UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM
Crohn's and Colitis Center

What's New with Biologics and Small Molecules

Maria T. Abreu, MD
Vice Chair of Research, Department of Medicine
Director, Crohn's and Colitis Center
Professor of Medicine
Professor of Microbiology and Immunology
University of Miami Miller School of Medicine, Miami, FL

Pharma Disclosures 2022

Consulting/Advisory Board

- Boehringer Ingelheim
- Gilead
- Landos Biopharma
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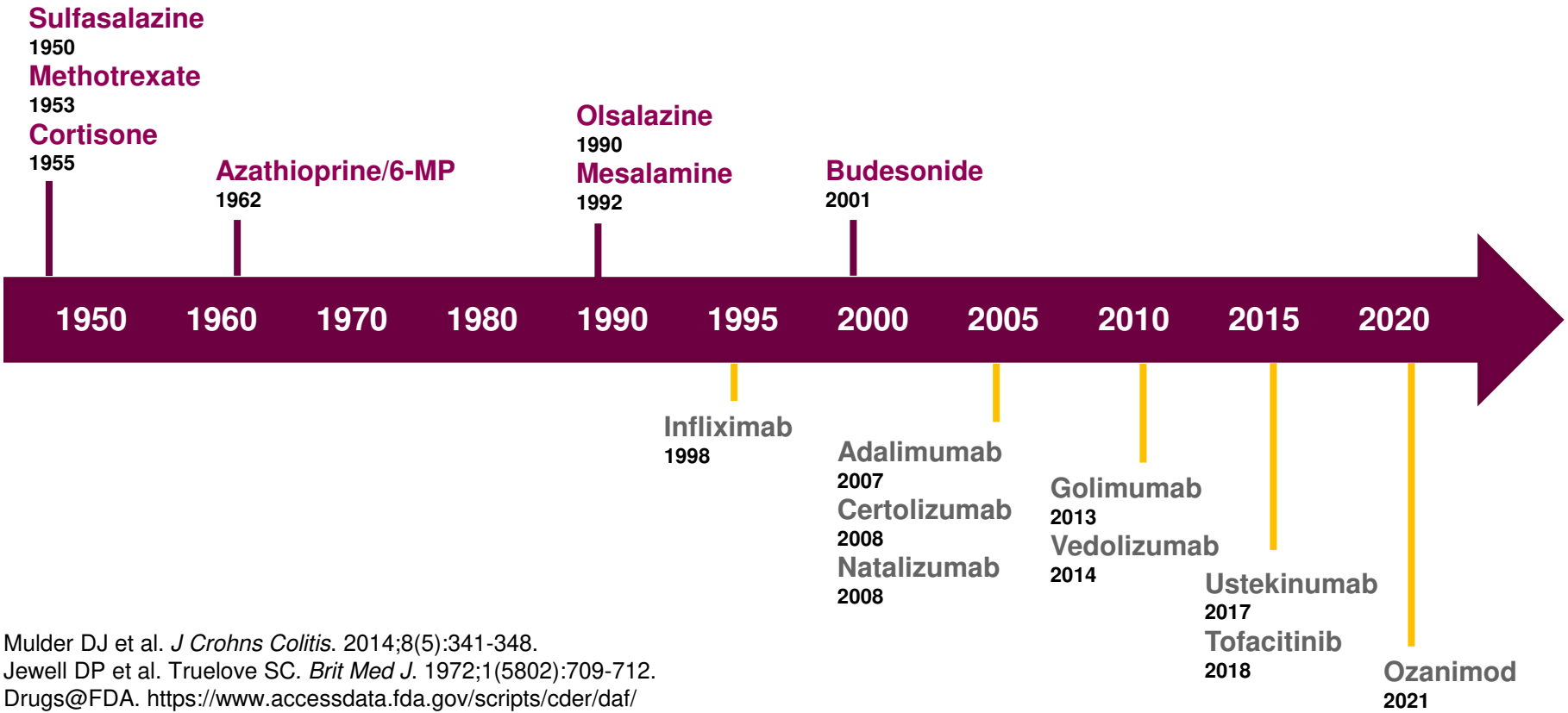
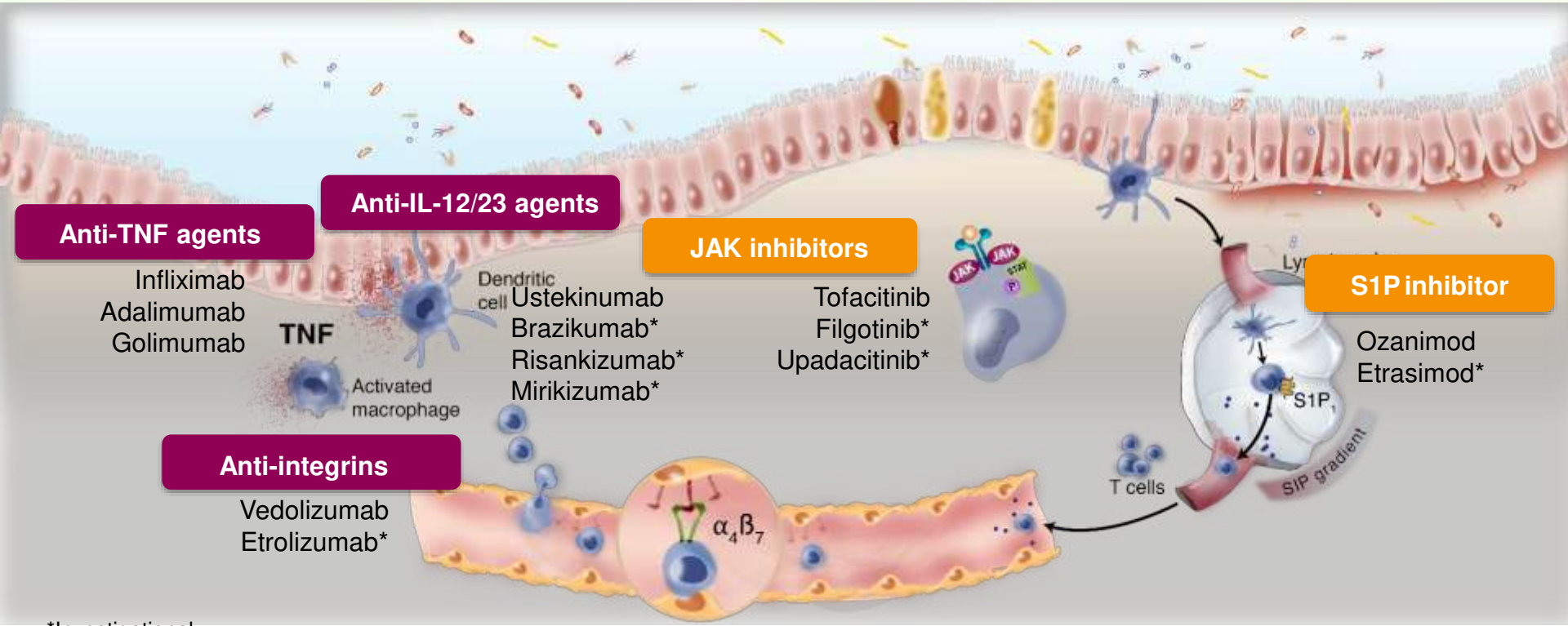
The Evolution of IBD Therapies



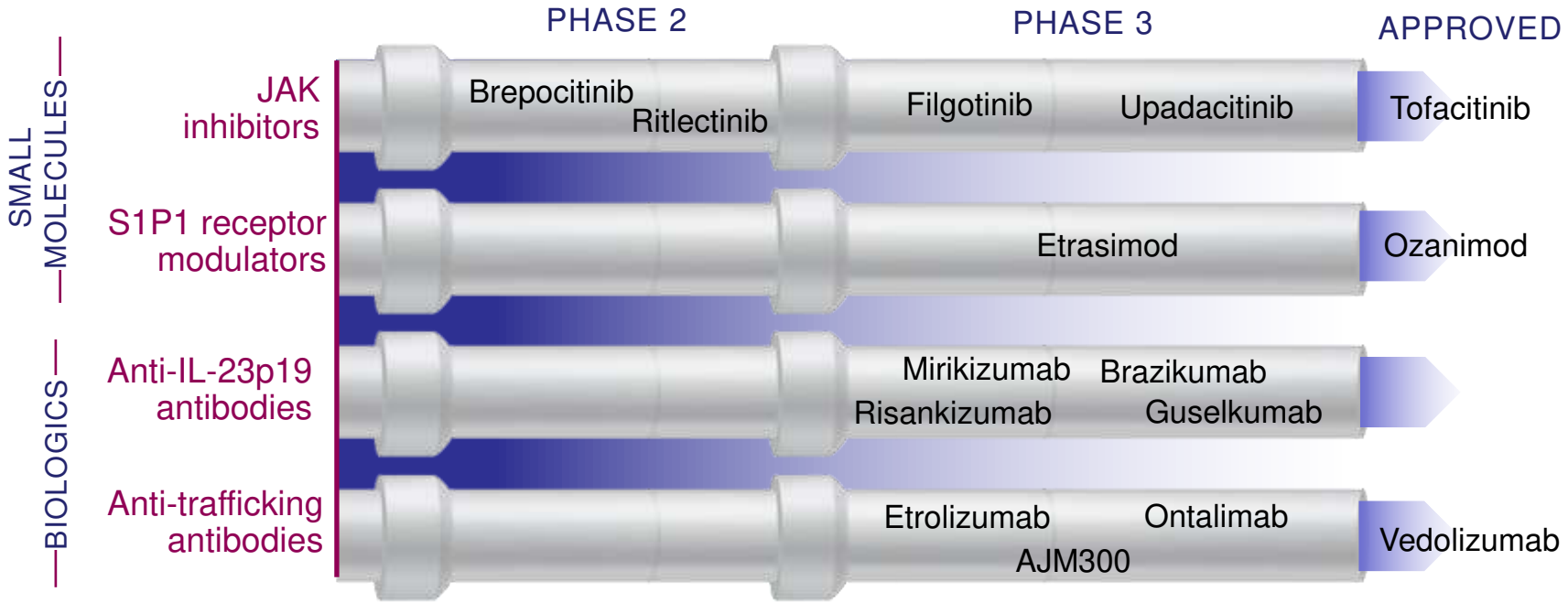
Mulder DJ et al. *J Crohns Colitis*. 2014;8(5):341-348.
Jewell DP et al. Truelove SC. *Brit Med J*. 1972;1(5802):709-712.
Drugs@FDA. https://www.accessdata.fda.gov/scripts/cder/daf/

Current and Emerging Strategies for IBD



*Investigational.
JAK = Janus kinase; TNF = tumor necrosis factor; S1P = sphingosine-1-phosphate.
Adapted from Coskun M et al. *Trends Pharmacol Sci*. 2017;38(2):127-142.

