Small-Molecule Therapies in IBD

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Small-Molecule Therapies in IBD

- **Janus kinase (JAK) inhibitors.**
- **Sphingosine-1-phosphate (S1P) receptor modulators.**
- **Mothers against decapentaplegic homolog 7 (SMAD7) inhibitors.**
- **Phosphodiesterase-4 (PDE4) inhibitors.**
- **TYK2 inhibitors**

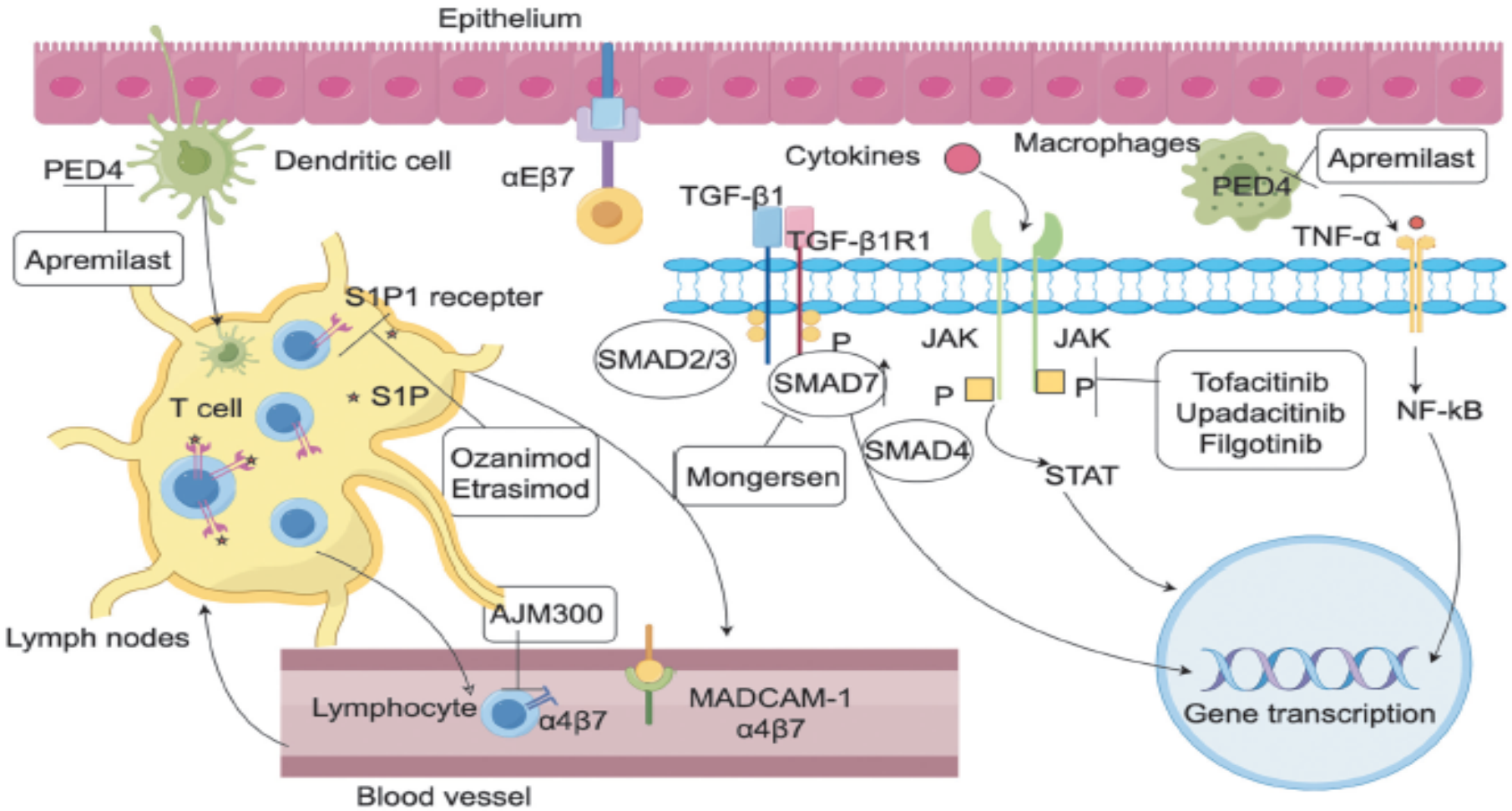
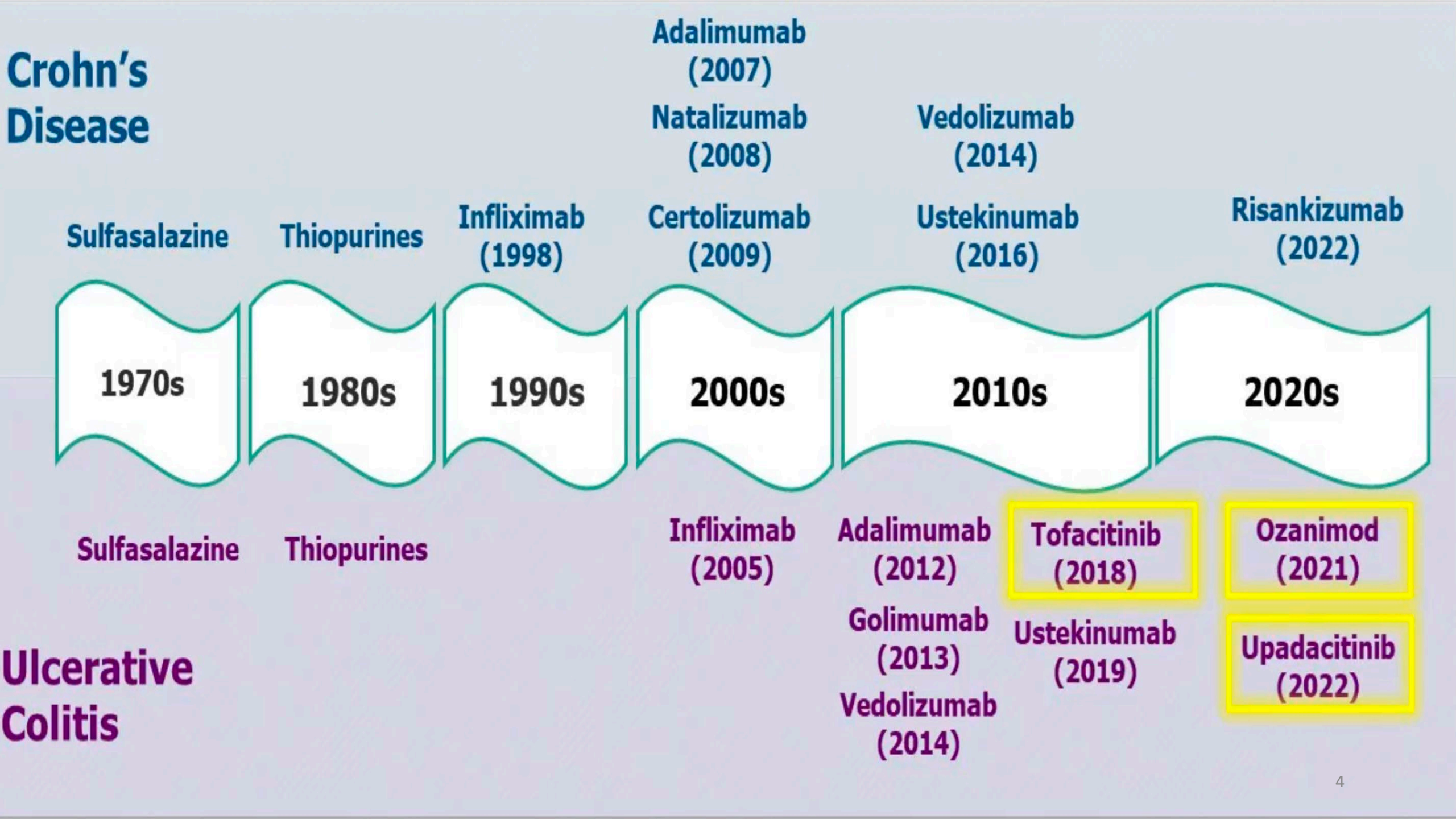
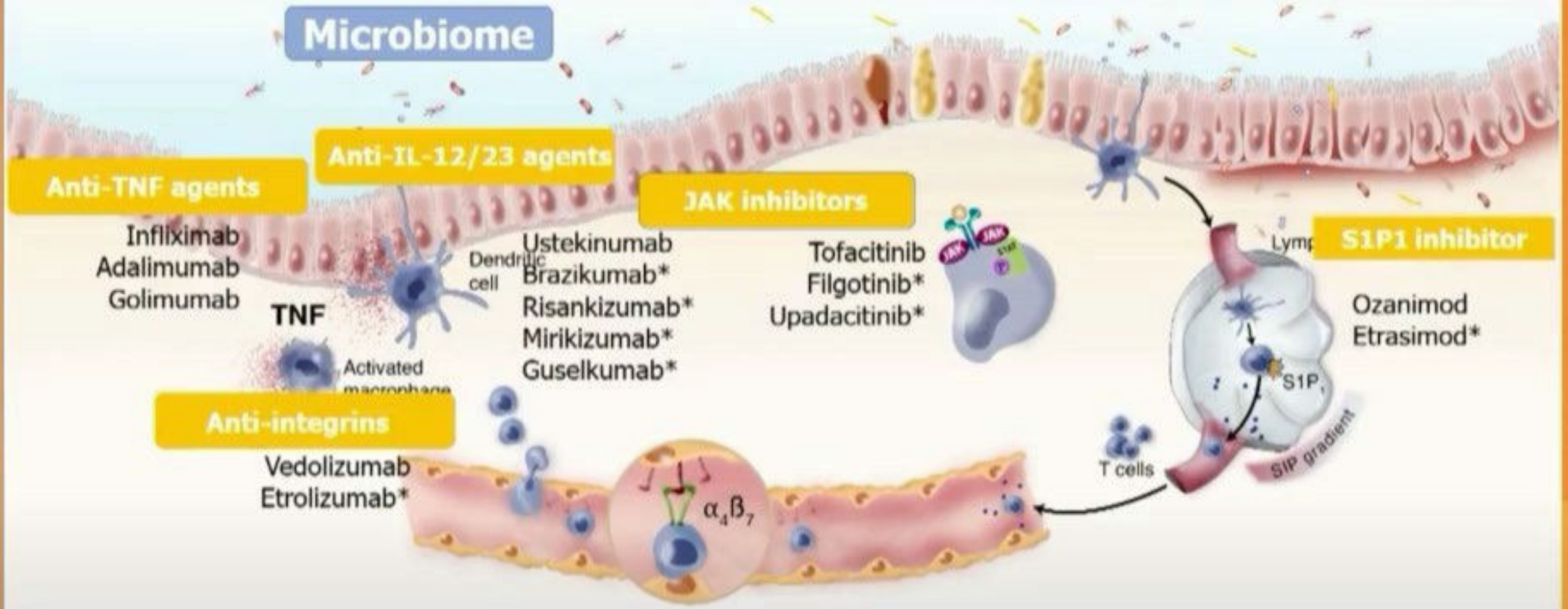


