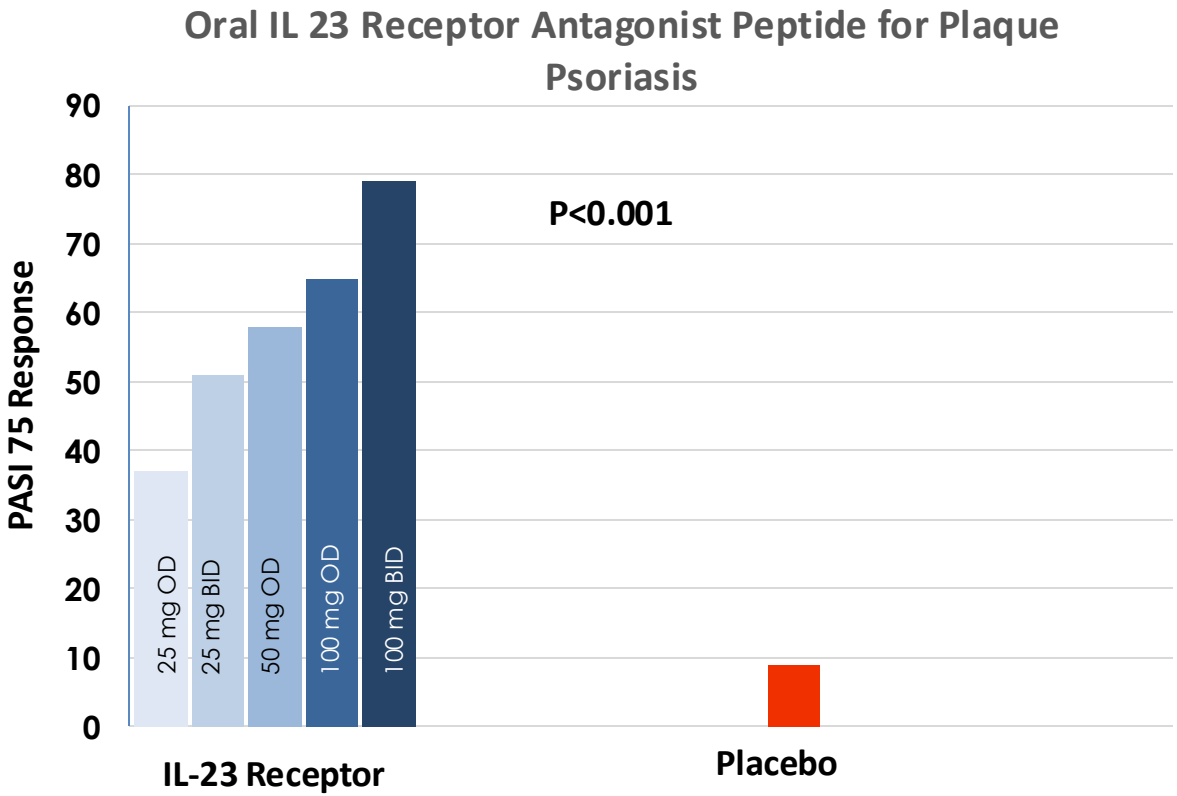
In this phase 2 dose-finding trial, we randomly assigned patients with moderate-to-severe plaque psoriasis to receive JNJ-77242113 at a dose of 25 mg once daily, 25 mg twice daily, 50 mg once daily, 100 mg once daily, or 100 mg twice daily or placebo for 16 weeks. The primary end point was a reduction from baseline of at least 75% in the Psoriasis Area and Severity Index (PASI) score (PASI 75 response; PASI scores range from 0 to 72, with higher scores indicating greater extent or severity of psoriasis) at week 16.

RESULTS

A total of 255 patients underwent randomization. The mean PASI score at baseline was 19.1. The mean duration of psoriasis was 18.2 years, and 78% of the patients across all the trial groups had previously received systemic treatments. At week 16, the percentages of patients with a PASI 75 response were higher among those in the JNJ-77242113 groups (37%, 51%, 58%, 65%, and 79% in the 25-mg once-daily, 25-mg twice-daily, 50-mg once-daily, 100-mg once-daily, and 100-mg twice-daily groups, respectively) than among those in the placebo group (9%), a finding that showed a significant dose–response relationship (P<0.001). The most common adverse events included coronavirus disease 2019 (in 12% of the patients in the placebo group and in 11% of those across the JNJ-77242113 dose groups) and nasopharyngitis (in 5% and 7%, respectively). The percentages of patients who had at least one adverse event were similar in the combined JNJ-77242113 dose group (52%) and the placebo group (51%). There was no evidence of a dose-related increase in adverse events across the JNJ-77242113 dose groups.

CONCLUSIONS

After 16 weeks of once- or twice-daily oral administration, treatment with the interleukin-23–receptor antagonist peptide JNJ-77242113 showed greater efficacy than placebo in patients with moderate-to-severe plaque psoriasis. (Funded by Janssen Research and Development; FRONTIER 1 ClinicalTrials.gov number, NCT05223868.)



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

Articles

ABX464 (obefazimod) for moderate-to-severe, active ulcerative colitis: a phase 2b, double-blind, randomised, placebo-controlled induction trial and 48 week, open-label extension

Severine Vermeire*, Bruce E Sands*, Herbert Tilg, Zsolt Tulassay, Radoslaw Kempinski, Silvio Danese, Ivan Bunganič, Josianne Nitcheu, Julien Santo, Didier Scherrer, Sophie Biguenet, Hartmut J Ehrlich, Jean-Marc Steens, Paul Gineste, William J Sandborn

Lancet Gastroenterol Hepatol 2022; 7: 1024–35

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Summary

Background ABX464 (obefazimod) is a small molecule that selectively upregulates miR-124 in immune cells. We aimed to assess ABX464 as a treatment for patients with moderate-to-severe, active ulcerative colitis.

Methods In this phase 2b, double-blind, randomised, placebo-controlled induction trial, patients were recruited from 95 centres (hospitals and health-care centres) in 16 countries. Eligible patients were aged 18–75 years, with a diagnosis of moderate-to-severe, active ulcerative colitis and a modified Mayo Score (MMS) of 5 points or higher, and a documented non-response or intolerance to previous treatment. Enrolled patients were randomly assigned (1:1:1:1) via an interactive voice and web response system to receive once daily oral ABX464 100 mg, ABX464 50 mg, ABX464 25 mg, or matched placebo. Randomisation was stratified according to study site (US *vs* non-US) and to whether the patient had previous exposure to second-line treatment with biologics or JAK inhibitors. The primary endpoint was the change from baseline in MMS at week 8. The primary efficacy analysis was done in the full analysis set (FAS), defined as all randomly assigned patients who received at least one dose of study treatment and had baseline data for at least one efficacy variable, and was analysed according to the principles of intention-to-treat. Safety analyses included patients who had been randomly assigned and who received at least one dose of study treatment. The 96 week open-label extension is ongoing. This study is registered with ClinicalTrials.gov, NCT04023396.

Findings Between Aug 13, 2019, and April 16, 2021, 254 patients were randomly allocated to ABX464 100 mg (n=64), ABX464 50 mg (n=63), ABX464 25 mg (n=63), or placebo (n=64). Two patients, both in the ABX464 25 mg group, were excluded from the FAS. In the FAS at week 8, the least squares mean (LSM) change from baseline in MMS was −2·9 (95% CI −3·4 to −2·5) for the ABX464 100 mg group, −3·2 (−3·7 to −2·7) for the ABX464 50 mg group, −3·1 (−3·6 to −2·6) for the ABX464 25 mg group, and −1·9 (−2·4 to −1·5) for placebo group; the magnitude of the difference in MMS from baseline was significantly greater in all three ABX464 groups compared with placebo (p=0·0039 for ABX464 100 mg *vs* placebo, p=0·0003 for ABX464 50 mg *vs* placebo, and p=0·0010 for ABX464 25 mg *vs* placebo). The most frequently reported adverse event was headache, which was reported for 27 (42%) of 64 patients in the ABX464 100 mg group, 19 (30%) of 63 in the 50 mg group, 13 (21%) of 62 in the 25 mg group, and five (8%) of 64 in the placebo group. Severe (grade 3) headache was reported for three (5%) patients in the ABX464 group 100 mg group, two (3%) in the ABX464 50 mg group, one (2%) in the ABX464 25 mg group, and none in the placebo group. The only serious adverse event reported for two or more patients in any group was ulcerative colitis (one in each of the ABX464 100 mg and 50 mg groups, and three [5%] in the placebo group).

Interpretation All doses of ABX464 significantly improved moderate-to-severe, active ulcerative colitis compared with placebo, as measured by changes in MMS from baseline to week 8. A phase 3 clinical programme is ongoing.

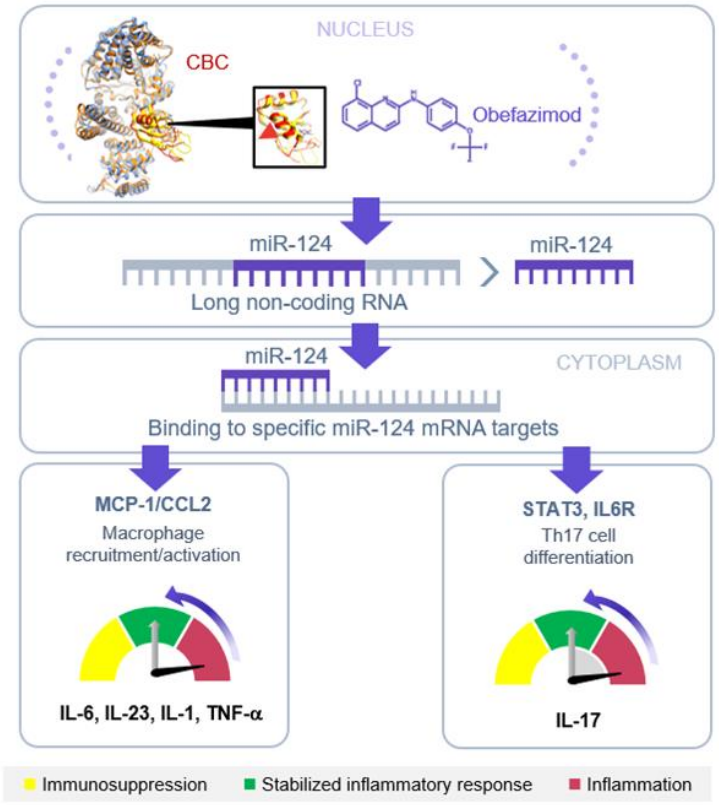
Funding Abivax.