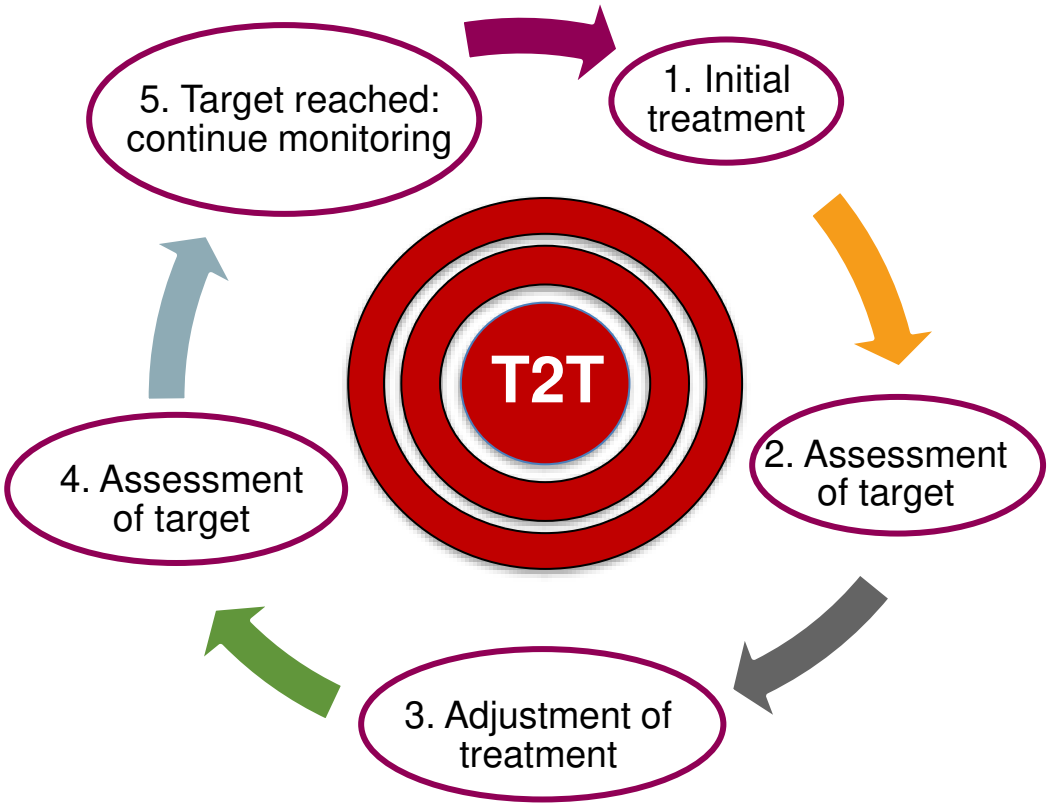
Key Classes in the IBD Pipeline



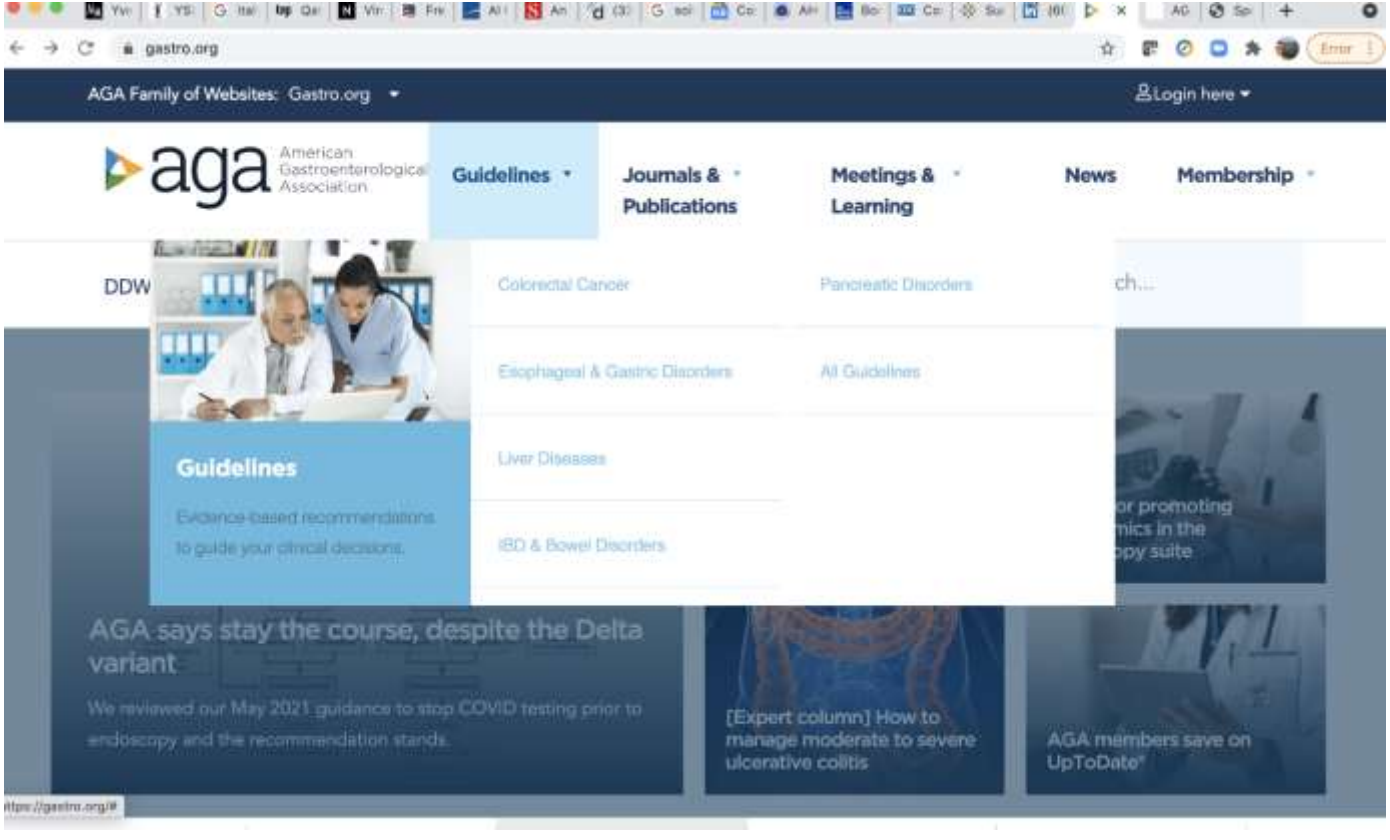
Ab = antibody; MAdCAM = mucosal addressin cell adhesion molecule.

Clinicaltrials.gov. https://clinicaltrials.gov. Accessed January 4, 2022.

Treat to Target (T2T) Is Approach That Uses Patient-derived and Objective Targets to Adjust Treatment: “Trust But Verify”



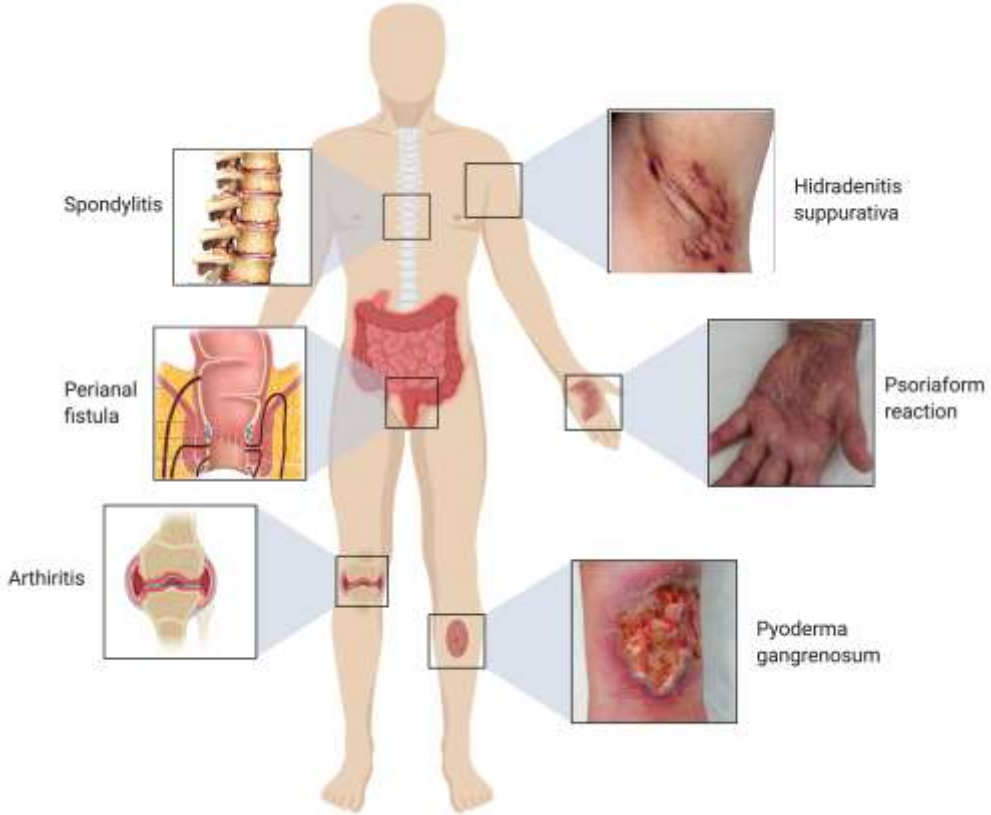
Good Resources



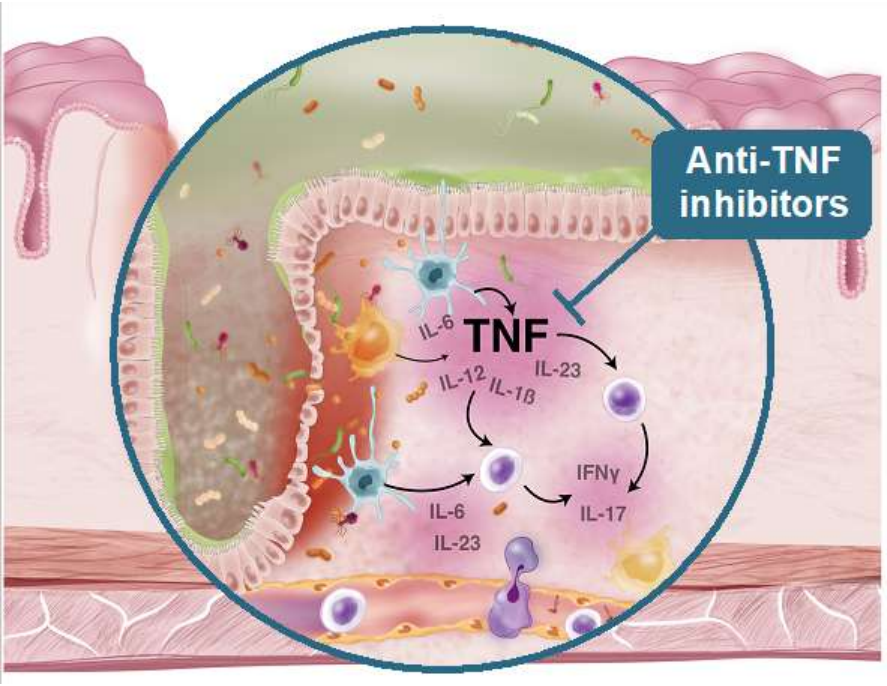
Factors in Choosing

- Patient factors:
  - Co-morbidities–e.g. cancer or cancer risk
  - Age
  - EIMs
  - Fistulas
  - Naïve patient versus previous biologic exposure
- Patient preference: IV, subq, oral
- Payors!

Need to Consider Diverse Manifestations of IBD When Choosing Therapy



Anti-TNF Inhibitors in IBD

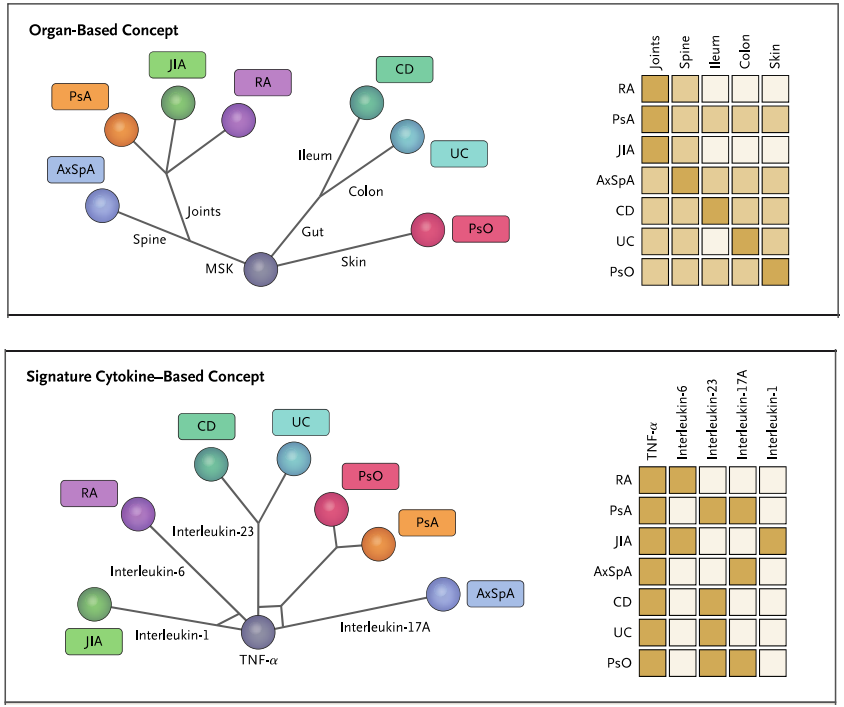


- Effective for induction and maintenance, with rapid onset of symptom control[1]
- Effective in achieving mucosal healing, improving HRQoL, reducing surgeries/hospitalizations, and in treating fistulizing disease[1,2]
- Combination therapy with an immunomodulator preferred due to potential for immunogenicity and loss of response[1,2]

HRQoL = health-related quality of life.

1. Hindryckx P et al. *J Crohn's Colitis.* 2018;12(1):105-119; 2. Lichtenstein GR et al. *Am J Gastroenterol.* 2018;113:481-517.

Why Does Blocking TNF Work so Well in Both UC and CD?