Figure 1: Mechanisms of action of small-molecule drugs for inflammatory bowel disease. PED4: Phosphodiesterase 4; TGF-β1: Transforming growth factor-β1; S1P: Sphingosine-1-phosphate; SMAD: Mothers against decapentaplegic homolog 7; JAK: Janus kinase; TNF-α: Tumor necrosis factor α; STAT: Signal transducer and activator of transcription; NF-κB: Nuclear factor kappa B; MADCAM-1: Mucosal addressin cell adhesion molecule 1.


Crohn's Disease
Sulfasalazine
Thiopurines
Infliximab (1998)
Adalimumab (2007)
Natalizumab (2008)
Certolizumab (2009)
Vedolizumab (2014)
Ustekinumab (2016)
Risankizumab (2022)
1970s
1980s
1990s
2000s
2010s
2020s
Sulfasalazine
Thiopurines
Infliximab (2005)
Adalimumab (2012)
Golimumab (2013)
Vedolizumab (2014)
Tofacitinib (2018)
Ustekinumab (2019)
Ozanimod (2021)
Upadacitinib (2022)
Ulcerative Colitis

Current and Emerging Strategies for IBD



TNF = tumor necrosis factor; IL = interleukin; JAK = Janus kinase; STAT = signal transducer and activator of transcription.
Adapted from Coskun M, et al. *Trends Pharmacol Sci*. 2017;38(2):127-142.

limitations of biologics:

- Risk for immunogenicity
- High rates of primary non-response or secondary loss of response
- safety concerns
- Requirement of parenteral administration

Advantages of Small molecule:

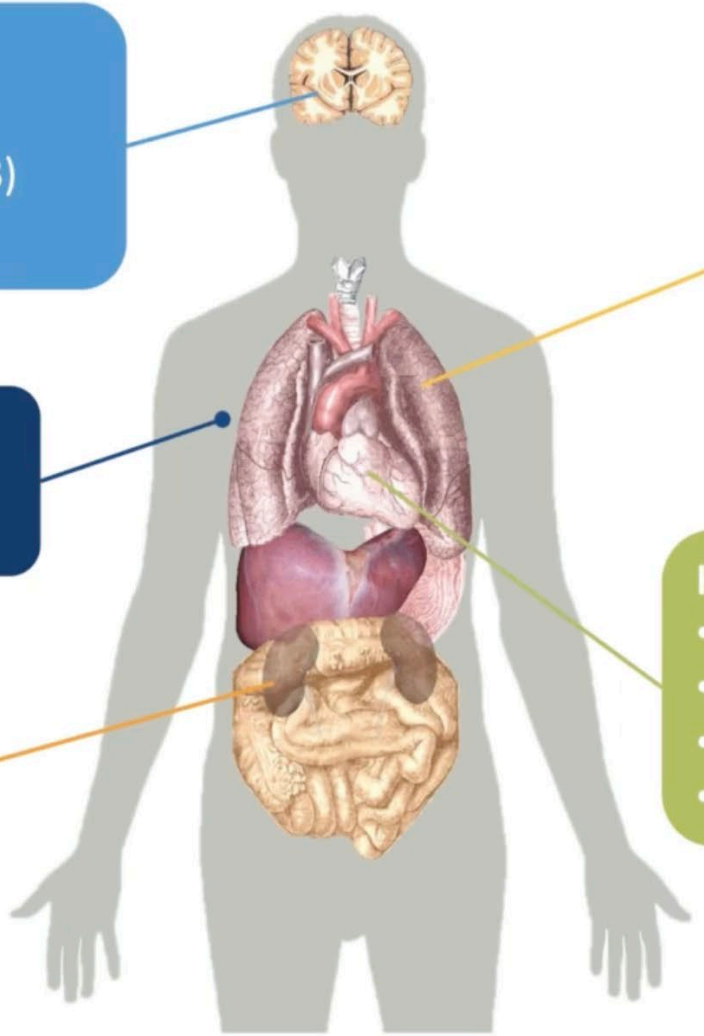
- Oral administration
- little to no risk of immunogenicity
- potential for rapidity of onset a high impact in pretreated and Naïve patients
- Short half-life of SMDs makes it easier to manage adverse events
- Relatively Cost-effective

Sphingosine-1-Phosphate Receptors: $S1P_{1-5}$ (Ozanimod is S1P1, P5; Etrasimod is S1P1, P4, P5)

Brain vasculature
- Endothelial permeability (S1P1)
- Transcellular transport (S1P1 and/or S1P3)
- Hearing and balance (S1P2 and/or S1P3)

Lymph nodes
- Lymphocyte sequestration (S1P1)
- Dendritic cell sequestration (S1P3

Kidneys
- Vascular leakage (S1P1)
- Inflammation (S1P1)



Lungs
- Leakage (S1P1 and/or S1P3)
- Inflammation (S1P1 and/or S1P2 and/or S1P3)
- Airway hyper-responsiveness (multiple S1P receptors)

Heart
- Heart rate (S1P3)
- Myocyte survival (S1P2 and/or S1P3)
- Inflammation (S1P1 and/or S1P3)
- Vascular resistance (S1P2 and/or S1P3)

Adapted from Marsolais D, Rosen H. *Nat Rev Drug Discov.* 2009;8(4):297-307; Rivera J, et al. *Nat Rev Immunol.* 2008;8(10):753-763.