Introduction

Ulcerative colitis is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which starts in the rectum and extends proximally in a continuous manner through part of the colon or the entire colon.[1] Bloody diarrhoea is the characteristic symptom of the disease. The choice of treatment for ulcerative colitis is generally based on the pattern of involvement of the disease and the degree of clinical activity.[2] In uncomplicated disease (eg, amenable to first-line treatment), 5-aminosalicylic acids (5-ASA), administered orally or rectally, is usually sufficient for inducing and sustaining remission. In patients with moderate-to-severe ulcerative colitis not responding to 5-ASA, additional therapy such as

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

Obefazimod MOA: enhanced expression of miR-124 results in a decrease in cytokines and immune cells



1 Obefazimod binds to cap binding complex (CBC) within the nucleus; demonstrated by cryo-electron microscopy* (CryoEM)

2 Selectively enhances the expression of a single micro-RNA (miRNA), miR-124

3 miR-124 reduces translation of mRNA targets

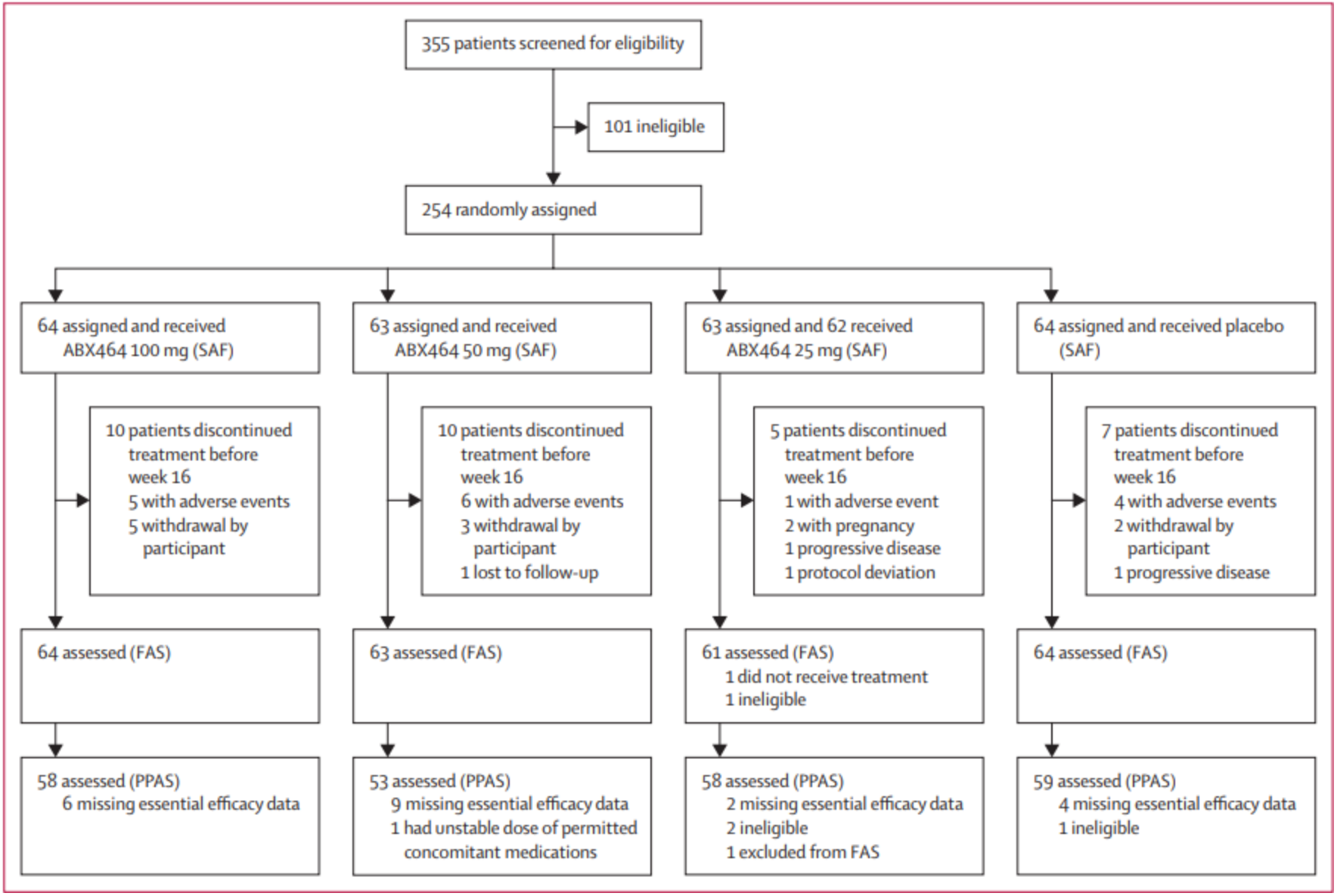
4 Levels of cytokines and immune cells are stabilized

* Cryo-electron microscopy is a technique to determine protein structure

Source: Vermeire S, et al. J Crohns Colitis. 2023; Data on file. Abivax

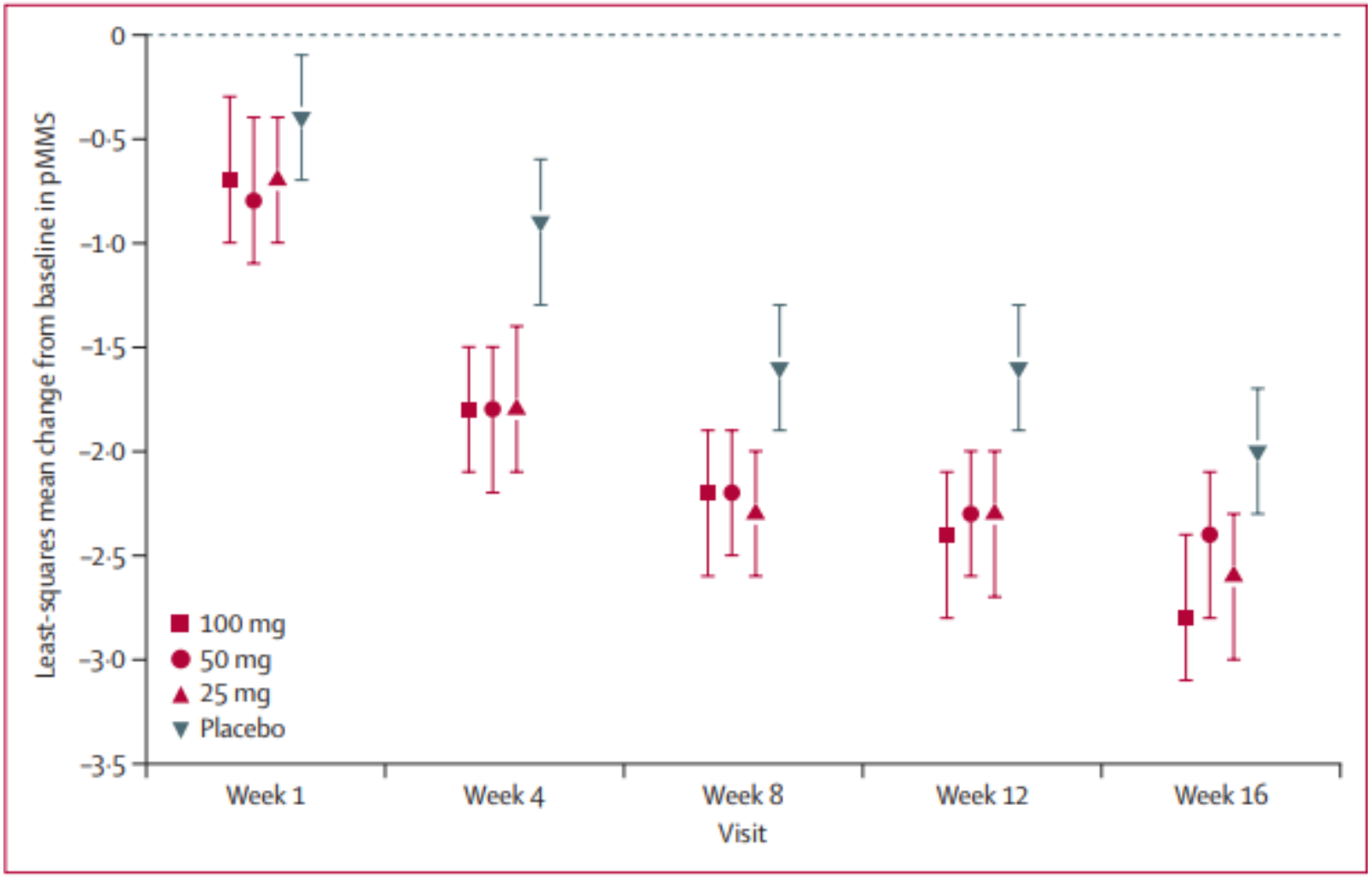
ABIVAX

Obefazimod Induction Therapy for UC



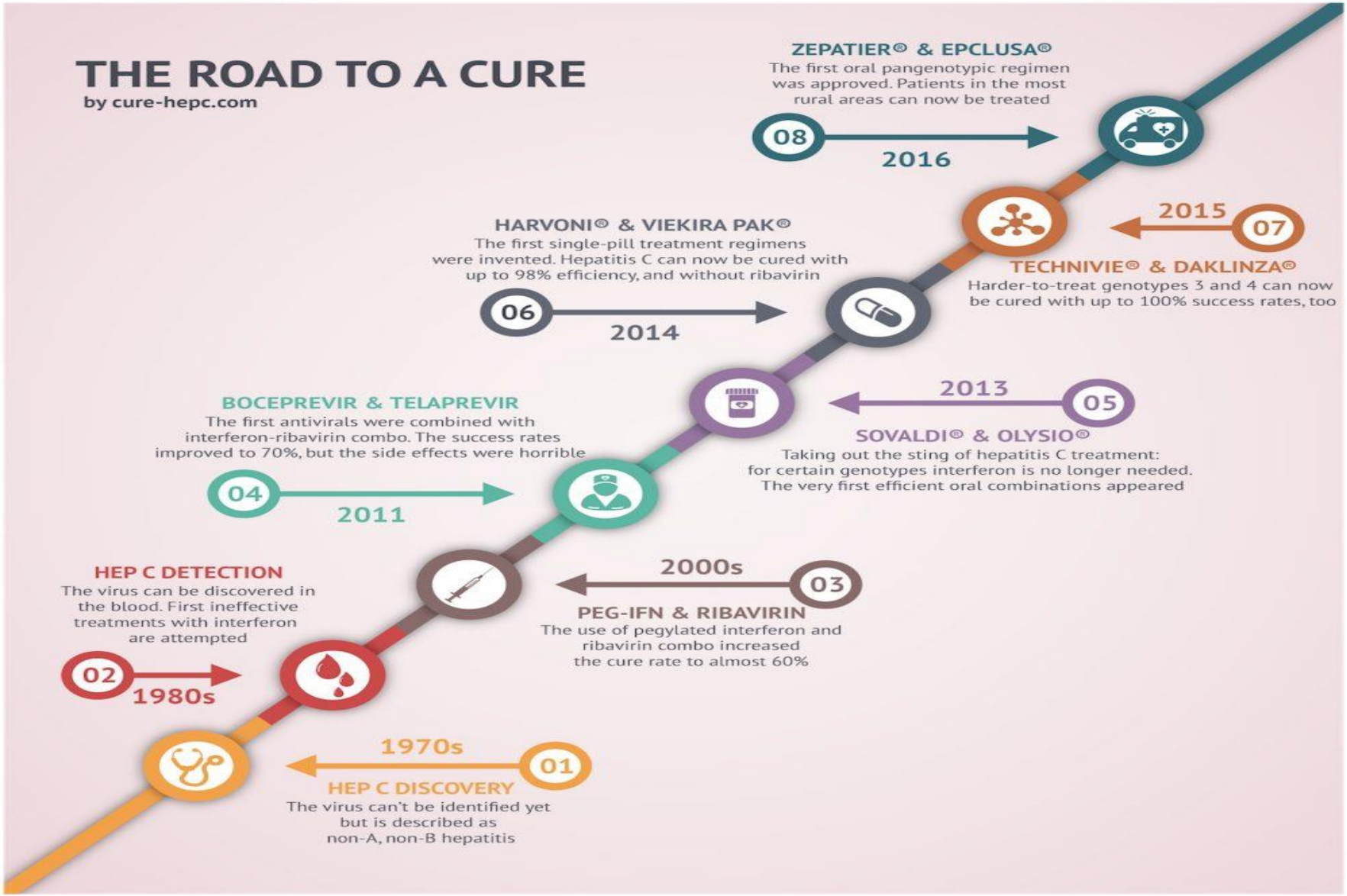
Vermiere S. et al. Lancet Gastro Hepatology. Sept 2022