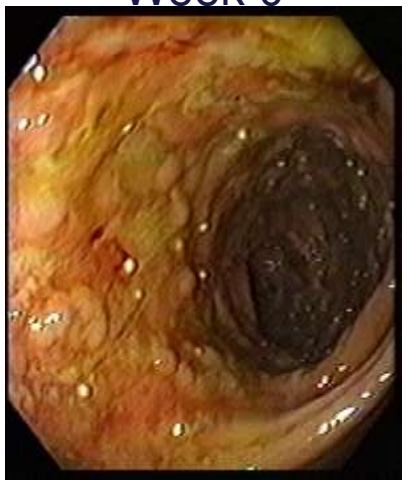
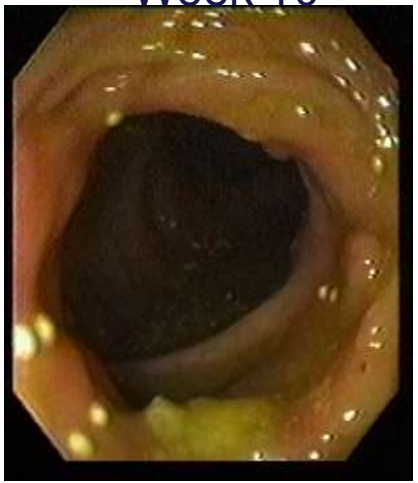
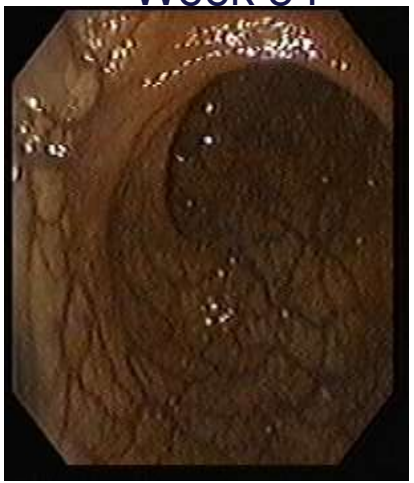


Schett G et al. *N Engl J Med*. 2021;385(7):628-639.

Anti-TNF Therapy Set a New Bar

Infliximab Endoscopic Healing Substudy

5 mg/kg maintenance treatment

Week 0	Week 10	Week 54
		
Baseline	Following induction regimen at Week 0, 2, and 6	Following infusions every 8 weeks after induction regimen

Rutgeerts P et al. *Gastrointest Endosc.* 2006;63(3):433-42; quiz 464.

How High Is the Bar Set?

The Problem With Anti-TNF Inhibitors

1/3

Patients will not respond to induction therapy with anti-TNF inhibitors (primary nonresponse)[1,2]

≈50%

Patients who do respond may lose response within a few years[1,2]

Why?

Neutralizing anti-drug antibodies/low serum trough levels?

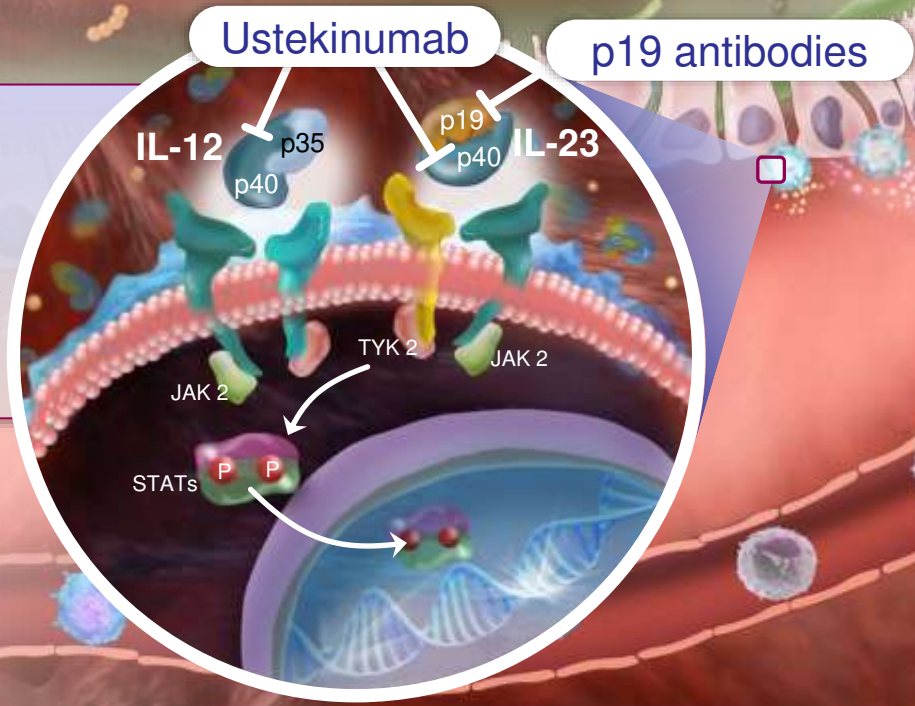
Other immune pathways are driving inflammation?

1. Cohen BL, Sachar DB, et al. *BMJ*. 2017;357:j25050; 2. Ford AC et al. *Am J Gastroenterol*. 2011;106:644-659.

IL-23 Inhibition

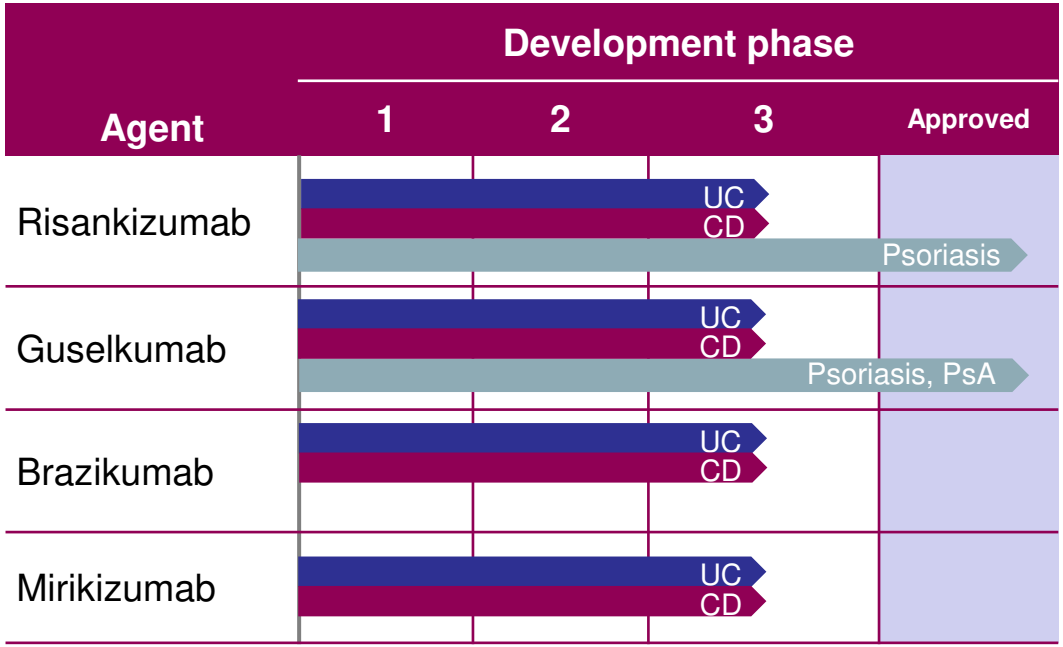
Mechanism of IL-12/23 and IL-23 Inhibitors

Specifically targeting the p19 subunit of IL-23 allows for normal IL-12–mediated Th1 responses while conferring the same efficacy as with p40 antibodies



Vignali DA, Kuchroo VK. *Nat Immunol*. 2012;13(8):722-728.

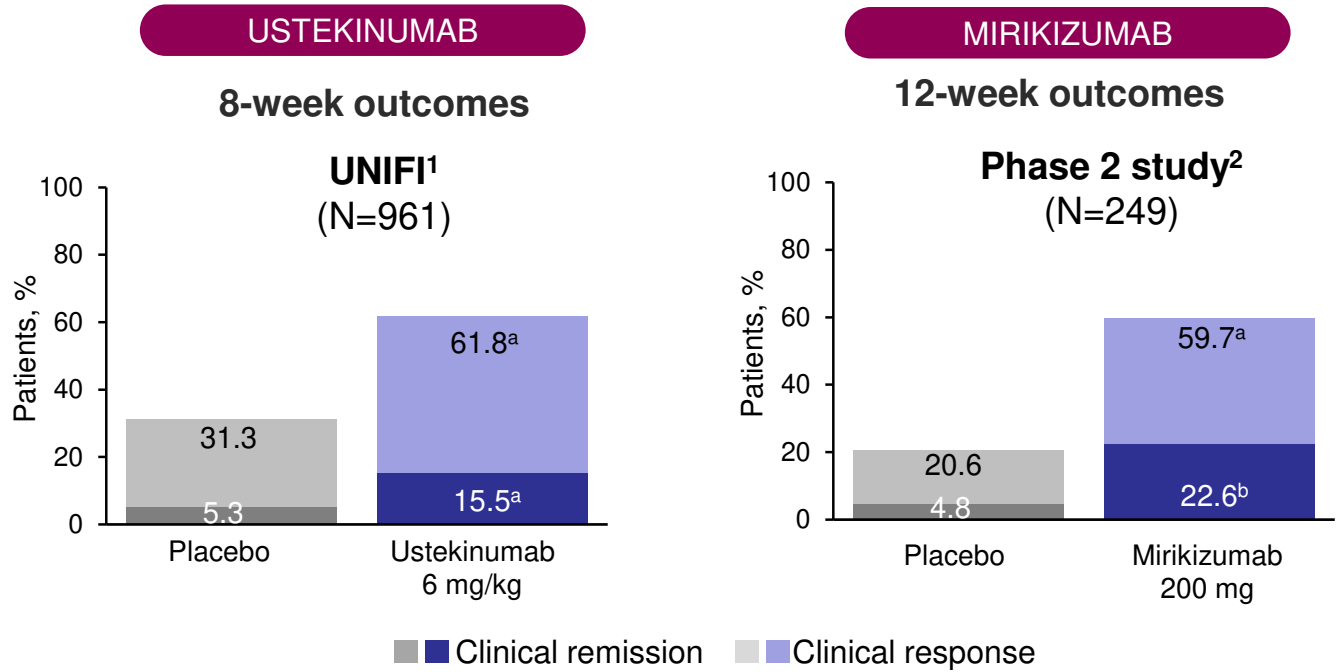
Key Approved and Investigational p19 Antibodies



AD, atopic dermatitis

1. ClinicalTrials.gov. www.clinicaltrials.gov. Accessed January 10, 2022. 2. D'Haens G et al. *J Crohns Colitis*. 2021 Nov 10;jjab201. doi: 10.1093/ecco-jcc/jjab201. Online ahead of print.3. Danese S et al. J Crohns Colitis. 2018;S578-S686.

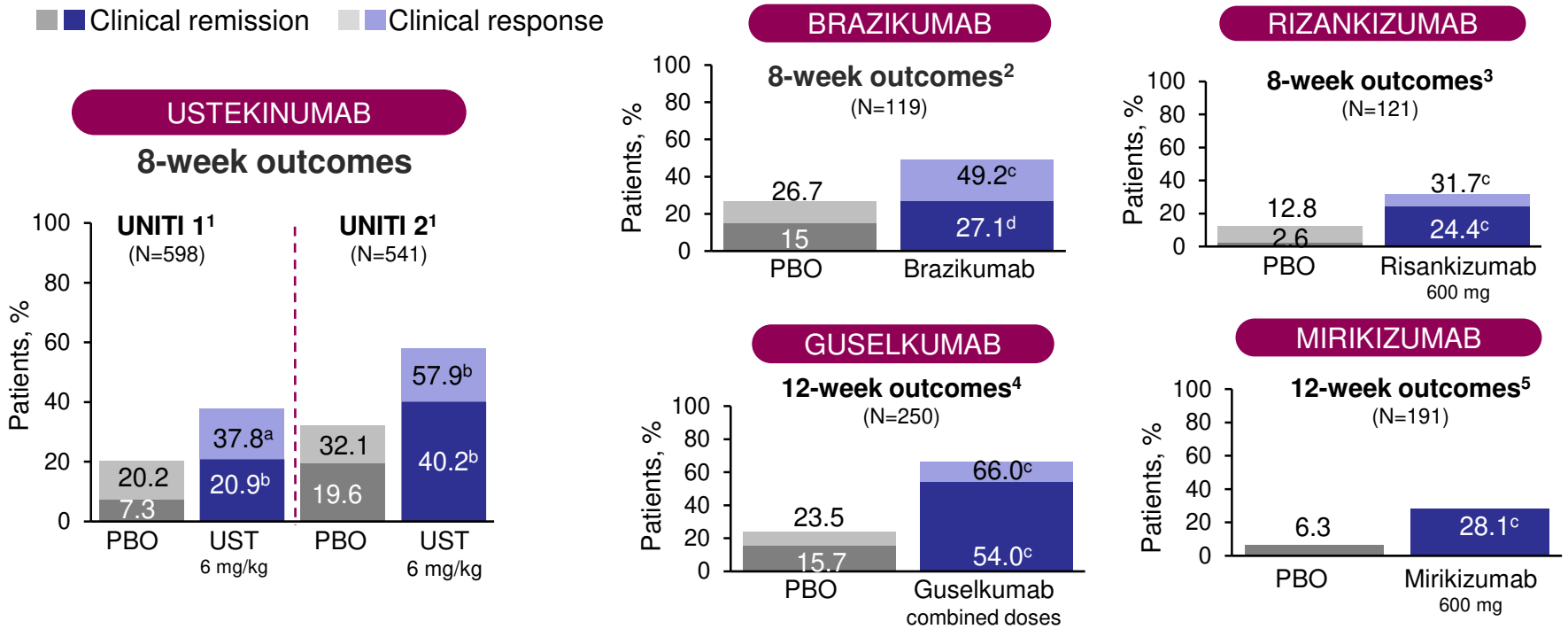
Induction Studies in UC With IL-12/23 and IL-23 Inhibitors



[a]*P*<0.001 vs placebo; [b]*P*=0.004 vs placebo.