How Ozanimod Works

Ozanimod stops lymphocytes from travelling around the body and causing inflammation in the gut

This reduces the symptoms of Colitis

Leukocyte Trafficking Analogy for Mechanism of Action: "The Harbor"

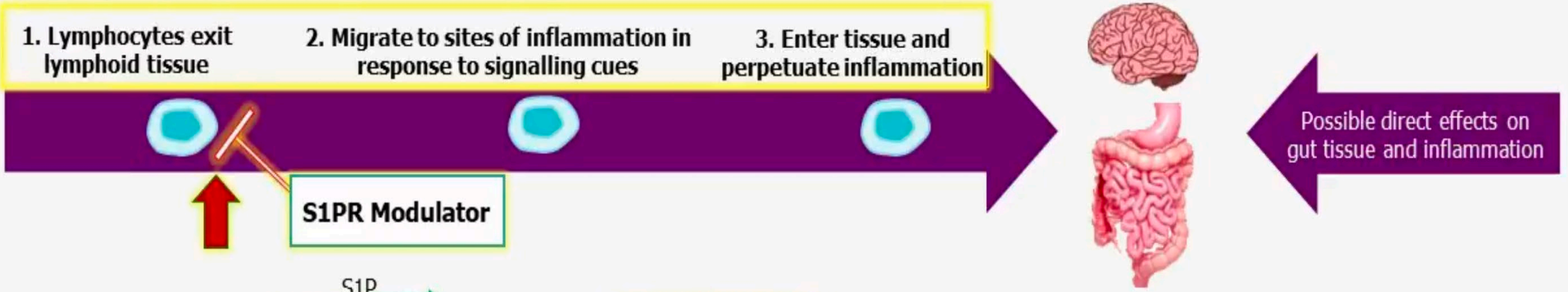


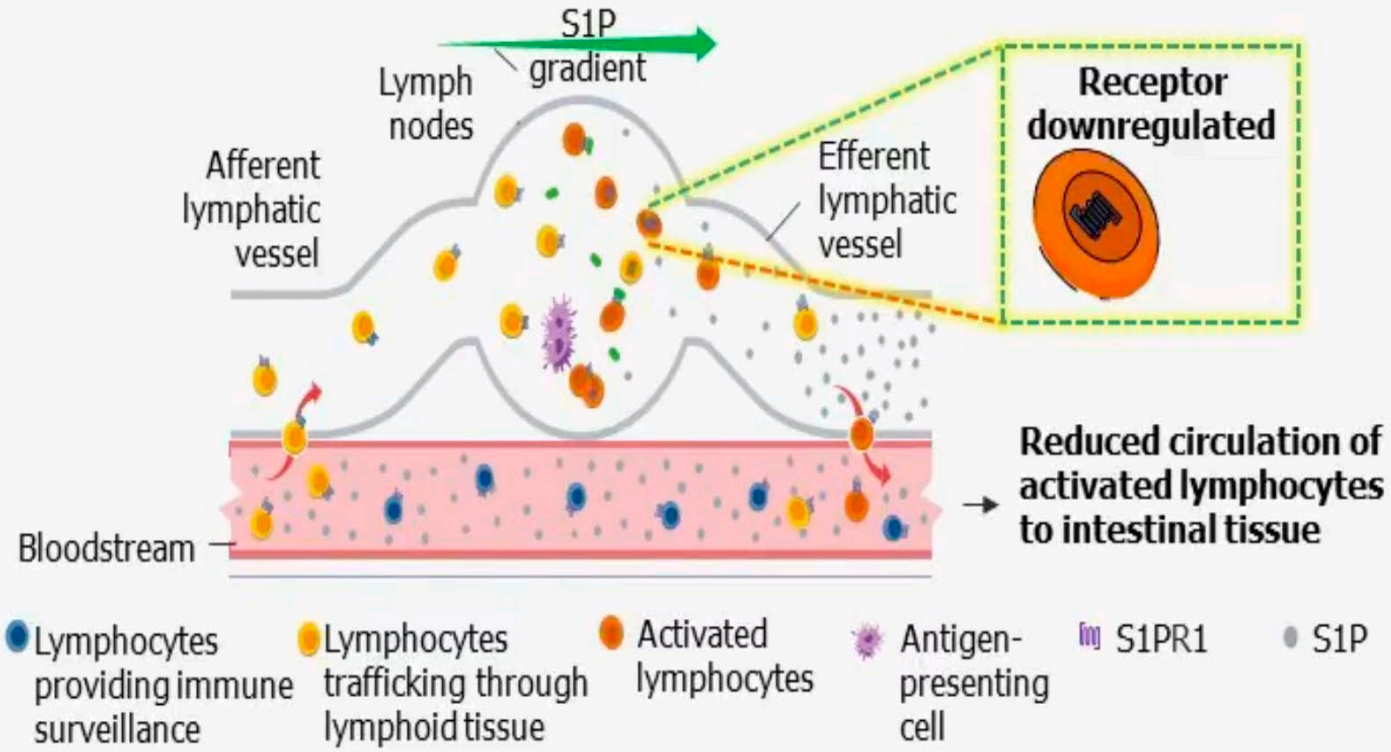


Anti-integrin therapy (vedolizumab) does not let the boats (WBCs) dock at their destination
S1PR modulator therapy (ozanimod) does not let the boats (WBCs) leave the harbor in the first place