Mean Change from Baseline MCS to Week 16



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

Combination Therapy….
Behold HCV treatment



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

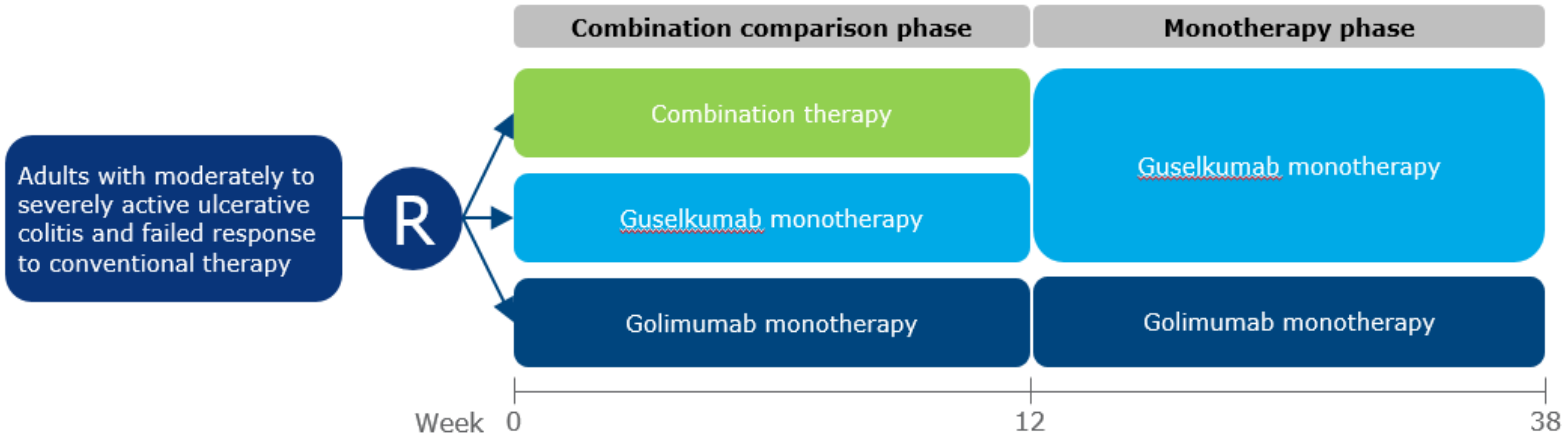
- To evaluate the safety and efficacy of combination therapy with guselkumab and golimumab in patients with moderately to severely active ulcerative colitis

PRIMARY ENDPOINT

- Clinical response at Week 12 defined by Mayo score

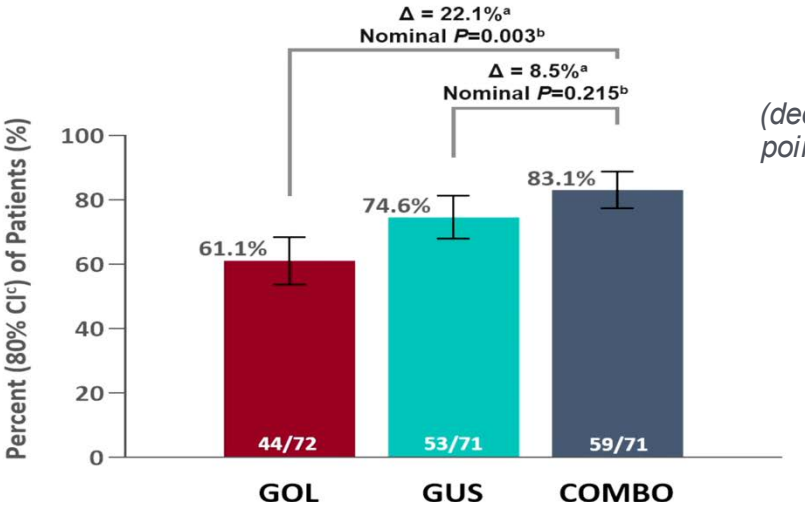
MAJOR SECONDARY ENDPOINTS

- Clinical remission at Week 12 defined by Mayo score



Feagan BG et al. Lancet Gastroenterol Hepatol.2023;8(4):307-320.

VEGA Clinical Response and Remission Week 12

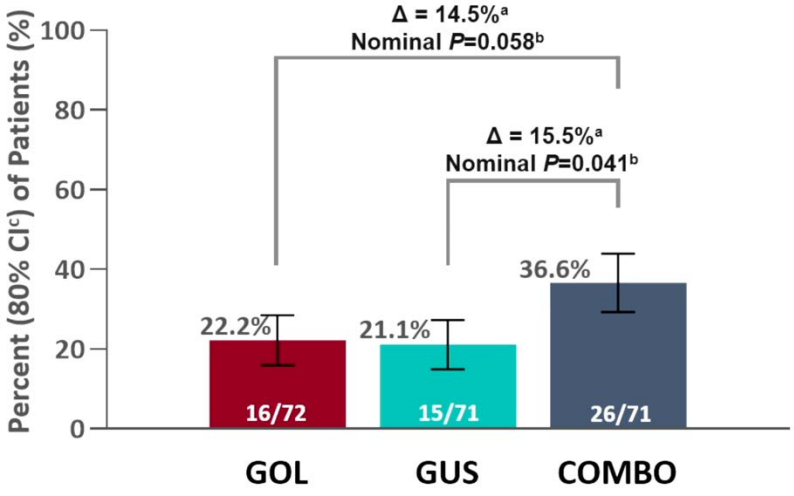


Clinical Response

(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)

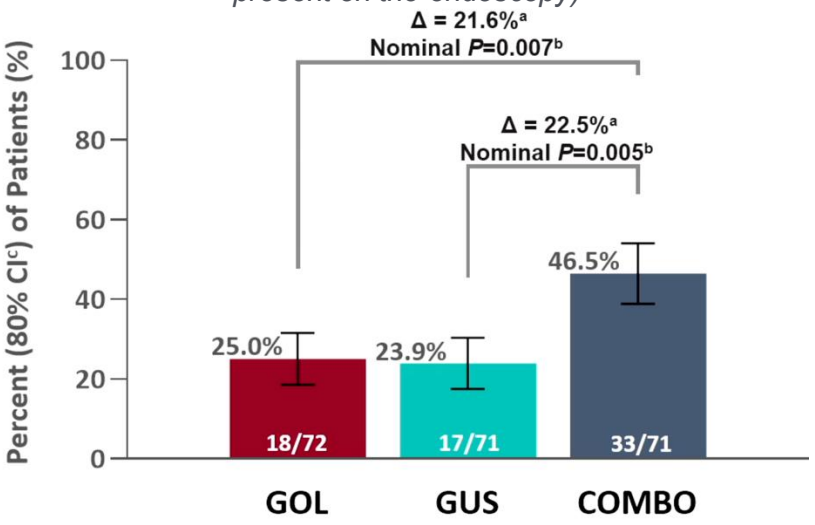
Clinical Remission

(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)



Feagan BG et al. Lancet Gastroenterol Hepatol.2023;8(4):307-320

Topic to be Discussed
Horizon Agents/Strategies

- More effective therapy for fistulizing/fibrostenosing CD
- Emerging treat to target strategies

Fibrostenosing/Fistulizing CD: A Critical Problem!