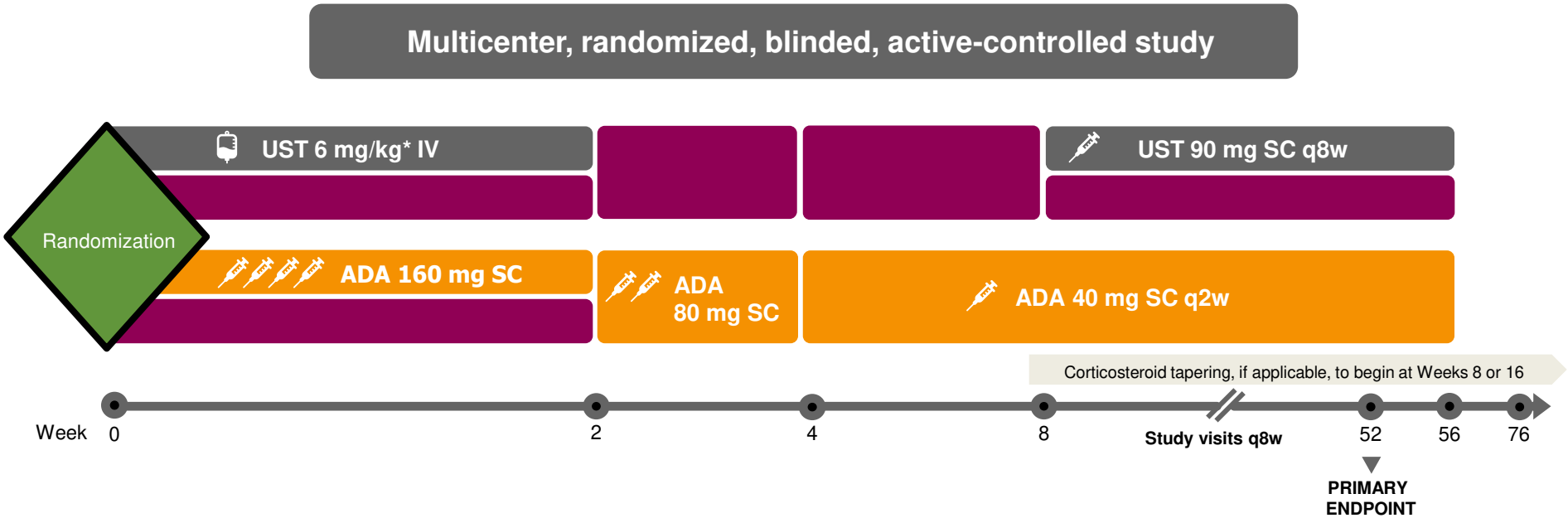
1. Sands BE et al. *N Engl J Med*. 2019;381(13):1201-1214. 2. Sandborn WJ et al. *Gastroenterology*. 2020;158(3):537-549.

Phase 2 Induction Studies in CD With IL-23 Inhibitors



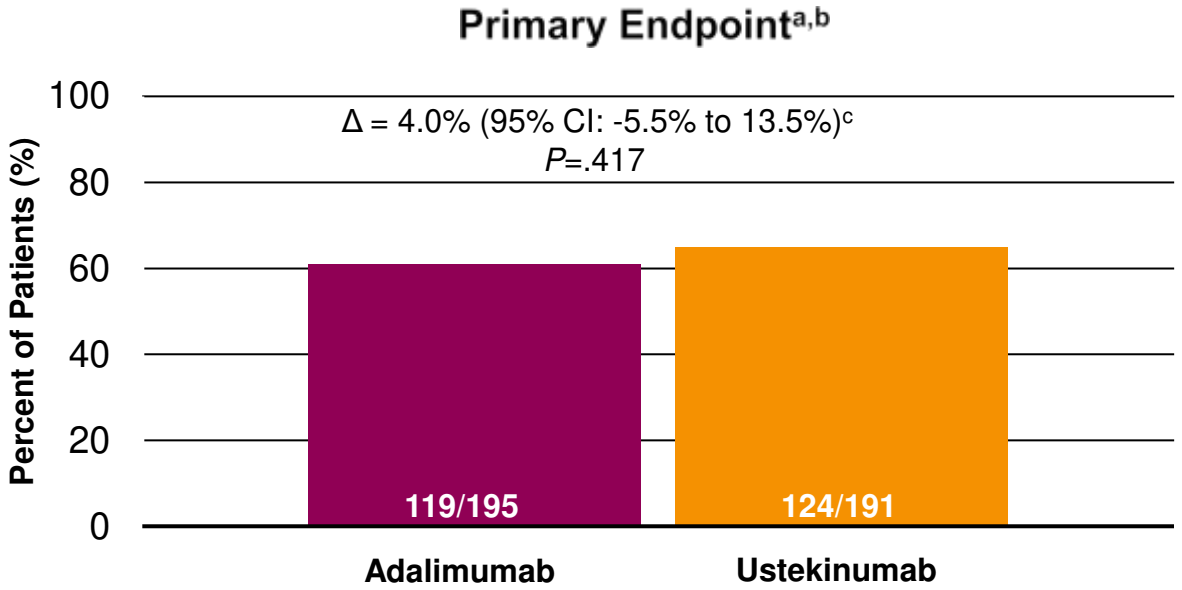
[a]*P*=0.001 vs placebo; [b]*P*<0.001 vs placebo; [c]*P*=0.05; [d]*P*=NS.
BID, twice daily; FIL, filgotinib; PBO, placebo; TOFA, tofacitinib; UPA, upadacitinib.
1. Feagan BG, et al. *N Engl J Med*. 2016;375(20):1946-1960. 2. Sands BE, et al. *Gastroenterology*. 2017;153(1):77-86.e6. 3.Feagan BG et al. *Lancet*. 2017;389(10080):1699-1709. 4. Danese 5. Sands BE et al. Presented at: Digestive Disease Week 2019; May 18-21, 2019; San Diego, CA. Abstract 1003.

Seavue: Head to Head Comparison of Adalimumab Versus Ustekinumab



*Ustekinumab (UST) 260 mg (weight ≤55 kg); UST 390 mg (weight >55 kg and ≤85 kg); UST 520 mg (weight >85 kg).
https://clinicaltrials.gov/ct2/show/record/NCT03464136.

Clinical Remission (CDAI <150) at Week 52



NOTE: Because primary endpoint was not met, formal testing of major secondary endpoints was not performed.

[a]Patients who had a prohibited CD-related surgery, had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an AE indicated to be of worsening CD prior to the designated analysis timepoint are considered not to be in clinical remission, regardless of their CDAI score

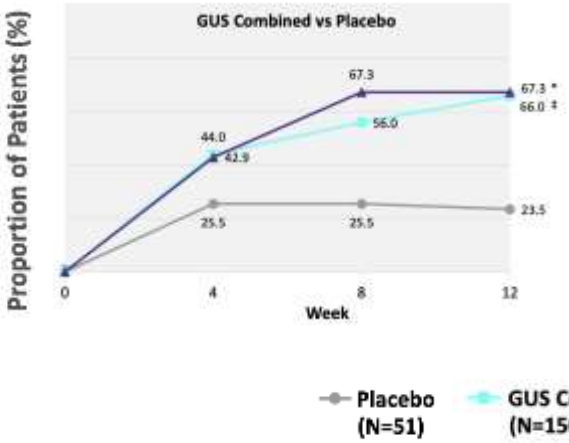
[b]Patients who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission.

[c]The confidence intervals were based on the Wald statistic with Mantel-Haenszel weight.

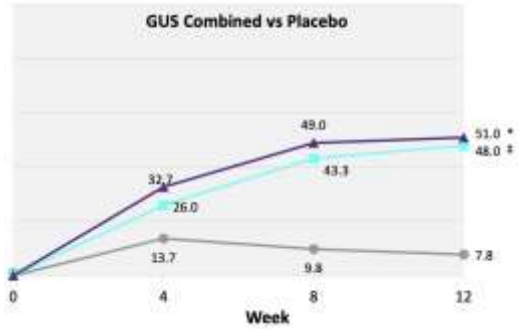
Sands BE et al. Presented at the *2021 Digestive Disease Week* Virtual. May 21-23, 2021.

Guselkumab: Higher Rates of Overall Clinical Remission, Response, Biomarker, and Endoscopic Response in CD Patients

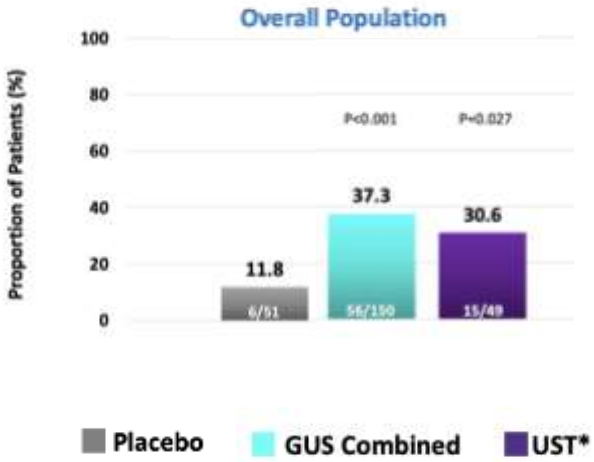
Clinical response: ≥100-point reduction from baseline in CDAI score or CDAI score <150



Clinical-biomarker response: Clinical response and ≥50% reduction from baseline in CRP or FeCal



Endoscopic response: At least 50% improvement from baseline in SES-CD score or SES-CD score ≤2



About 50% bio-naïve, 40+% 1 anti-TNF, the rest more than 2 anti-TNFs, +/- vedolizuma

Danese et al. *Journal of Crohn's and Colitis*.2021;15(Suppl):S027-S028.
D'Haens et al. *Gastroenterology*.2021;160(6):S-91.
Sands et al. Digestive Disease Week 2021.

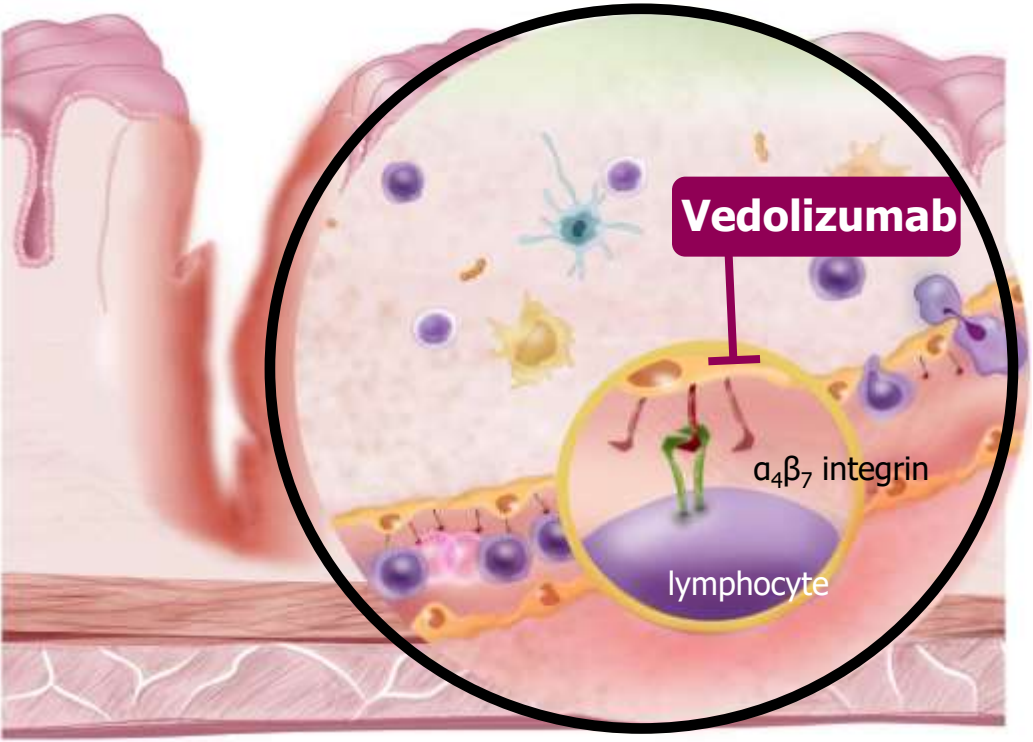
Key Safety Findings From Maintenance Baseline Through Week 156: Patients Treated in the LTE