WBCs = white blood cells.
Slide courtesy of Ray Cross, MD.

S1PR Modulator: Mechanism of Action





- Under physiologic conditions, approximately 2% of the total lymphocyte pool in the human body is in the circulation[1]
- S1P regulates lymphocyte migration from lymphoid tissue to sites of inflammation[2]
- Cells involved in immune surveillance (eg, monocytes and NK cells) are not negatively affected and continue to circulate[3]

INDICATIONS & Approvals

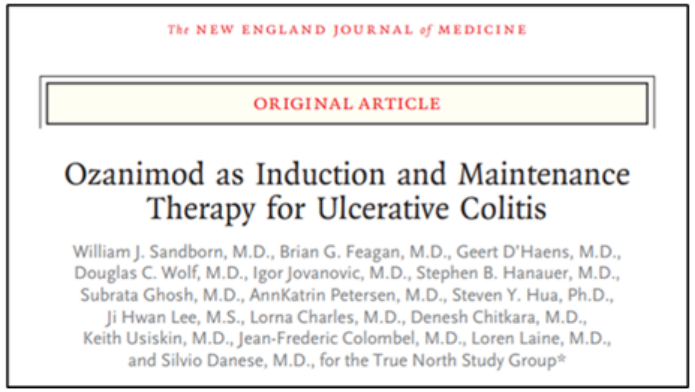
Two oral S1P receptor modulators (ozanimod and etrasimod) have been approved in the United States for treating adults with moderate to severe UC .
Use of S1P receptor modulators does not require previous failure of immunosuppressant, glucocorticoids, biologics, or other small molecules.
Data have suggested that most patients have symptomatic improvement (fewer stools, less rectal bleeding) within two weeks of initiating therapy.

Ozanimod as a selective immunosuppressants is indicated for the treatment of:

1. **Moderately to severely active ulcerative colitis (UC) in adults.**
2. Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Highlights with ozanimod:

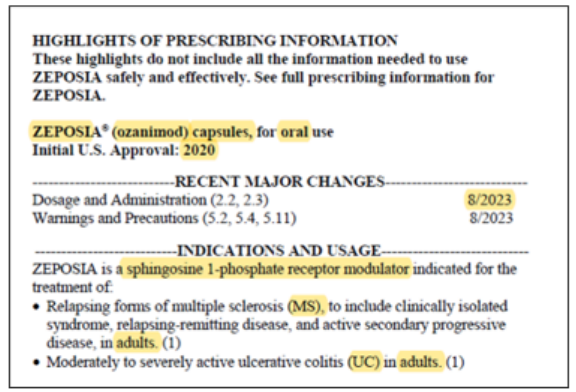
- ✓ Highly selective Oral
- ✓ Rapid Response
- ✓ Sustained Remission
- ✓ Well-stablished safety Profile


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis

William J. Sandborn, M.D., Brian G. Feagan, M.D., Geert D'Haens, M.D., Douglas C. Wolf, M.D., Igor Jovanovic, M.D., Stephen B. Hanauer, M.D., Subrata Ghosh, M.D., AnnKatrin Petersen, M.D., Steven Y. Hua, Ph.D., Ji Hwan Lee, M.S., Lorna Charles, M.D., Denesh Chitkara, M.D., Keith Usiskin, M.D., Jean-Frederic Colombel, M.D., Loren Laine, M.D., and Silvio Danese, M.D., for the True North Study Group*


HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPOSIA safely and effectively. See full prescribing information for ZEPOSIA.