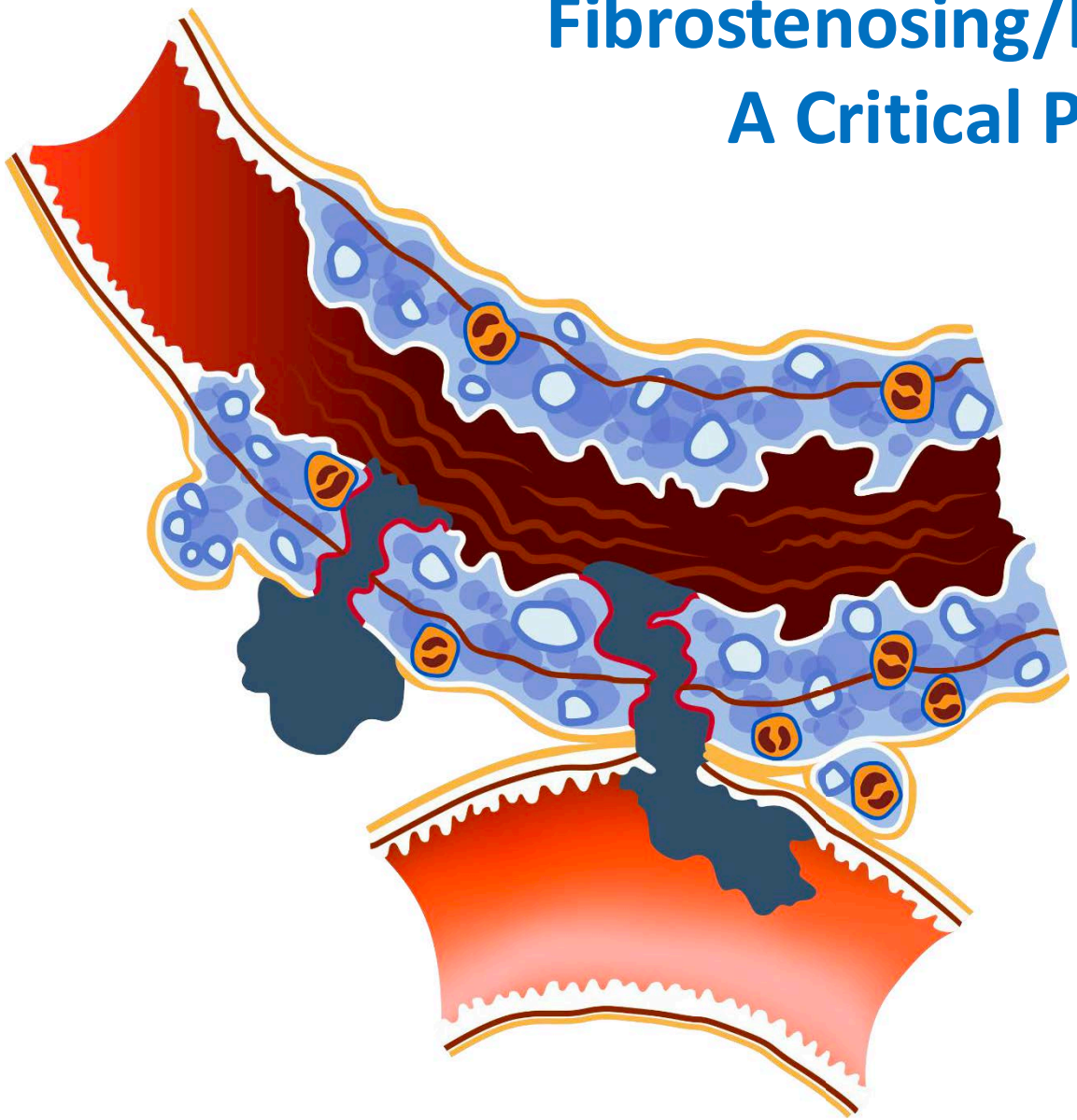
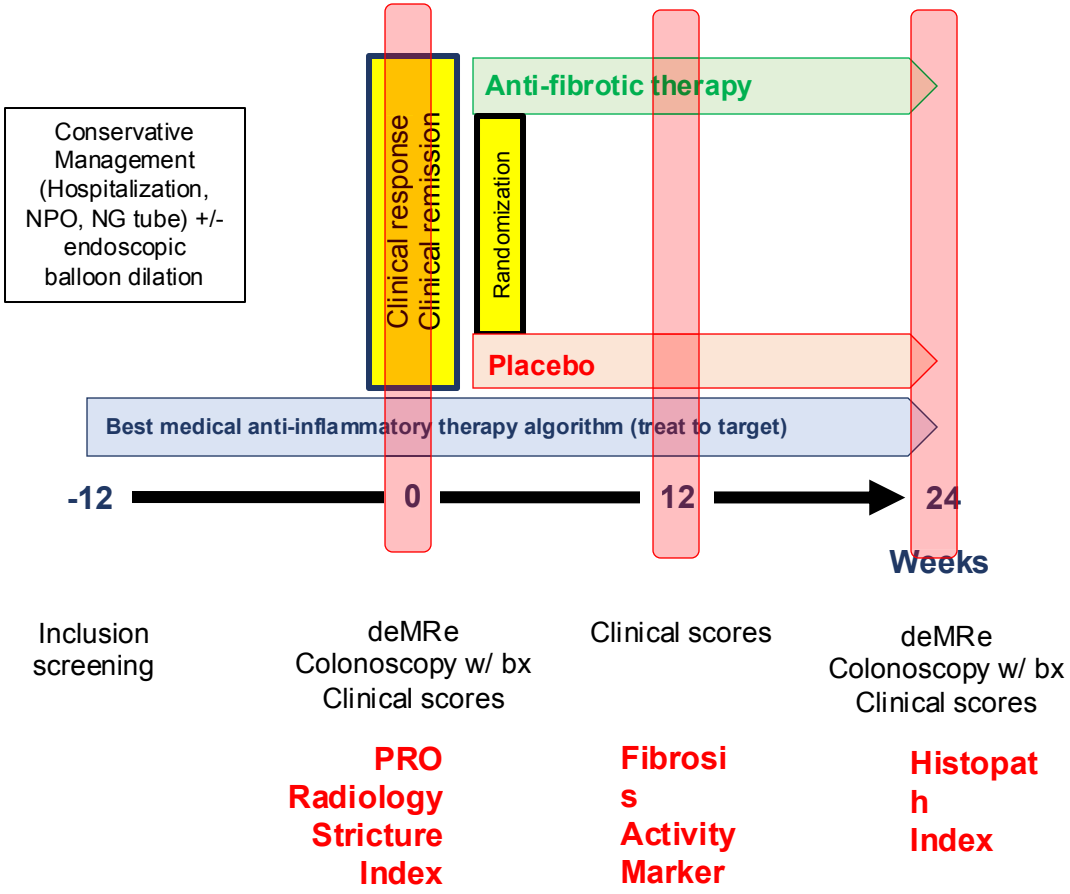


Figure adapted from Rubin E, Farber JL. Pathology 4th ed. Philadelphia. Lipponcott Wilkins, 2005.

CONSTRICT Study Group: Potential Phase II Proof of Concept Study Design



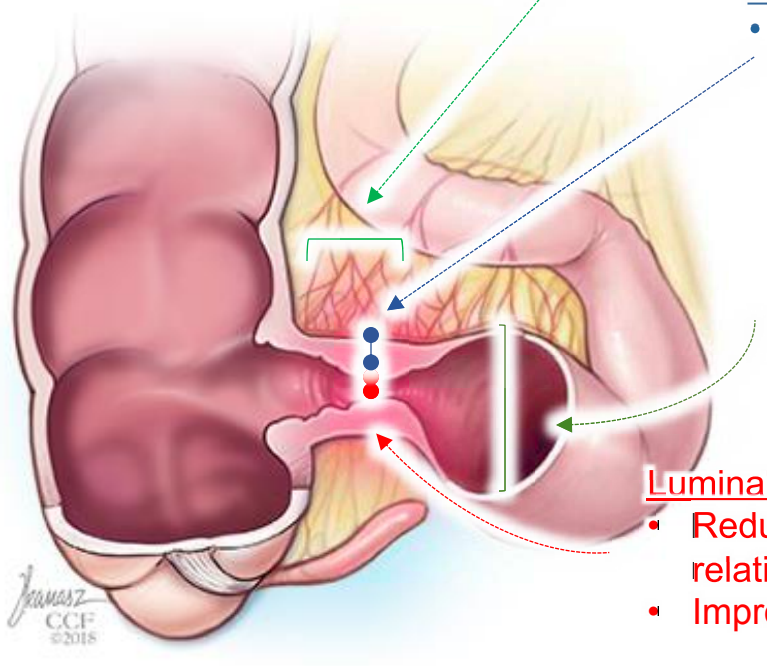
expMRe: experimental MR enterography; CSP: Colonoscopy; FC: Fecal Calprotectin; CRP: C-reactive protein
Clinical scores: Crohn's disease stricture score, Crohn's disease activity index

Rieder et al. APT. 2018

Definitions for Successful Treatment on Radiology

Reduction in:

- Localized luminal narrowing
- Bowel wall thickening
- Pre-stricture dilation
- Stricture length



Length
- Reduction of length by 50%

Wall thickness
- Reduction of thickening by 50%

Prestenotic dilation
- Diameter less than 2.5 cm
- Reduction of pre-stricture dilation by 50%
- Diameter equal to normal bowel

Luminal diameter
- Reduction less than 50% measured relative to normal adjacent bowel
- Improvement by 50%

Rieder et al. APT. 2018

Radiology

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Reliability of CT Enterography for Describing Fibrostenosing Crohn Disease

Florian Rieder, MD • Christopher Ma, MD* • Jurij Hanzel, MD • Joel G. Fletcher, MD • Mark E. Baker, MD • Zhongya Wang, MS • Leonardo Guizzetti, PhD • Lisa M. Shackelton, PhD • Julie Rémillard, MS • Mihir Patel, MD • Jiafei Niu, MD • Ronald Ottichilo, MS • Cynthia S. Santillan, MD • Nunzia Capozzi, MD • Stuart A. Taylor, MD • David H. Bruining, MD • Guangyong Zou, PhD • Brian G. Feagan, MD • Vipul Jairath, MD** • Jordi Rimola, MD** • for the Stenosis Therapy and Anti-Fibrotic Research (STAR) Consortium*

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Supported by Alimentiv, Pfizer (unrestricted grant), the National Institutes of Health (NIH R01 DK123233, NIH R01 132038), and the Helmsley Charitable Trust.

* F.R. and C.M. contributed equally to this work.

** V.J. and J. Rimola are co-senior authors.

Conflicts of interest are listed at the end of this article.

See also the article by Rieder et al in this issue.

See also the editorial by Galgano and Summerlin in this issue.

Radiology 2024; 312(2):e233038 • https://doi.org/10.1148/radiol.233038 • Content codes: GI MR CT

Background: Standardized methods to measure and describe Crohn disease strictures at CT enterography are needed to guide clinical decision making and for use in therapeutic studies.

Purpose: To assess the reliability of CT enterography features to describe Crohn disease strictures and their correlation with stricture severity.

Materials and Methods: A retrospective study was conducted in 43 adult patients with symptomatic terminal ileal Crohn disease strictures who underwent standard-of-care CT enterography at a tertiary care center at the Cleveland Clinic between January 2008 and August 2016. After training on standardized definitions, four abdominal radiologists blinded to all patient information assessed imaging features (seven continuous measurements and nine observations) of the most distal ileal stricture in two separate sessions (separated by ≥2 weeks) in random order. Features with an interrater intraclass correlation coefficient (ICC) of 0.41 or greater (ie, moderate reliability or better) were considered reliable. Univariable and multivariable linear regression analysis identified reliable features associated with a visual analog scale of overall stricture severity. Significant reliable features were assessed as components of a CT enterography–based model to quantitate stricture severity.

Results: Examinations in 43 patients (mean age, 52 years ± 16 [SD]; 23 female) were evaluated. Five continuous measurements and six observations demonstrated at least moderate interrater reliability (interrater ICC range, 0.42 [95% CI: 0.25, 0.57] to 0.80 [95% CI: 0.67, 0.88]). Of these, 10 were univariably associated with stricture severity, and three continuous measurements—stricture length (interrater ICC, 0.64 [95% CI: 0.42, 0.81]), maximal associated small bowel dilation (interrater ICC, 0.80 [95% CI: 0.67, 0.88]), and maximal stricture wall thickness (interrater ICC, 0.50 [95% CI: 0.34, 0.62])—were independently associated (*P* value range, <.001 to .003) with stricture severity in a multivariable model. These three measurements were used to derive a well-calibrated (optimism-adjusted calibration slope = 1.00) quantitative model of stricture severity.

Conclusion: Standardized CT enterography measurements and observations can reliably describe terminal ileal Crohn disease strictures. Stricture length, maximal associated small bowel dilation, and maximal stricture wall thickness are correlated with stricture severity.

Supplemental material is available for this article.