		UST		
	PBO SC[a] (N=188)	90 mg SC q12w[b] (N=141)	90 mg SC q8w[c] (N=376)	Combined (N=457)
Avg duration of follow-up (weeks)	117.5	127.0	129.6	145.8
Total patient-years of follow-up	425.0	344.4	937.2	1281.6
Number of specified events per hundred patient-years of follow-up (95% CI)[d]				
Death	0.00 (0.00, 0.70)	0.00 (0.00, 0.87)	0.11 (0.00, 0.59)	0.08 (0.00, 0.43)
Adverse events	204.48 (191.11, 218.54)	218.94 (203.59, 235.15)	242.00 (232.15, 252.17)	235.81 (227.47, 244.37)
Serious adverse events	7.53 (5.15, 10.63)	6.68 (4.23, 10.02)	8.11 (6.39, 10.15)	7.73 (6.28, 9.40)
Infections[e]	61.18 (53.97, 69.09)	73.18 (64.42, 82.79)	73.52 (68.13, 79.22)	73.43 (68.81, 78.27)
Serious infections[e]	2.35 (1.13, 4.33)	2.90 (1.39, 5.34)	2.13 (1.30, 3.30)	2.34 (1.58, 3.34)
AEs leading to discontinuation of study agent	3.76 (2.15, 6.11)	2.03 (0.82, 4.19)	2.77 (1.81, 4.06)	2.58 (1.77, 3.62)
All malignancies	0.47 (0.06, 1.70)	0.87 (0.18, 2.55)	0.64 (0.23, 1.39)	0.70 (0.32, 1.33)
Excluding nonmelanoma skin cancer	0.24 (0.01, 1.31)	0.00 (0.00, 0.87)	0.00 (0.00, 0.32)	0.00 (0.00, 0.23)
Nonmelanoma skin cancer	0.24 (0.01, 1.31)	0.87 (0.18, 2.55)	0.64 (0.23, 1.39)	0.70 (0.32, 1.33)

aIncludes 1) data from maintenance Week 8 onward for patients who were in clinical response to UST IV induction dosing and were randomized to PBO SC on entry into the maintenance study, up to the dose adjustment during LTE; and 2) data from Week 0 of maintenance for patients who were in clinical response to PBO IV induction dosing and received PBO SC on entry into the maintenance study.
bIncludes data from maintenance Week0 through Week 156, or up to the dose adjustment if patients had a dose adjustment during the LTE, for patients who were in clinical response to UST IV induction dosing and were randomized to UST 90 mg SC q12w on entry into the maintenance study.
cIncludes 1) patients who were in clinical response to UST IV induction dosing and were randomized to receive UST 90 mg SC q8w on entry into the maintenance study, with data from maintenance Week 0 through Week 156; 2) patients who were in clinical response to UST IV induction dosing, randomized to receive PBO SC or UST 90 mg SC q12w on entry into the maintenance study, and had a dose adjustment to UST SC 90 mg q8w, with data from the time of dose adjustment onward; 3) patients who were not in clinical response to UST at induction Week 8 but were in clinical response at induction Week 16 after a SC administration of UST at induction Week 8 and received UST 90 mg SC q8w on entry into the maintenance study with data from maintenance Week 0 through Week 156.
dConfidence intervals based on an exact method assuming that the observed number of events follows a Poisson distribution.
eInfection as assessed by the investigator.

Abreu MT et al. Presented at: *16th Congress of ECCO*; July 8-10, 2021; Virtual. DOP83.

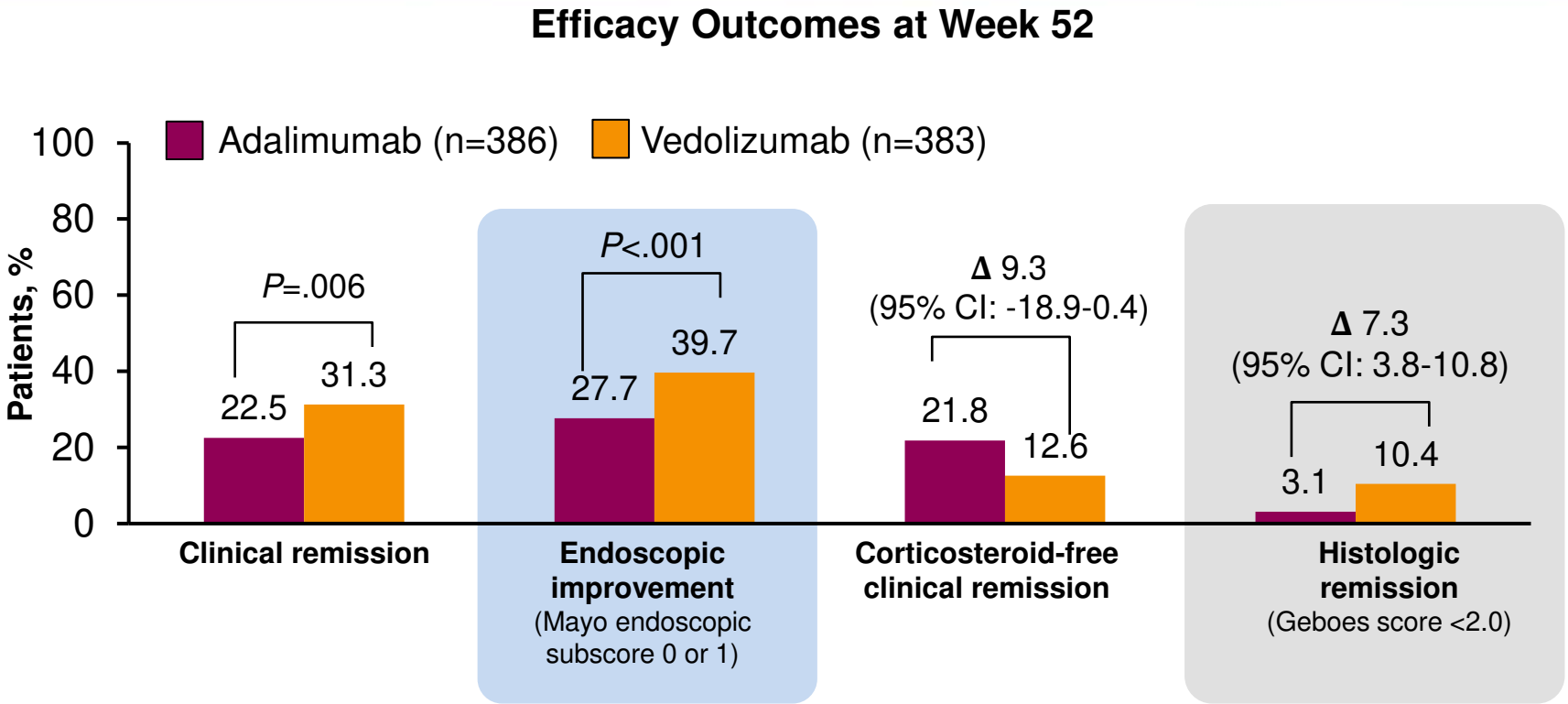
Vedolizumab



- Vedolizumab is a humanized monoclonal antibody to α4β7 integrin that modulates gut lymphocyte trafficking[1]
- Approved in 2014 for moderate to severely active UC and CD[2]
  - **Induction**: 300 mg by infusion at 0, 2, and 6 weeks
  - **Maintenance**: 300 mg Q8weeks

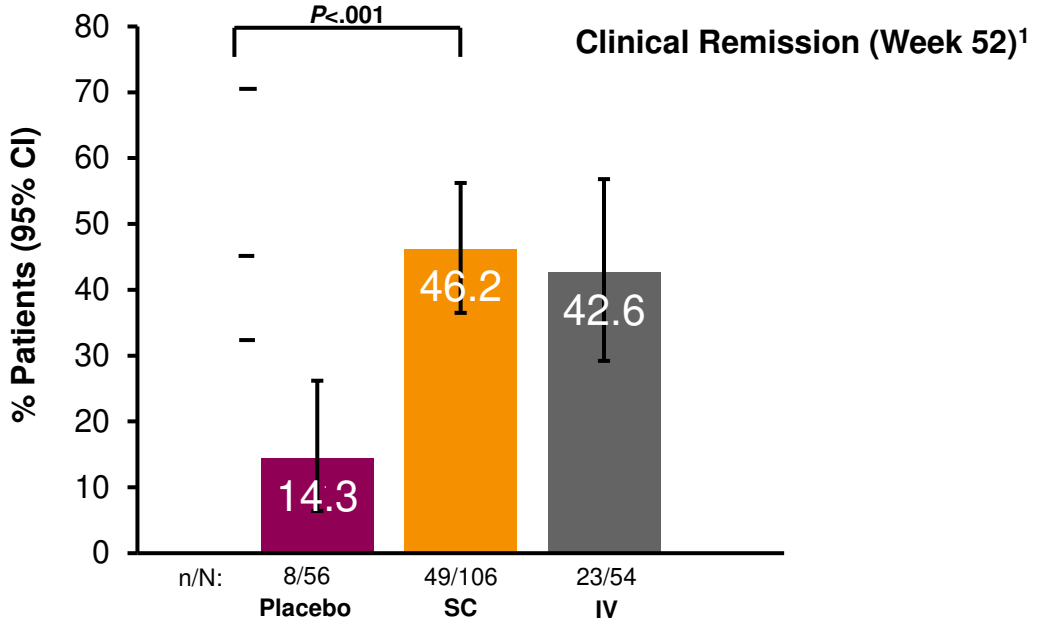
1. Sandborn WJ et al. *N Engl J Med*. 2013;369(8):711-721; 2. Vedolizumab. Package Insert. Takeda Pharmaceuticals America, Inc; 2014.

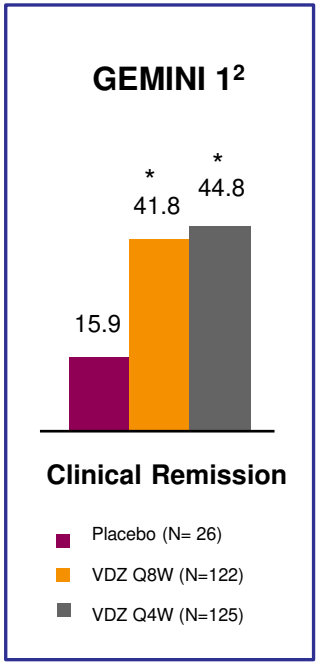
Vedolizumab Versus Adalimumab for Moderate-to-Severe UC: VARSITY Study



Sands BE et al. *N Engl J Med*. 2019;381:1215-1226.

VISIBLE: SC Vedolizumab Is Effective After IV Induction: Clinical Remission at Week 52 (1º Outcome)





CI = confidence interval; IV = intravenously; SC = subcutaneous; VDZ = vedolizumab; Q8/4W = every 8/4 weeks.
* indicates *P*<.001
Clinical remission: complete Mayo score of ≤2 points and no individual subscore >1 point
1. Feagan BC et al. *N Engl J Med.* 2013;22;369(8):699-710; 2. Sandborn WJ et al. *Gastroenterol.* 2020;158(3):562-572. Open Access.