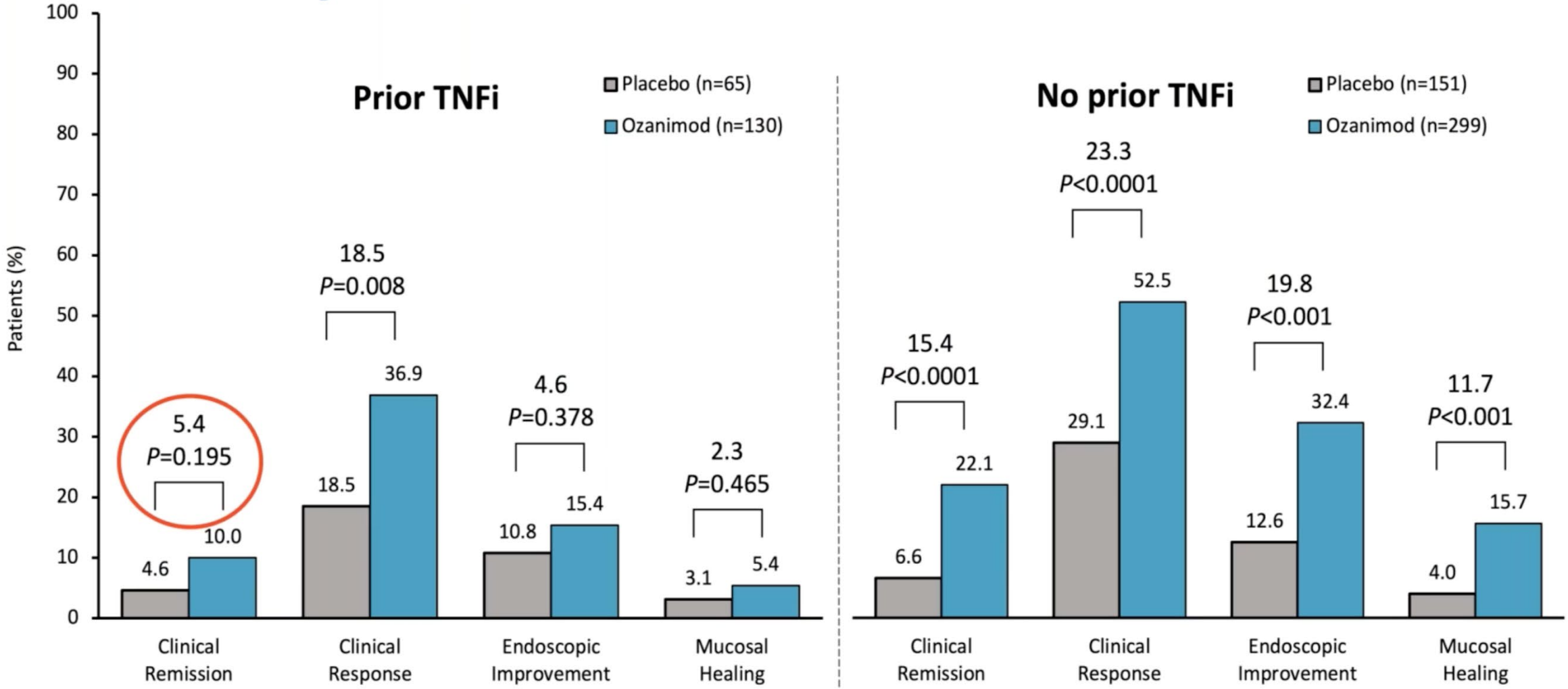
ZEPOSIA® (ozanimod) capsules, for oral use
Initial U.S. Approval: 2020

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.2, 2.3) 8/2023
Warnings and Precautions (5.2, 5.4, 5.11) 8/2023

----------INDICATIONS AND USAGE----------
ZEPOSIA is a sphingosine 1-phosphate receptor modulator indicated for the treatment of:
- Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. (1)
- Moderately to severely active ulcerative colitis (UC) in adults. (1)