Radiology

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

Reliability of MR Enterography Features for Describing Fibrostenosing Crohn Disease

Florian Rieder, MD • Mark E. Baker, MD • David H. Bruining, MD • Jeff L. Fidler, MD • Eric C. Ehman, MD • Shannon P. Sheedy, MD • Jay P. Heiken, MD • Justin M. Ream, MD • David R. Holmes III, PhD • Akitoshi Inoue, MD • Payam Mohammadinejad, MD • Yong S. Lee, PhD • Stuart A. Taylor, MD • Jaap Stoker, MD • Guangyong Zou, PhD • Zhongya Wang, MS • Julie Rémillard, MS • Rickey E. Carter, PhD • Ronald Ottichilo, MS • Norma Atkinson, MD • Mohamed Tausif Siddiqui, MD • Venkata C. Sunkesula, MD • Christopher Ma, MD • Claire E. Parker, MLIS • Julian Panés, MD • Jordi Rimola, MD • Vipul Jairath, MD • Brian G. Feagan, MD • Joel G. Fletcher, MD • for the Stenosis Therapy and Anti-Fibrosis Research (STAR) Consortium

From the Department of Inflammation and Immunity, Lerner Research Institute (F.R., R.O., N.A.), Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases (F.R., M.T.S., V.C.S.), and Program for Global Translational Inflammatory Bowel Disease Research (F.R., R.O.), Cleveland Clinic Foundation, Cleveland, Ohio; Section of Abdominal Imaging, Imaging, Digestive Diseases and Surgery and Cancer Institutes (M.E.B.) and Department of Diagnostic Radiology (J.M.R.) Cleveland Clinic Foundation, Cleveland, Ohio; Division of Gastroenterology and Hepatology (D.H.B.), Biomedical Imaging Resource (D.R.H.), and Department of Radiology (J.L.F., E.C.E., S.P.S., J.P.H., D.R.H., Y.S.L., J.G.F.), Mayo Clinic, 200 First St, Rochester, MN 55905; Department of Radiology, Shiga University of Medical Science, Shiga, Japan (A.I.); Department of Radiology, University of Texas Medical Branch, Galveston, Tex (P.M.); Centre for Medical Imaging, University College London, London, United Kingdom (S.A.T.); Department of Radiology and Nuclear Medicine, Amsterdam University Medical Centre, University of Amsterdam, Amstedam, the Netherlands (J.S.); Alimentiv, London, Ontario, Canada (G.Z., Z.W., J. Rémillard, C.M., C.E.P., V.J., B.G.F.); Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada (G.Z., V.J., B.G.F.); Department of Quantitative Health Sciences, Mayo Clinic, Jacksonville, Fla (R.E.C.); Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta, Canada (C.M.); Departments of Gastroenterology (J.P.) and Radiology (J. Rimola), Hospital Clínic de Barcelona, Barcelona, Spain; and Department of Medicine, Division of Gastroenterology, Western University, London, Ontario, Canada (V.J., B.G.F.). Received November 10, 2023; revision requested January 2, 2024; final revision received April 12; accepted April 23. **Address correspondence to** J.G.F. (email: *fletcher.joel@mayo.edu*).

Supported by Alimentiv, the Leona M. and Harry B. Helmsley Charitable Trust, and Pfizer (unrestricted grant). F.R. supported by the National Institutes of Health (NIH R01 DK123233, NIH R01 132038).

Conflicts of interest are listed at the end of this article.

See also the article by Rieder and Ma et al in this issue.

See also the editorial by Galgano and Summerlin in this issue.

Radiology 2024; 312(2):e233039 • https://doi.org/10.1148/radiol.233039 • Content codes: GI MR CT

Background: Clinical decision making and drug development for fibrostenosing Crohn disease is constrained by a lack of imaging definitions, scoring conventions, and validated end points.

Purpose: To assess the reliability of MR enterography features to describe Crohn disease strictures and determine correlation with stricture severity.

Materials and Methods: A retrospective study of patients with symptomatic terminal ileal Crohn disease strictures who underwent MR enterography at tertiary care centers (Cleveland Clinic: September 2013 to November 2020; Mayo Clinic: February 2008 to March 2019) was conducted by using convenience sampling. In the development phase, blinded and trained radiologists independently evaluated 26 MR enterography features from baseline and follow-up examinations performed more than 6 months apart, with no bowel resection performed between examinations. Follow-up examinations closest to 12 months after baseline were selected. Reliability was assessed using the intraclass correlation coefficient (ICC). In the validation phase, after five features were redefined, reliability was re-estimated in an independent convenience sample using baseline examinations. Multivariable linear regression analysis identified features with at least moderate interrater reliability (ICC ≥0.41) that were independently associated with stricture severity.

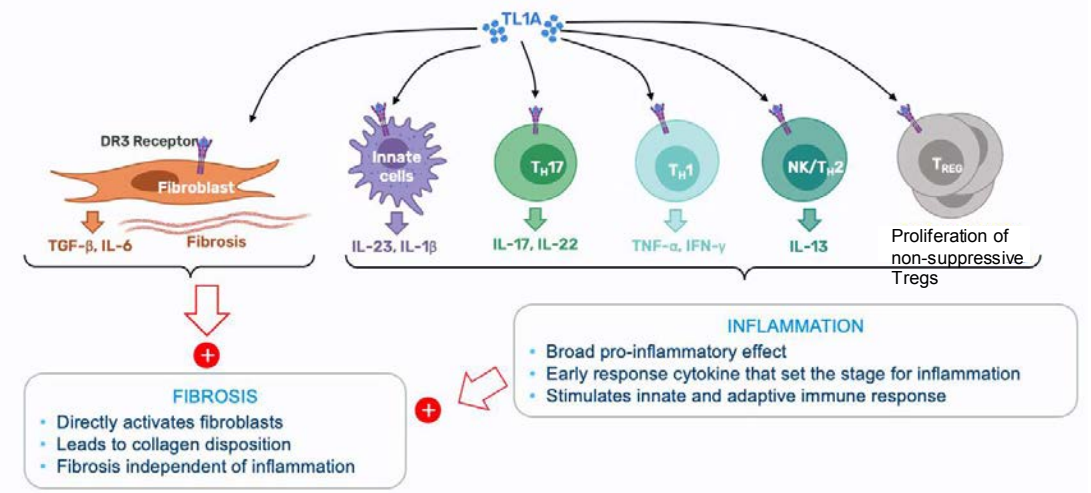
Results: Ninety-nine (mean age, 40 years ± 14 [SD]; 50 male) patients were included in the development group and 51 (mean age, 45 years ± 16 [SD]; 35 female) patients were included in the validation group. In the development group, nine features had at least moderate interrater reliability. One additional feature demonstrated moderate reliability in the validation group. Stricture length (ICC = 0.85 [95% CI: 0.75, 0.91] and 0.91 [95% CI: 0.75, 0.96] in development and validation phase, respectively) and maximal associated small bowel dilation (ICC = 0.74 [95% CI: 0.63, 0.80] and 0.73 [95% CI: 0.58, 0.87] in development and validation group, respectively) had the highest interrater reliability. Stricture length, maximal stricture wall thickness, and maximal associated small bowel dilation were independently (regression coefficients, 0.09–3.97; $P < .001$) associated with stricture severity.

Conclusion: MR enterography definitions and scoring conventions for reliably assessing features of Crohn disease strictures were developed and validated, and feature correlation with stricture severity was determined.

Supplemental material is available for this article.

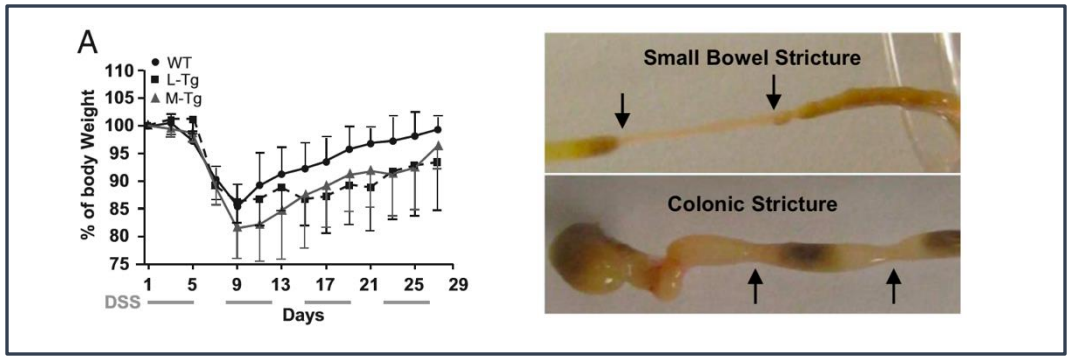
TL1A: First IBD Target That Mediates Inflammation & Fibrosis

- TNF-like cytokine 1A, member of the TNF superfamily[1,2]
- Expressed in antigen presenting cells, lymphocytes, and endothelial cells.
- Since its first discovery in 2001 delete, TL1A has been linked to multiple autoinflammatory & fibrotic diseases, including IBD[3,4]
  - Transgenic mice develop colitis and intestinal fibrosis
  - Murine anti-TL1A antibody alleviates inflammation and fibrosis
  - Variants in the TL1A-encoding gene (TNFSF15) are associated with increased IBD risk
    - TL1A likely a differential disease driver in a subgroup of IBD patients
    - Genetically-based diagnostic test being developed to identify patients with higher likelihood of response

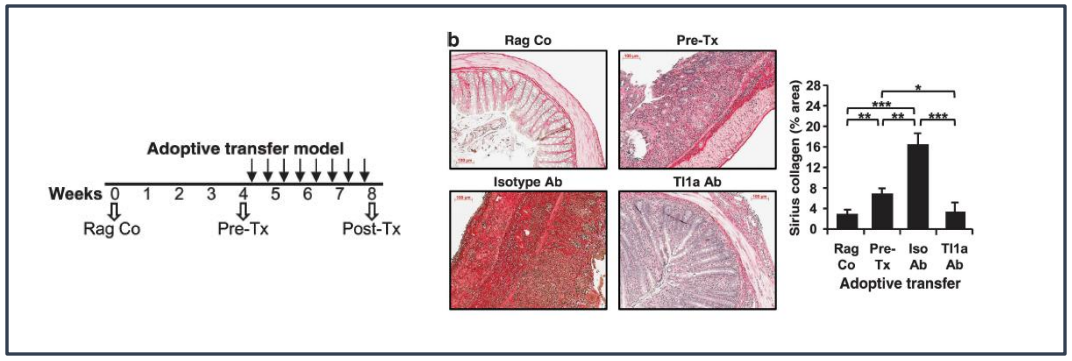


[1]Ruuls et al. Immunity 2001
[2] Yue et al. J Biol Chem 1999.
[3]Furfaro et al. Curr Drug Targets 2021.
[4]Xu et al. Front Immunol 2022.