Vedolizumab Has Demonstrated a Favorable Safety Profile

- Autoimmune events (infrequent)
- Infusion-related reactions (infrequent)
- Enteric infections (infrequent)
- Immunogenicity

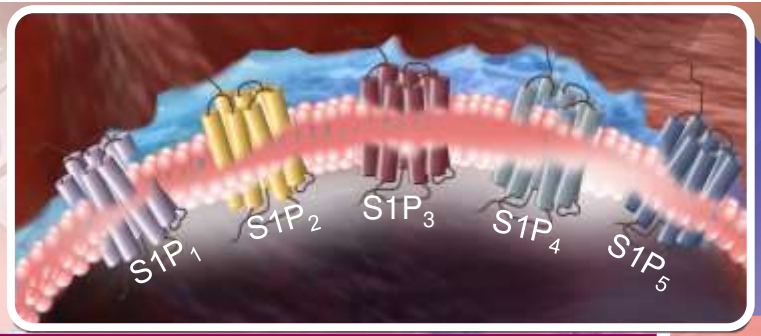
Not associated with increased risk of serious or opportunistic infections[1]

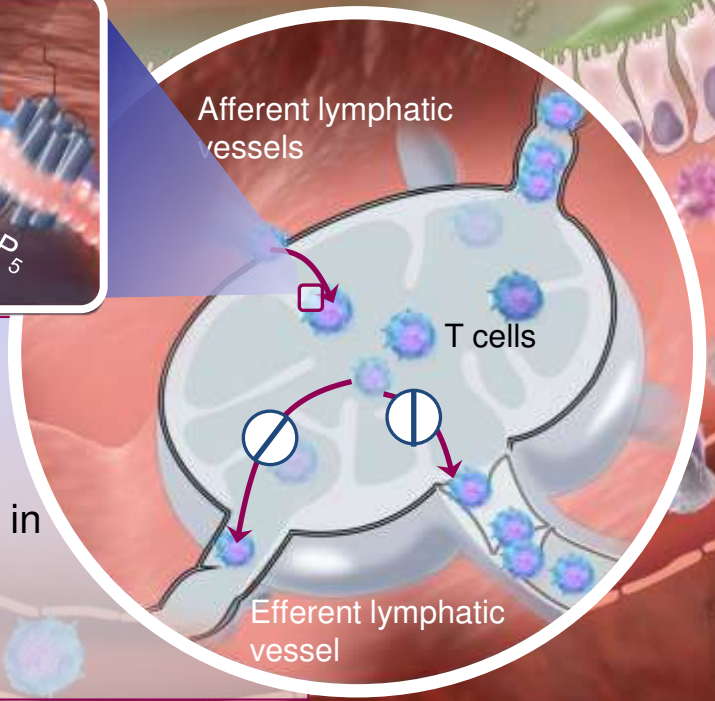
Rate of malignancy consistent with that observed in IBD patients normally[1]

1 PML seen in patient multi-immunocompromised

1. Colombel JF et al. *Gut*. 2016;0:1-13; 2. Vedolizumab. Package Insert. *Takeda Pharmaceuticals America, Inc*. 2018.

S1PR 1 Agonist Causes Sequestration of Lymphocytes in Lymph Nodes



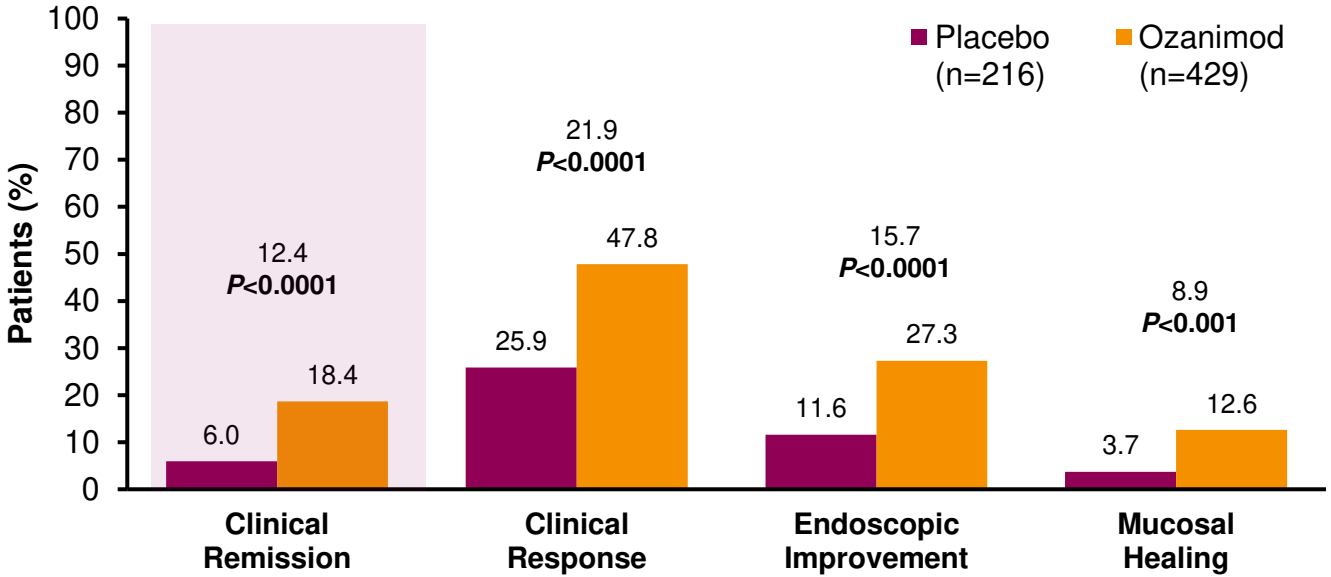


S1PR1 agonism induces receptor internalization on lymphocytes resulting in **functional antagonism** and loss of ability to respond to the S1P gradient

S1P modulators trap some types of activated lymphocytes in secondary lymphoid organs (eg, lymph nodes), preventing their migration to areas of peripheral tissues, including intestinal tissues[1]

Danese S. *Gastroenterology*. 2020;158(3):467-470.

Efficacy of Ozanimod in Moderate-to-Severe UC at Week 10 (Induction, ITT)

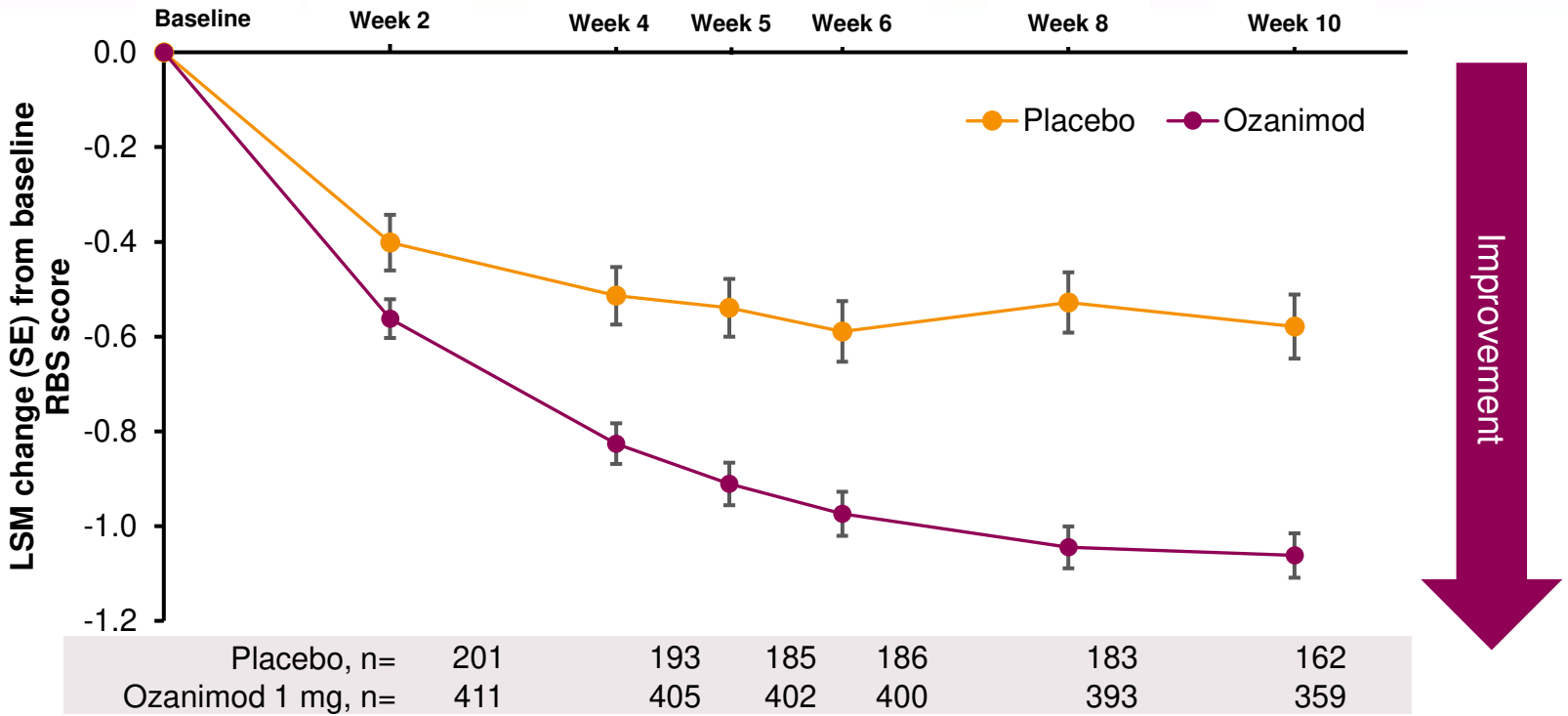


[a]3-component Mayo score results: rectal bleeding score (RBS) = 0, stool frequency score ≤1 and ≥1-point reduction from baseline, and mucosal endoscopy score (MES) ≤1 without friability; [b]Reduction in 3-component Mayo score of ≥2 points and ≥35%, and reduction in RBS of ≥1 point or absolute RBS of ≤1 point; [c]MES ≤1 without friability; [d]Endoscopic improvement plus histological remission (Geboes<2.0; no neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue) in the same patient.

Data based on all randomized patients who received ≥1 dose of study treatment (intent-to-treat population). Missing data handled using non-responder imputation. P-values refer to odds ratios (not shown) based on 2-sided Cochran-Mantel-Haenszel test.

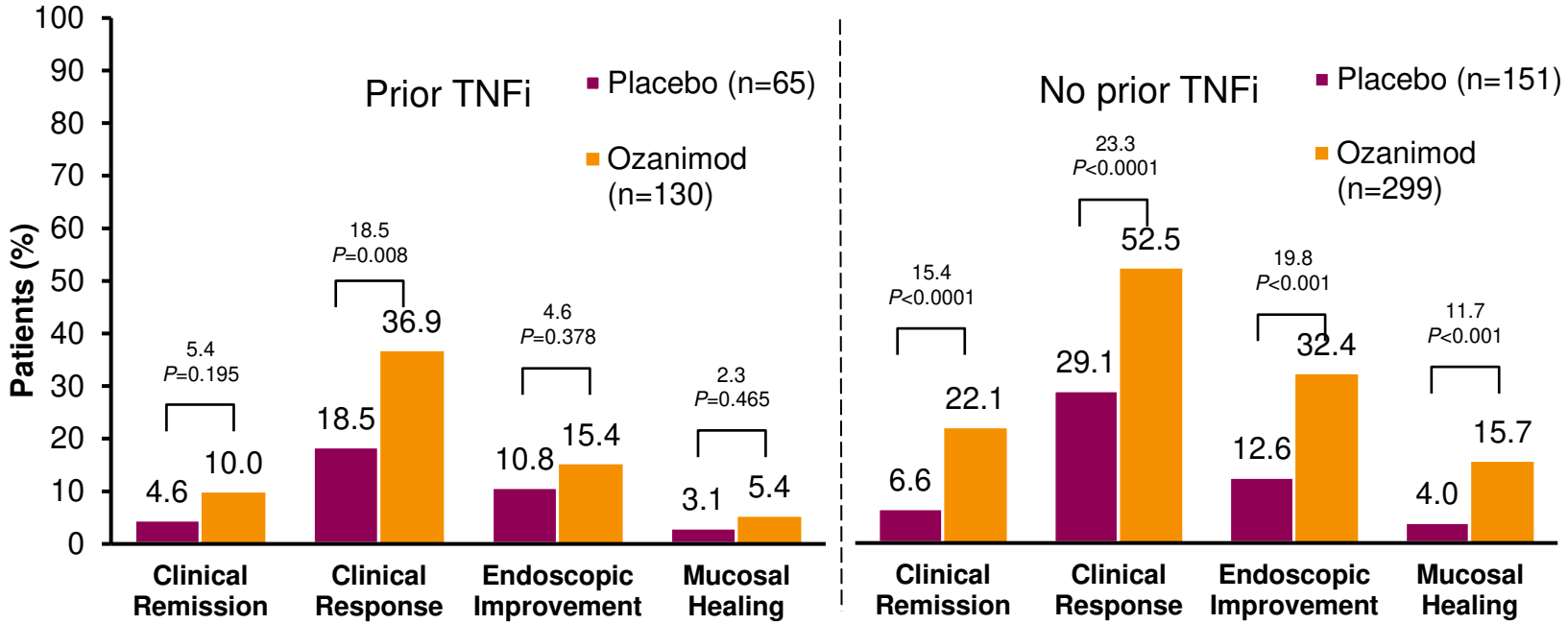
Sandborn WJ et al. *UEGW 2020*. October 2020. Presentation LB02.

Mean Change from Baseline in Rectal Bleeding Score for Ozanimod vs. Placebo over 10 Weeks[a]



[a]Post hoc analysis.
LSM, least squares mean; RBS, rectal bleeding subscore; SE, standard error.
Sandborn WJ et al. *UEGW 2020*. October 2020. Presentation LB02.