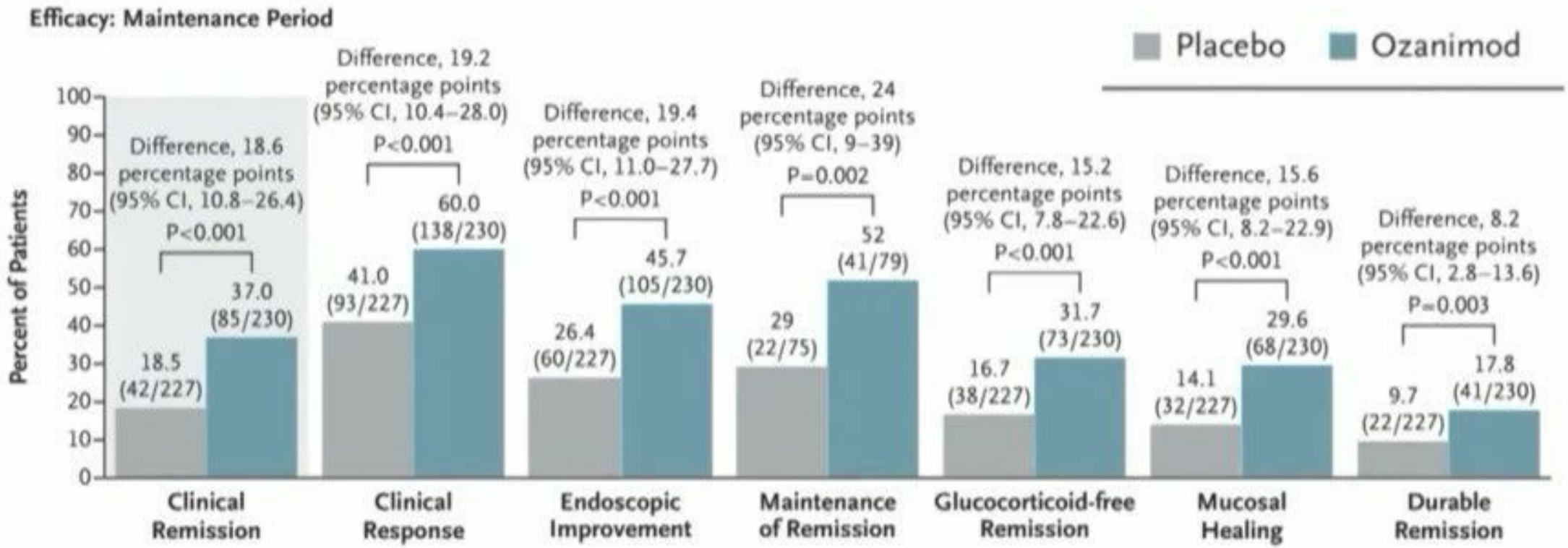
FDA & EMA Approved in March 2021

Ozanimod for Induction of UC by Prior TNF Inhibitor Use at Week 10



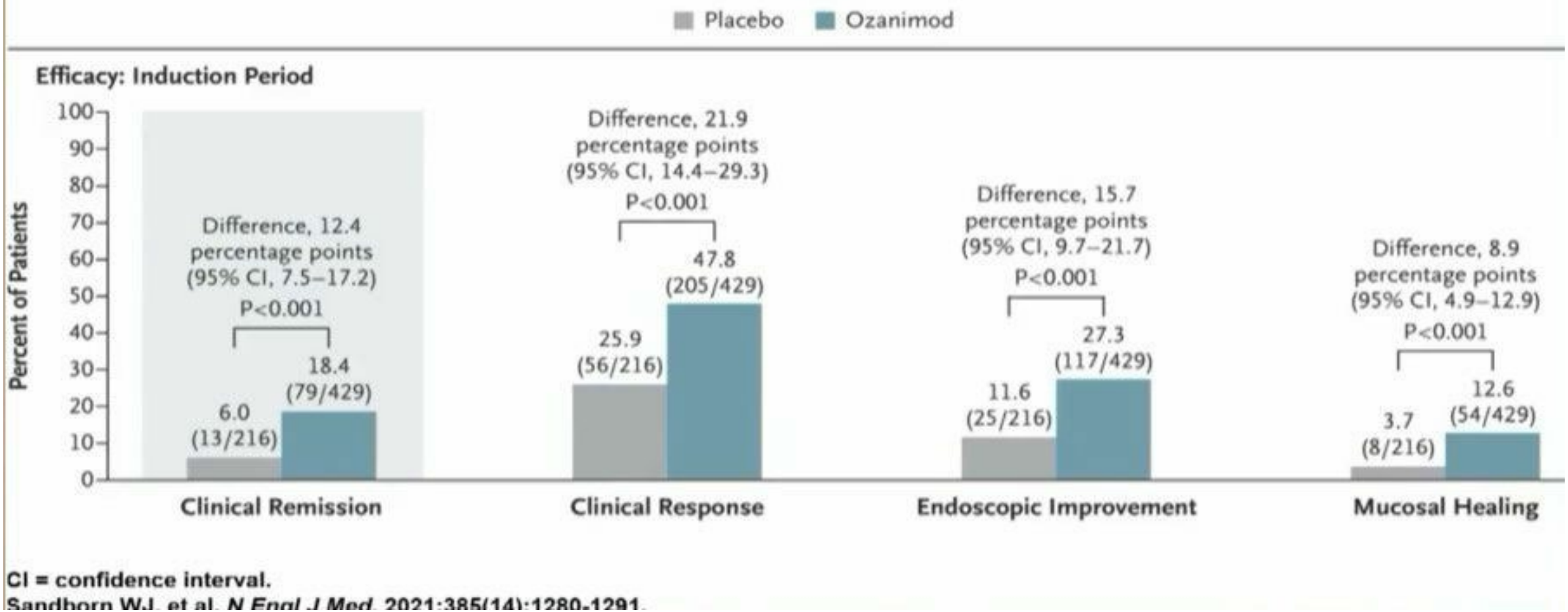
Sandborn WJ, et al. *N Engl J Med.* 2021 Sep 30;385(14):1280-1291.

Ozanimod Efficacy: Maintenance



Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.