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

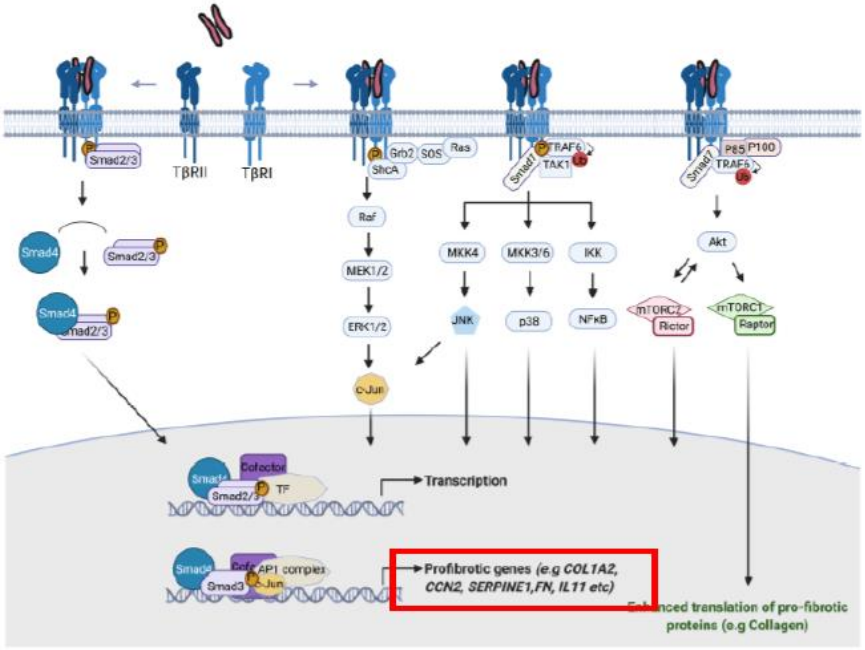


- TL1A antibody treatment reverses established fibrosis in murine colitis
- This was observed in two different mouse models of chronic colitis in a study conducted by Cedars-Sinai

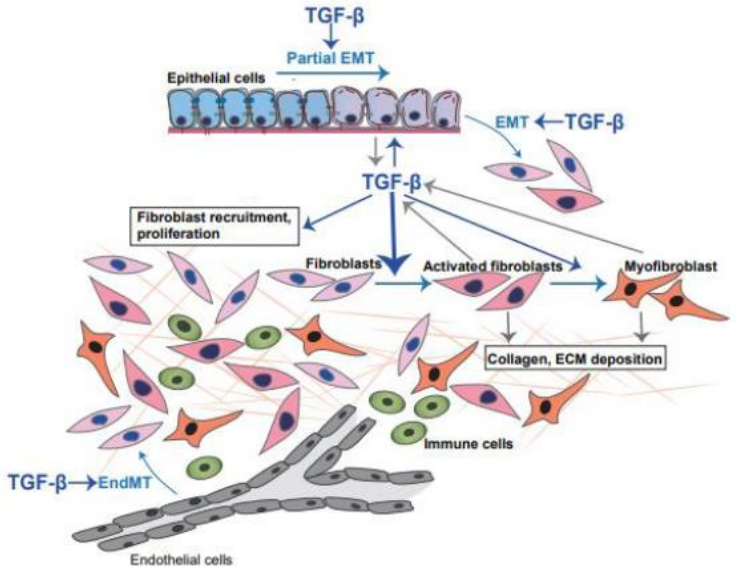
TGF-Beta is a Dominant Driver of Fibrosis

MoA: TGF-β directly activates fibrogenic genes and EMT/endMT

- TGFβ directly activates transcription of fibrogenic genes such as **serpine-1 (PAI-1), IL-11, collagens** and **fibronectin**

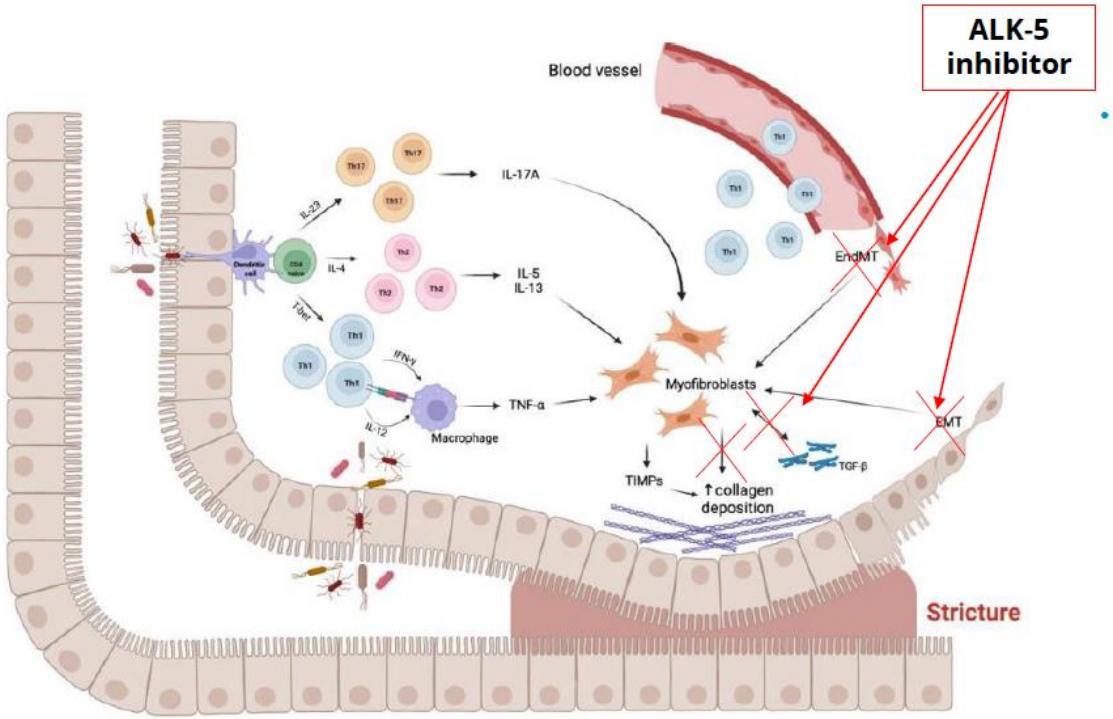


- TGFβ recruits but also generates new myofibroblasts from epithelial and endothelial cells through induction of EMT/EndMT
- TGF-β directly activates genes involved in EMT such as Snail



Inhibition of Alk-5 Downregulates TGF-beta

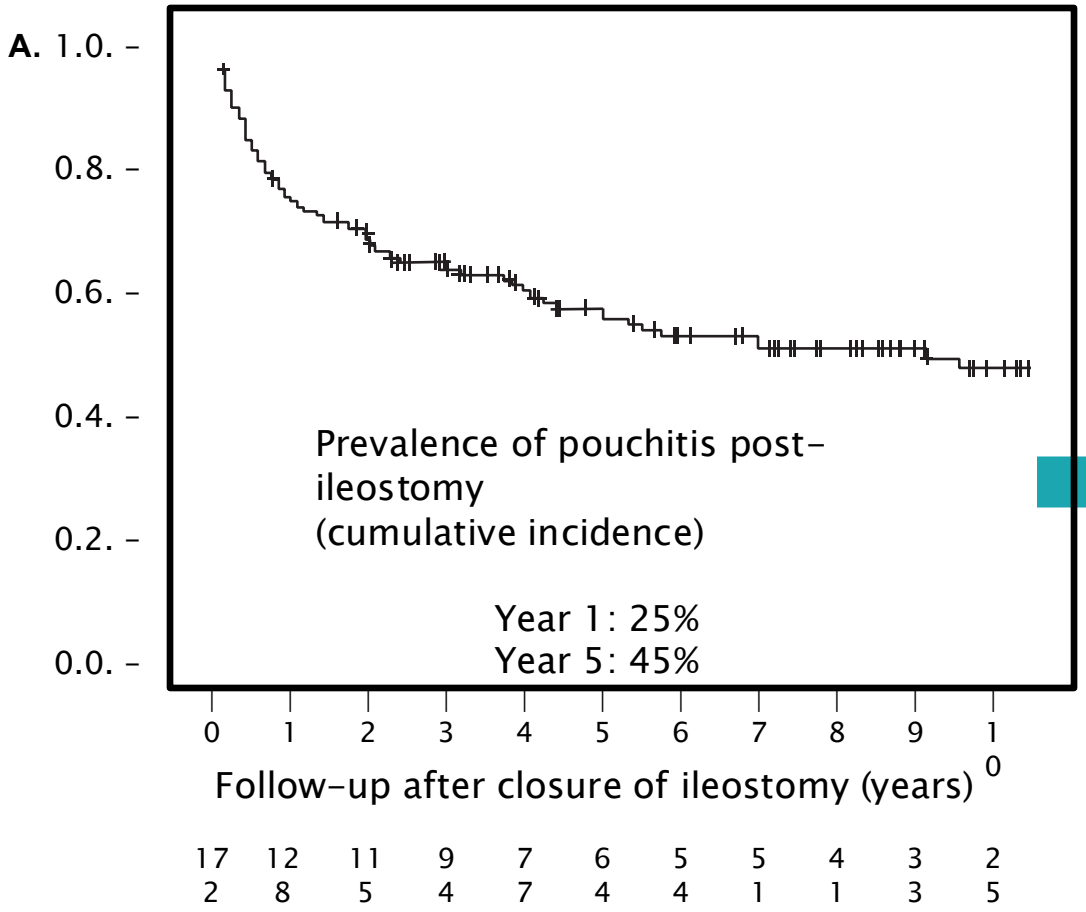
MoA: blocking TGF-β can address all relevant drivers of intestinal fibrosis



- TGFβ stimulates epithelial to mesenchymal transition (EMT) and endothelial to mesenchymal transition (EndoMT), and the production of excessive extracellular matrix by fibroblasts and myofibroblasts

Santacroce, Cells, 2022

Over 45% of Patients Develop Pouchitis after Ileostomy



Pouchitis patients who will develop chronic occurrence:

41%

Ferrante et al, 2008. JCC 2, 142–151

The EARNEST Trial: Vedolizumab for Pouchitis

Phase 4, randomized, double-blind, placebo-controlled, multicentre study

Key Eligibility Criteria

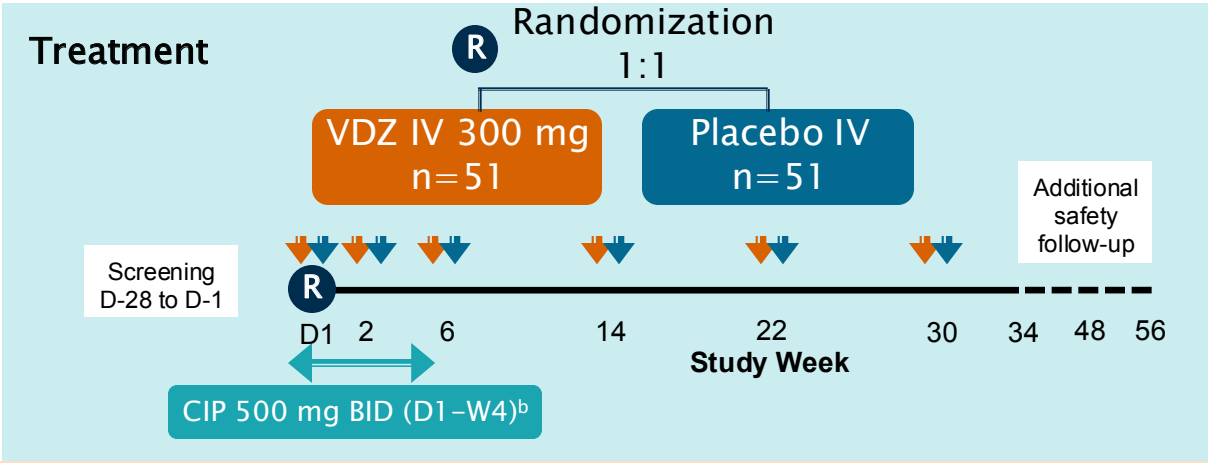
Inclusion

- Aged 18–80 years
- IPAA for UC for ≥1 year with chronic or recurrent pouchitis[a]

Exclusion

- CD or CD of the pouch (known or suspected), irritable pouch syndrome, mechanical complications of pouch, planned surgery for UC during study
- Prior treatment with VDZ, natalizumab, efalizumab, rituximab, etrolizumab, or MAdCAM-1 therapy

NCT02790138
EudraCT 2015-003472-7



Key Endpoints

Primary

- mPDAI remission[c] at W14

Safety

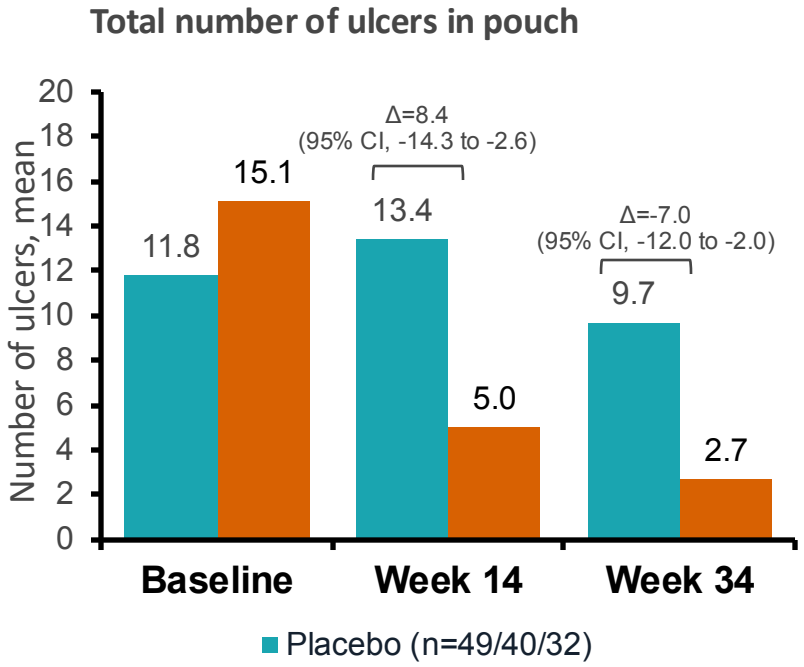
- Adverse events

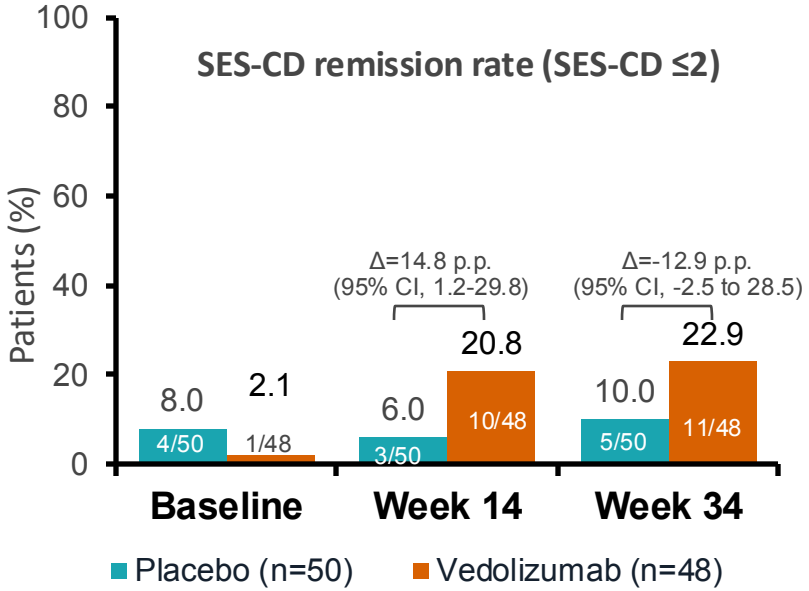
Secondary

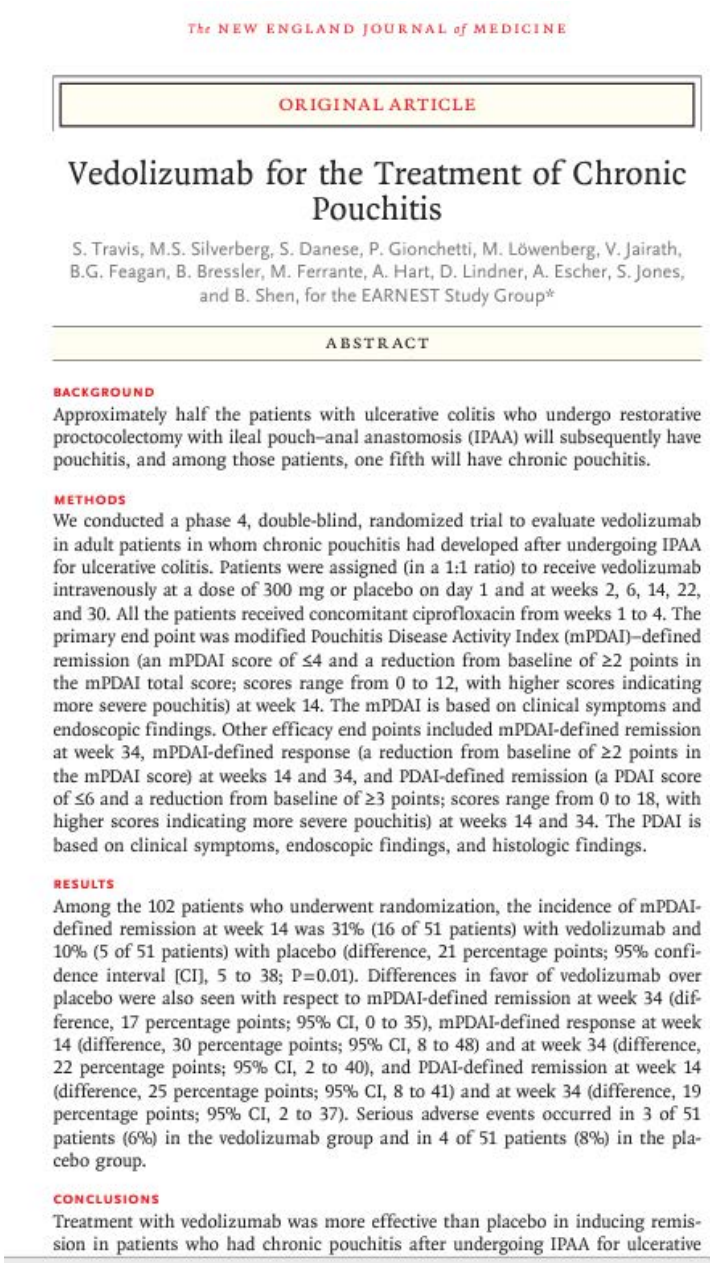
- mPDAI remission[c] at W34
- PDAI remission[d] at W14 and W34
- mPDAI response[e] at W14 and W34
- Quality of life (IBDQ)

Travis S et al. *United European Gastroenterol J* 2021;9(Suppl 1).

Results: Endoscopic Outcomes







The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vedolizumab for the Treatment of Chronic Pouchitis

S. Travis, M.S. Silverberg, S. Danese, P. Gionchetti, M. Löwenberg, V. Jairath, B.G. Feagan, B. Bressler, M. Ferrante, A. Hart, D. Lindner, A. Escher, S. Jones, and B. Shen, for the EARNEST Study Group*

ABSTRACT

BACKGROUND

Approximately half the patients with ulcerative colitis who undergo restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) will subsequently have pouchitis, and among those patients, one fifth will have chronic pouchitis.

METHODS

We conducted a phase 4, double-blind, randomized trial to evaluate vedolizumab in adult patients in whom chronic pouchitis had developed after undergoing IPAA for ulcerative colitis. Patients were assigned (in a 1:1 ratio) to receive vedolizumab intravenously at a dose of 300 mg or placebo on day 1 and at weeks 2, 6, 14, 22, and 30. All the patients received concomitant ciprofloxacin from weeks 1 to 4. The primary end point was modified Pouchitis Disease Activity Index (mPDAI)–defined remission (an mPDAI score of ≤4 and a reduction from baseline of ≥2 points in the mPDAI total score; scores range from 0 to 12, with higher scores indicating more severe pouchitis) at week 14. The mPDAI is based on clinical symptoms and endoscopic findings. Other efficacy end points included mPDAI-defined remission at week 34, mPDAI-defined response (a reduction from baseline of ≥2 points in the mPDAI score) at weeks 14 and 34, and PDAI-defined remission (a PDAI score of ≤6 and a reduction from baseline of ≥3 points; scores range from 0 to 18, with higher scores indicating more severe pouchitis) at weeks 14 and 34. The PDAI is based on clinical symptoms, endoscopic findings, and histologic findings.

RESULTS

Among the 102 patients who underwent randomization, the incidence of mPDAI-defined remission at week 14 was 31% (16 of 51 patients) with vedolizumab and 10% (5 of 51 patients) with placebo (difference, 21 percentage points; 95% confidence interval [CI], 5 to 38; P=0.01). Differences in favor of vedolizumab over placebo were also seen with respect to mPDAI-defined remission at week 34 (difference, 17 percentage points; 95% CI, 0 to 35), mPDAI-defined response at week 14 (difference, 30 percentage points; 95% CI, 8 to 48) and at week 34 (difference, 22 percentage points; 95% CI, 2 to 40), and PDAI-defined remission at week 14 (difference, 25 percentage points; 95% CI, 8 to 41) and at week 34 (difference, 19 percentage points; 95% CI, 2 to 37). Serious adverse events occurred in 3 of 51 patients (6%) in the vedolizumab group and in 4 of 51 patients (8%) in the placebo group.