Efficacy of Ozanimod in Moderate-to-Severe UC by Prior TNF Inhibitor Use at Week 10

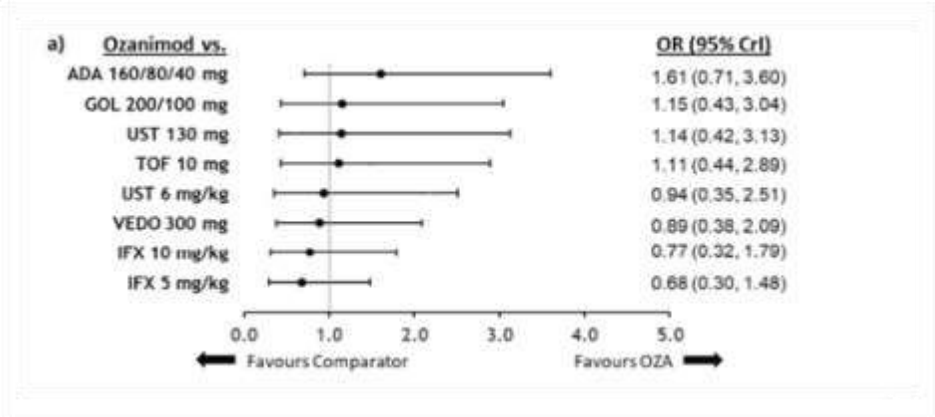


Data based on all randomized patients who received ≥1 dose of study treatment (intent-to-treat population). Missing data handled using non-responder imputation. P-values refer to odds ratios (not shown) based on 2-sided Cochran-Mantel-Haenszel test.

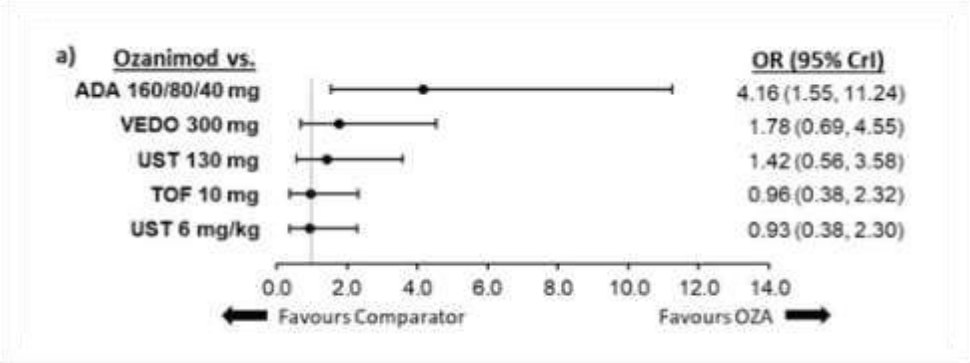
Sandborn WJ et al. *UEGW 2020*. October 2020. Presentation LB02.

Network Analysis for Clinical Remission

Clinical Remission in Biologic-Naïve Patients



Clinical Remission in Biologic-Experienced Patients



Eaton K et al. *J Crohns Colitis*. 2021;15(suppl_1):S103-S105.

Safety of Ozanimod in Moderate-to-Severe UC Phase 3 True North Study

	Induction Period (Week 10)		Maintenance Period (Week 52)	
	Placebo (n=216)	Ozanimod (n=429)	Placebo (n=227)	Ozanimod (n=230)
Any treatment-emergent adverse event (TEAE)	82 (38.0)	172 (40.1)	83 (36.6)	113 (49.1)
Common TEAEs (≥3% in any group)				
Anemia	12 (5.6)	18 (4.2)	4 (1.8)	3 (1.3)
Nasopharyngitis	3 (1.4)	15 (3.5)	4 (1.8)	7 (3.0)
Headache	4 (1.9)	14 (3.3)	1 (0.4)	8 (3.5)
Alanine aminotransferase increased	0	11 (2.6)	1 (0.4)	11 (4.8)
Gamma glutamyl transferase increased	0	5 (1.2)	1 (0.4)	7 (3.0)
Arthralgia	3 (1.4)	10 (2.3)	6 (2.6)	7 (3.0)
Serious TEAEs	7 (3.2)	17 (4.0)	18 (7.9)	12 (5.2)
UC exacerbation[a]	4 (1.9)	6 (1.4)	9 (4.0)	1 (0.4)
Anemia[a]	0	4 (0.9)	0	1 (0.4)
Appendicitis/Complicated appendicitis[a]	0	1 (0.2)	3 (1.2)	0
Severe TEAEs	4 (1.9)	14 (3.3)	9 (4.0)	9 (3.9)
TEAEs leading to treatment discontinuation	7 (3.2)	14 (3.3)	6 (2.6)	3 (1.3)

[a]Occurring in ≥2 patients in any group.

Sandborn WJ et al. *UEGW 2020*. October 2020. Presentation LB5.

Users Guide, Ozanimod

- No restriction in label
- 1 mg daily, titration of dose initially
- Baseline testing of CBC, CMP, ECG
  - Repeat CBC 1 week
  - Repeat CBC and CMP at 2 to 3 weeks
- Contraindicated in secondary heart block
- Relatively contraindicated if uveitis or diabetic retinopathy; routine ophthalmology visit is not required otherwise

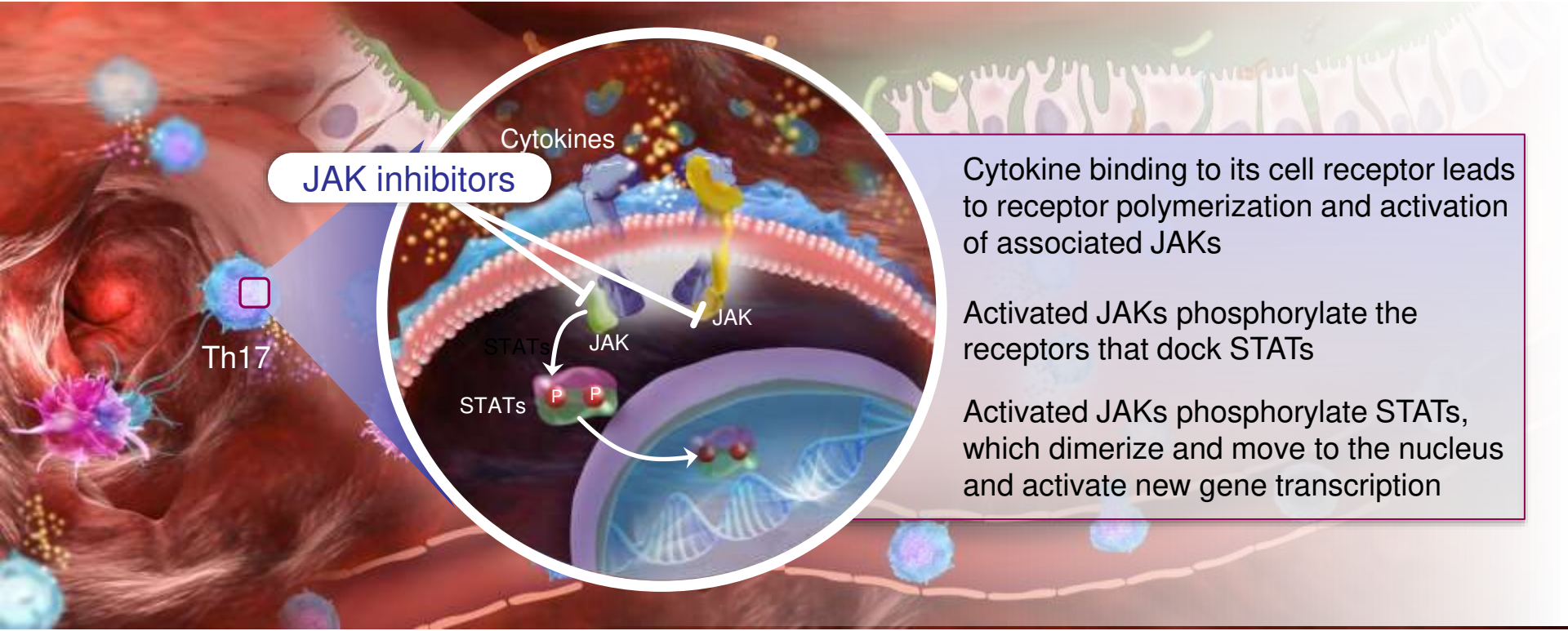
CBC = complete blood cell count; CMP = comprehensive metabolic panel; ECG = electrocardiogram.

Ozanimod. Package insert. Celgene Corporation. 2020.

JAK Inhibitors

(Tofacitinib, Upadacitinib)

Binding of Cytokine Receptors by Cytokines Activates JAK Pathways Signaling



Cytokine binding to its cell receptor leads to receptor polymerization and activation of associated JAKs

Activated JAKs phosphorylate the receptors that dock STATs

Activated JAKs phosphorylate STATs, which dimerize and move to the nucleus and activate new gene transcription

JAK, janus kinase; STAT, signal transducer and activator of transcription.

Shukla T, Sands BE. *Curr Gastroenterol Rep.* 2019;21(5):22.

Key Immunoregulatory Cytokines Linked TO JAK PATHWAY

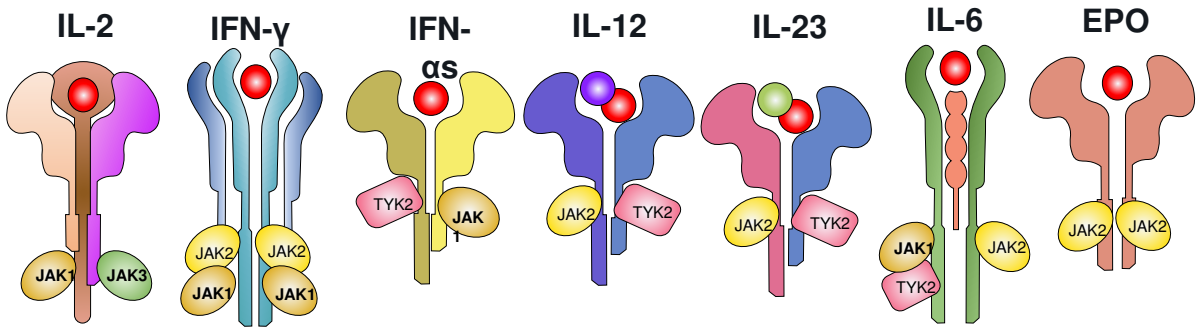
Different JAK inhibitors target several cytokines linked to UC inflammation

Tofacitinib JAK1 JAK3

Filgotinib
Upadacitinib JAK1

Peficitinib
Ritlecitinib JAK3

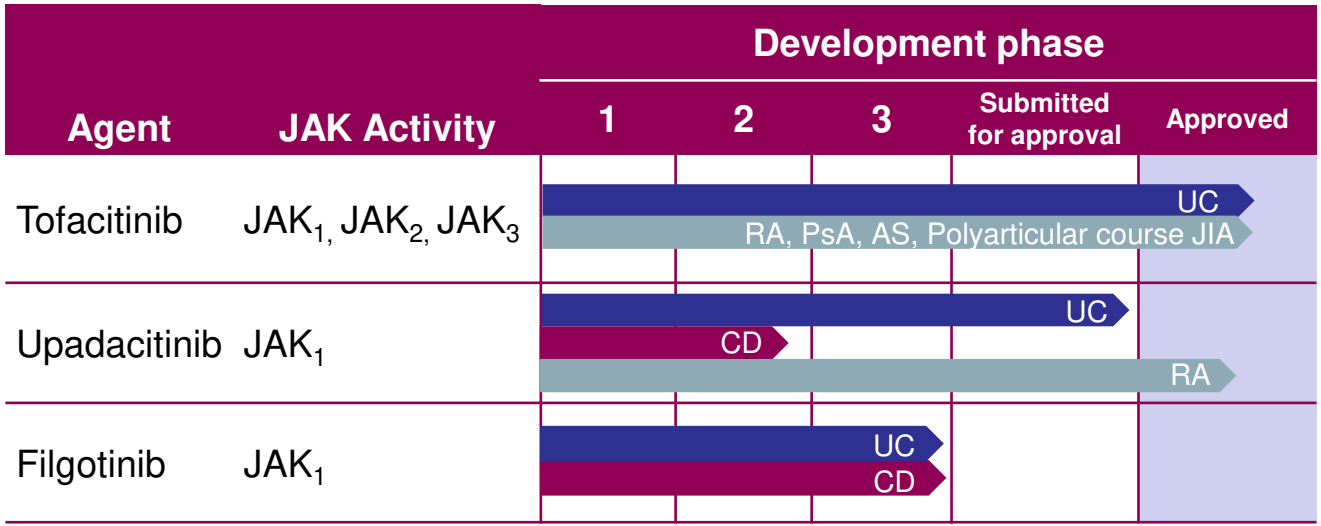
Brepocitinib
Deucravacitinib TYK2



INHIBITOR	IL-2	IFN-γ	IFN-αs	IL-12	IL-23	IL-6	EPO
JAK1	+	+	+	-	-	+	-
JAK2	-	+	+	+	+	+	+
JAK3	+	-	-	-	-	-	-
TYK2	-	-	+	+	+	-	-

Abbreviations: EPO, erythropoietin; IFN, interferon.
O'Shea J, Plenge R. *Immunity.* 2012;36(4):542-550.