CONCLUSIONS

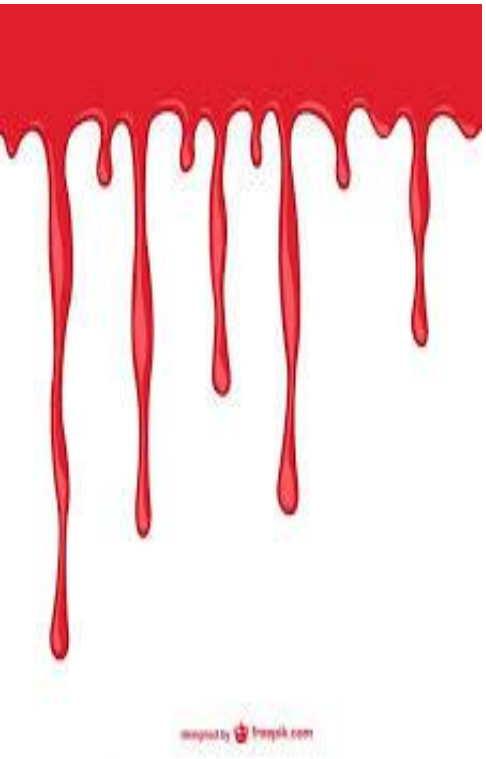
Treatment with vedolizumab was more effective than placebo in inducing remission in patients who had chronic pouchitis after undergoing IPAA for ulcerative

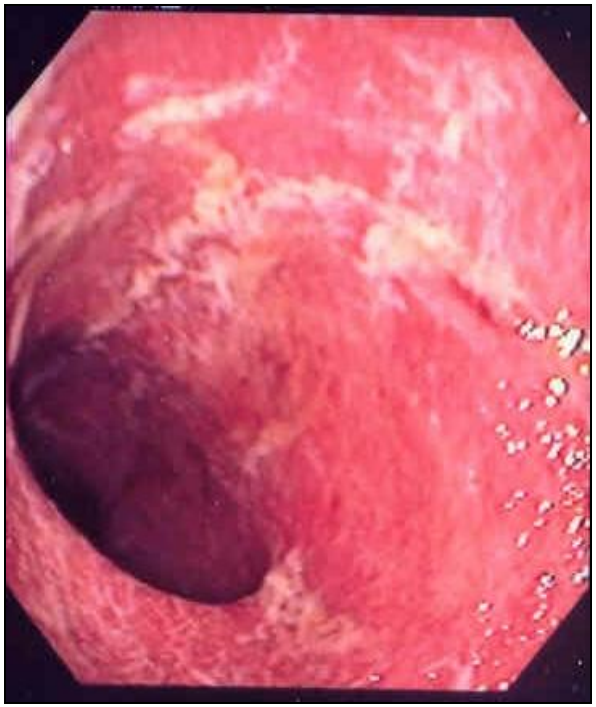
Travis S et al New England J Med.2023;388(13):1191-1200.

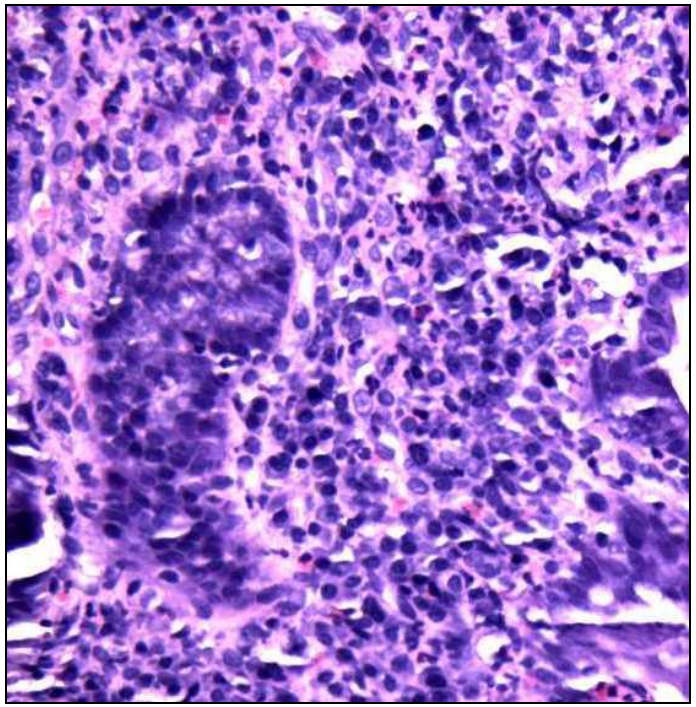
Horizon Indications/Strategies

- Effective therapy for fibrostenosing CD/pouchitis
- More effective strategies in both UC and CD

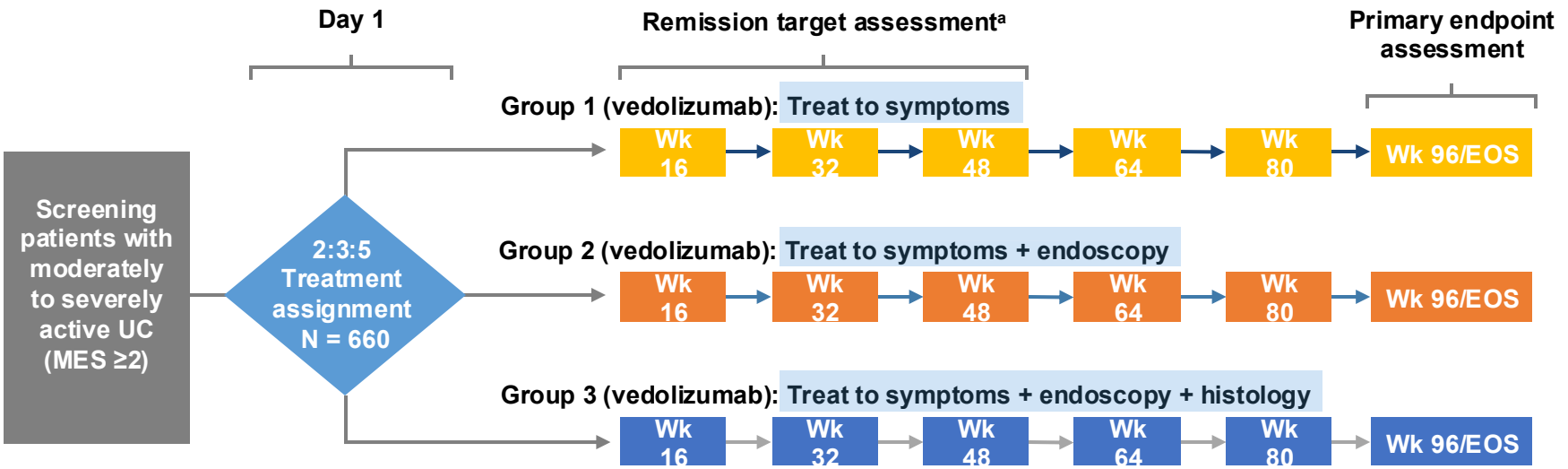
What is the Treatment Target in UC? Symptoms vs Endoscopy vs Histopathology







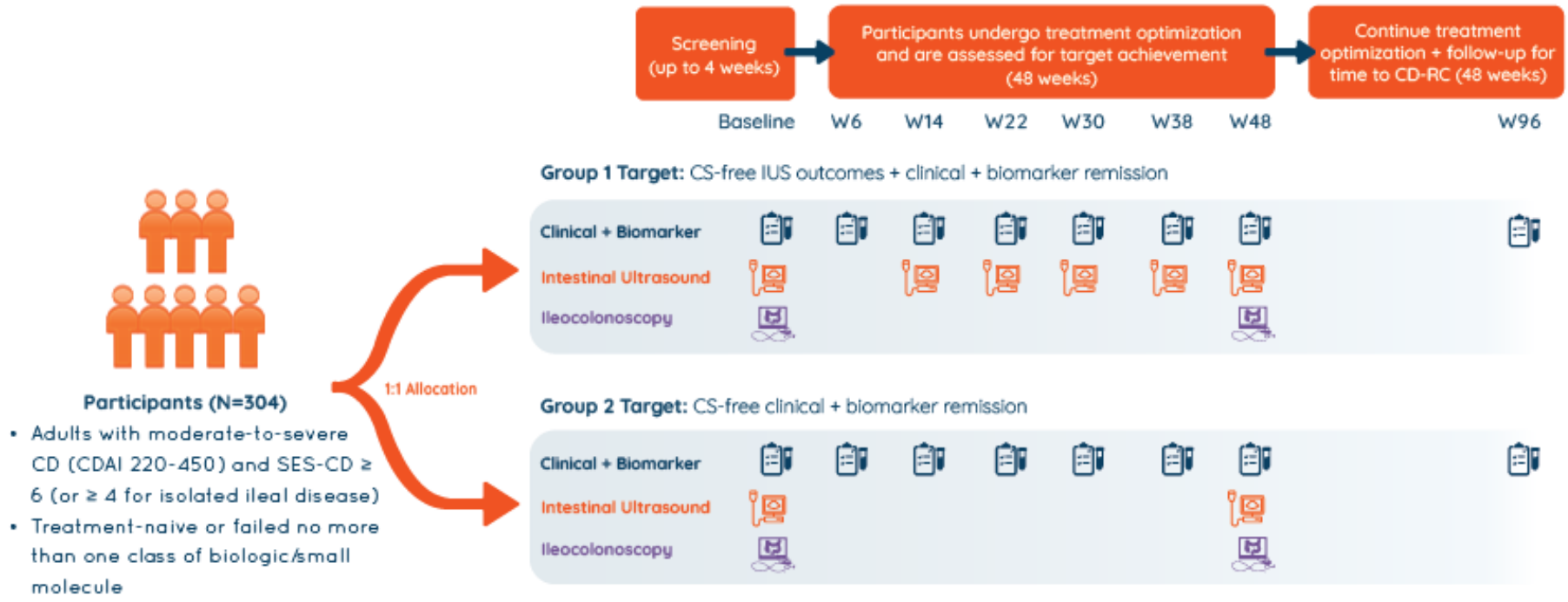
Prospective Study to Evaluate Therapeutic Targets in Ulcerative Colitis (VERDICT)



Primary endpoint: UC-related complications including hospitalisation, colectomy, use of rescue therapy, and UC treatment-related or disease-related complications

[a]Periodic interim analyses to check allocation ratio and sample size based on achievement of target. Futility analysis conducted for Week (Wk) 32.
EOS, end of study; MES, Mayo Endoscopic Subscore; UC, ulcerative colitis.
Clinicaltrials.gov NCT04259138. Takeda Pharmaceuticals International AG, data on file.

VECTORS – STUDY DESIGN



Conclusions

- Multiple new agents/approaches are on the horizon
- TL1A monoclonals, oral alpha 4 beta,7-IL-23s and mRNA silencing are exciting new therapeutic approaches
- Combination therapy is the new black!
- New strategies are part of the big picture
- Future is bright!
- (yet) Phase 3 looms!