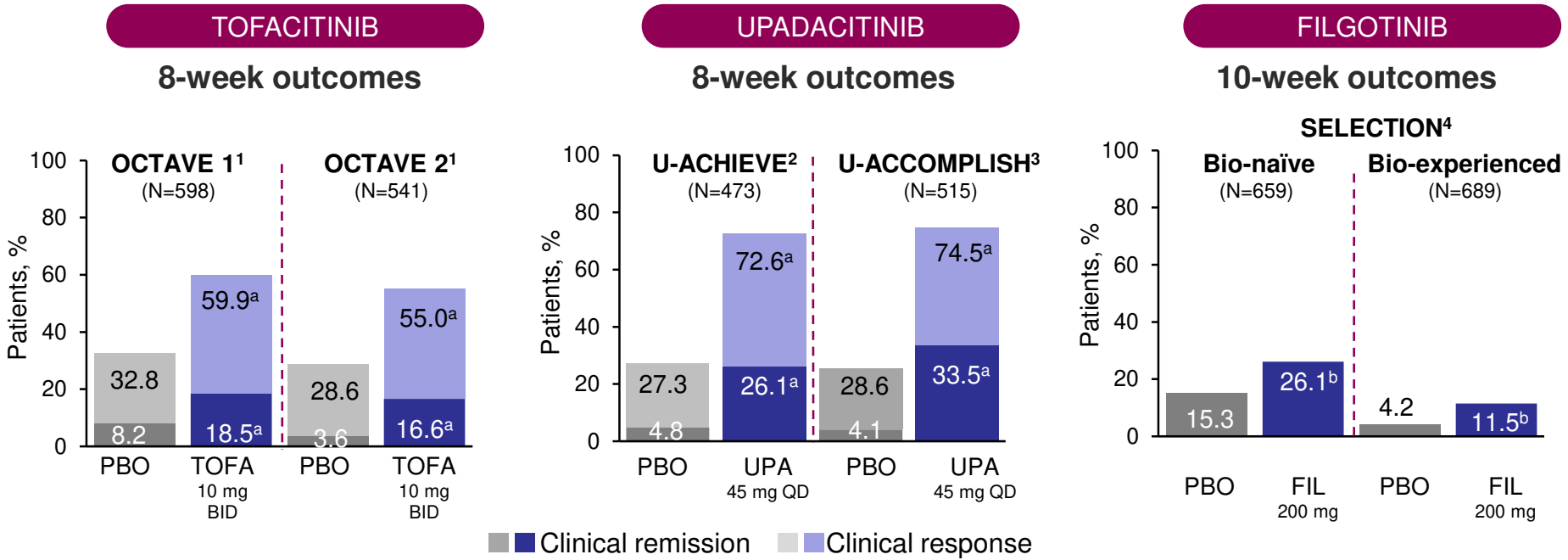
Key Approved and Investigational JAK Inhibitors



AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; S1P, sphingosine-1-phosphate.

1. ClinicalTrials.gov. www.clinicaltrials.gov. Accessed January 10, 2022. 2. D'Haens G et al. *J Crohns Colitis*. 2021 Nov 10;jjab201. doi: 10.1093/ecco-jcc/jjab201. Online ahead of print.3. Danese S et al. J Crohns Colitis. 2018;S578-S686.

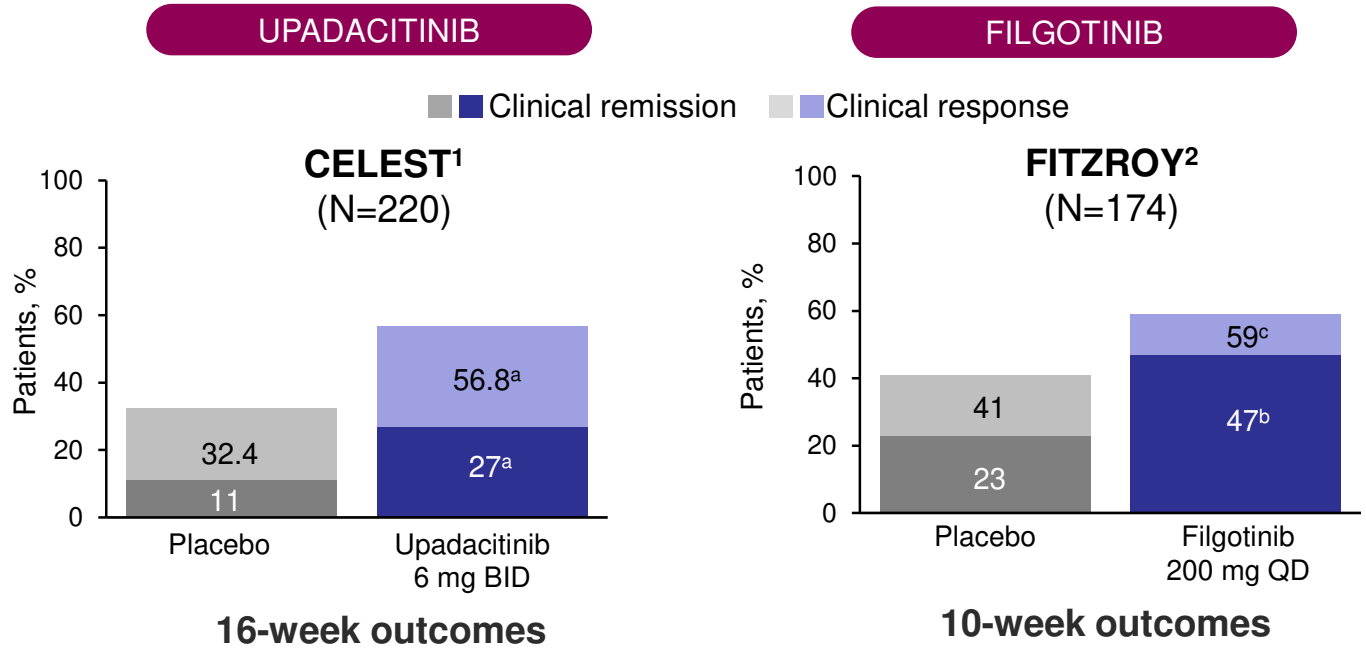
Pivotal Induction Studies of JAK Inhibitors in Moderate to Severe UC



[a]*P*<0.001 vs placebo; [b]*P*=0.01 vs placebo.
BID, twice daily; FIL, filgotinib; PBO, placebo; TOFA, tofacitinib; UPA, upadacitinib.

1. Sandborn WJ et al. *N Engl J Med.* 2017;376(18):1723-1736. 2. Denise S, et al. Presented at: 16th Congress of ECCO; IBD Horizons, Scientific Session 8; July 8-10, 2021. Copenhagen. OP24. 3. Vermeire S, et al. Presented at: 16th Congress of ECCO; IBD Horizons, Scientific Session 8; July 8-10, 2021. Copenhagen. OP23. 4. Feagan BG, et al. *Lancet.* 2021;397(10292):2372-2384.

Phase 2 Induction Studies of JAK Inhibitors in Moderate to Severe CD

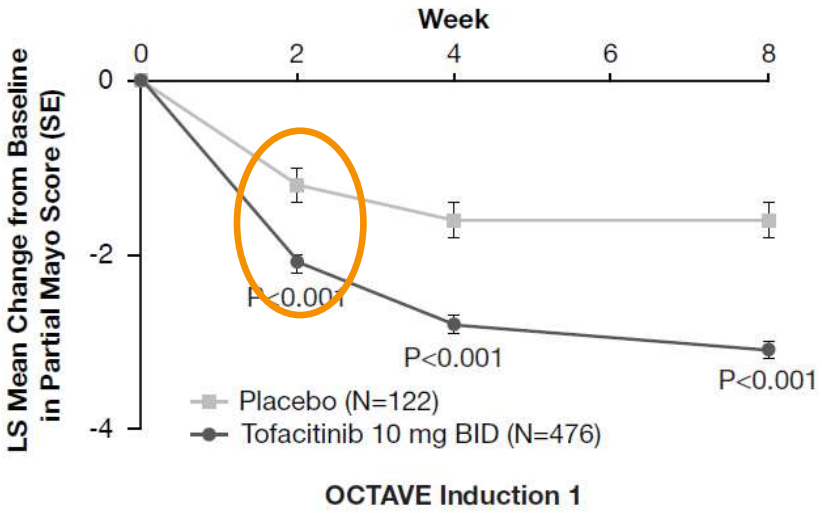


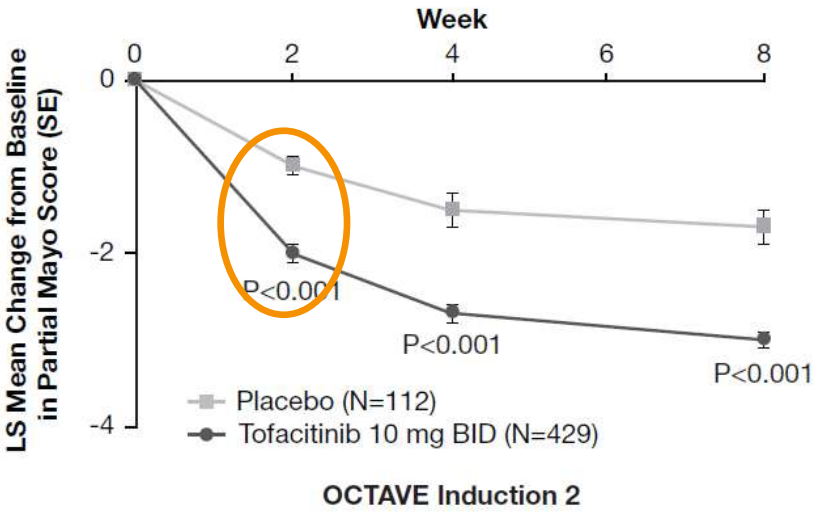
a$P<0.1$; b$P=0.0077$; c$P<0.05$.

1. Sandborn WJ, et al. *Gastroenterology.* 2020;158(8):2123-2138.e8. 2. Vermeire S, et al. *Lancet.* 2017;389(10066):266-275.

Tofacitinib Works Quickly

Partial Mayo Score





Sandborn WJ et al. *N Engl J Med*. 2017;376:1723-1736.

Tofacitinib in UC: How and When to Use It?

Advantages of tofacitinib

- Oral dosing
- Rapid onset of action
- Patients with poor PK for biologic (low albumin)
- May lower to 5mg BID if deep remission
- Bridge to other biologic?
- Non-immunogenic
  - Patients with history of ADA
  - Patients at risk of interrupting meds

Limitations of tofacitinib

- After failure of anti-TNF
- Contraindicated during conception/pregnancy
- DVT/PE risk factors (eg, elderly, cancer)
- No live virus vaccines

ADA, anti-drug antibodies; DVT, deep venous thrombosis; PE, pulmonary embolism; PK, pharmacokinetic.

Bernstein JA et al. *Clin Gastroenterol Hepatol.* 2019;17(5):988-990; Vermeire S et al. *Gut.* 2021;15(7):1130-1141. Open Access.

The IBD Pipeline

	Agent	Target	Development phase					
			Crohn's disease			Ulcerative colitis		
			1	2	3	1	2	3
Anti-trafficking	~~Etrolizumab~~	~~β_7-integrin~~						
	~~SHP647~~	~~MAdCAM-1~~						
	Ozanimod	$S1P_1/SIP_5$						
	Etrasimod	$S1P_1$						
JAK inhibitors	Filgotinib	JAK1						
	Upatacitinib	JAK1						
Cytokine-based therapies	Brazikumab	IL-23 (p19)						
	Risankizumab	IL-23 (p19)						
	Guselkumab	IL-23 (p19)						
Other	Apremilast	PDE4						
	ABBV-23	CD40						

MMP = matrix metalloproteinase.

Amiot A, Peyrin-Biroulet L. Ther Adv Gastroenterol. 2015;8(2):66-82. Open Access; 2. ClinicalTrials.gov. Accessed September 30, 2021.

Summary

- Biologic therapy is safe and effective for moderate to severe CD and UC
  - Vedolizumab and ozanimod can be used first line in ulcerative colitis
  - Ustekinumab can be used first line in Crohn's disease
  - I still think anti-TNFs are most effective for fistulizing disease–ustekinumab second line; JAK inhibitors and p19 being tested
  - Tofacitinib and JAK inhibitors also fast acting, especially in naive patients
- Key considerations for initiating and monitoring biologic therapies include chest x-ray/TB testing, vaccination status (Shingrix vaccine for JAKi), cholesterol, skin checks

Unanswered Questions

- Best sequence of biologics
  - Ideally biomarker-based
  - Insurance decides (sorry to burst your bubble)
- Take into account the full picture:
  - Severity of inflammation at induction—how quickly do you need it to work?
  - Extraintestinal manifestations, fistulizing disease
  - Age and comorbidities

Thank You