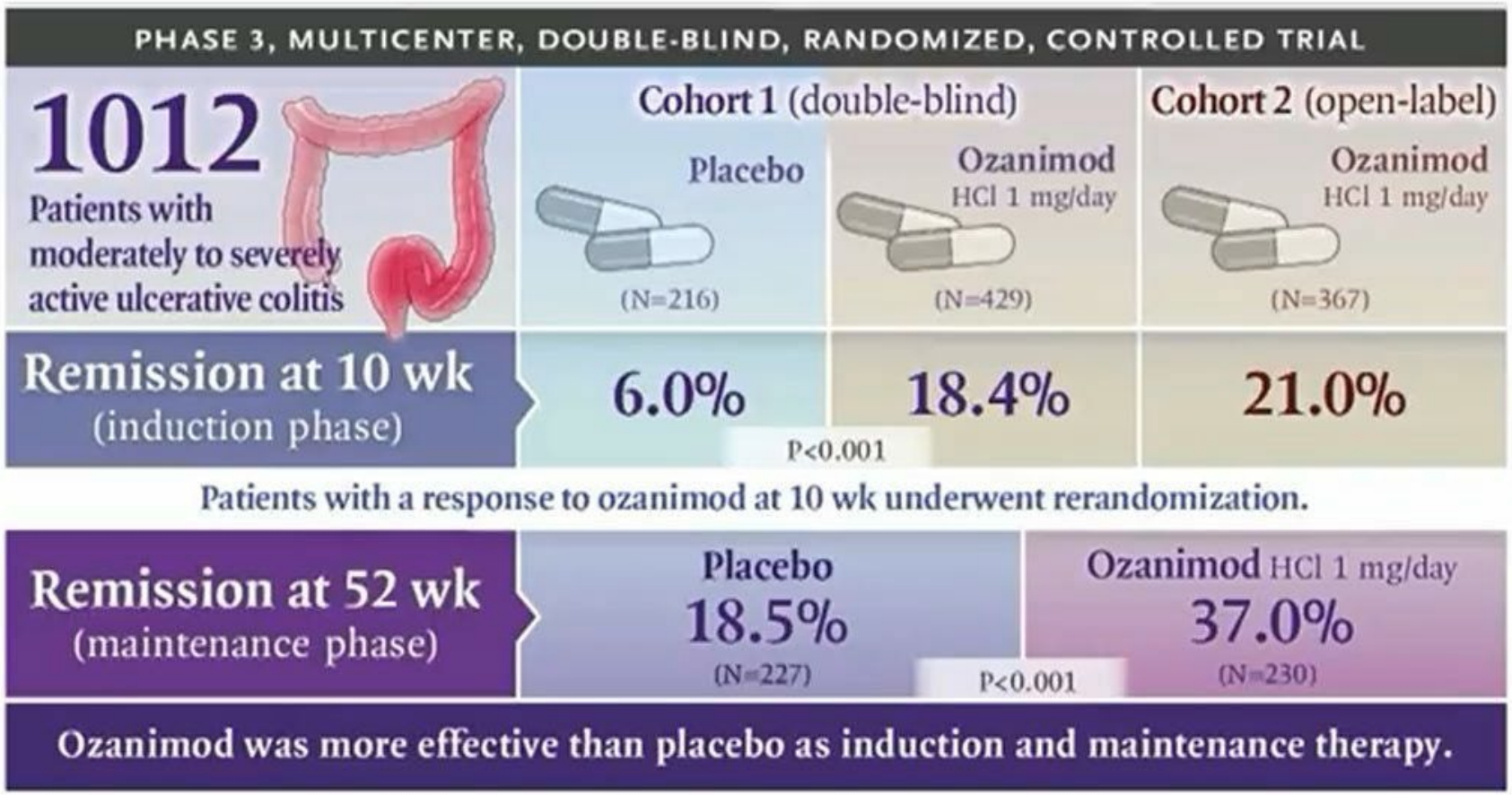
Ozanimod Efficacy: Induction



CI = confidence interval.

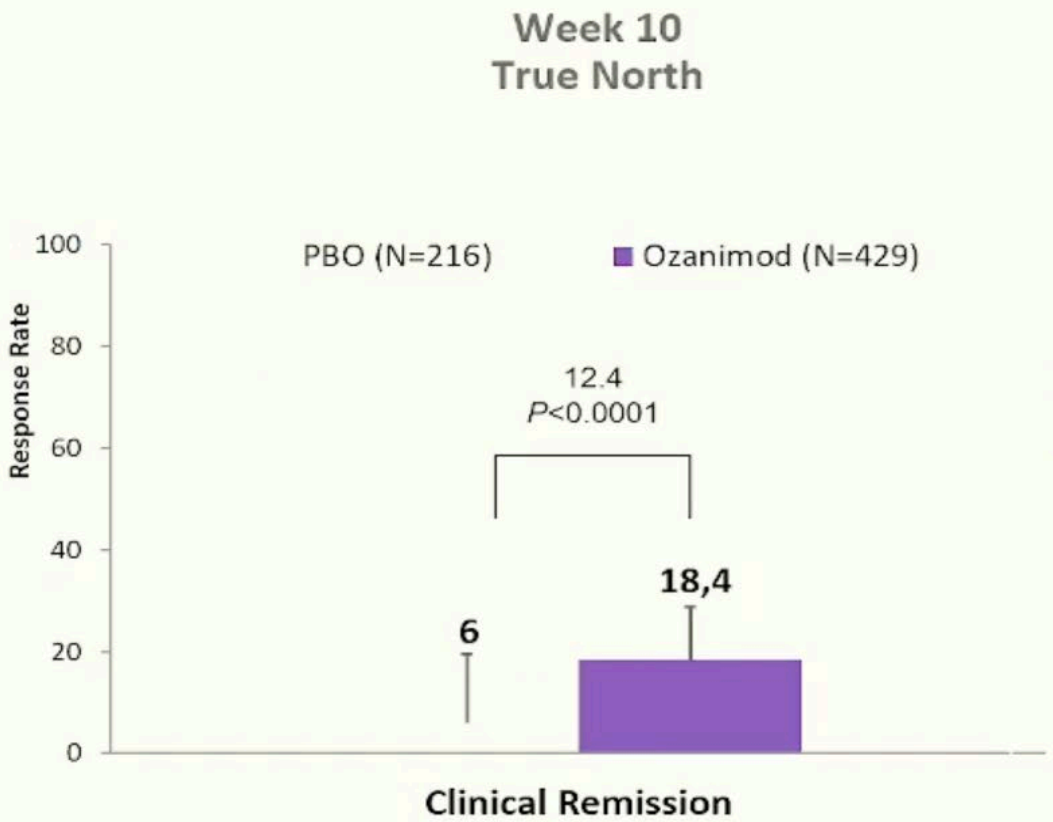
Sandborn W.J. et al. *N Engl J Med*. 2021;385(14):1280-1291.

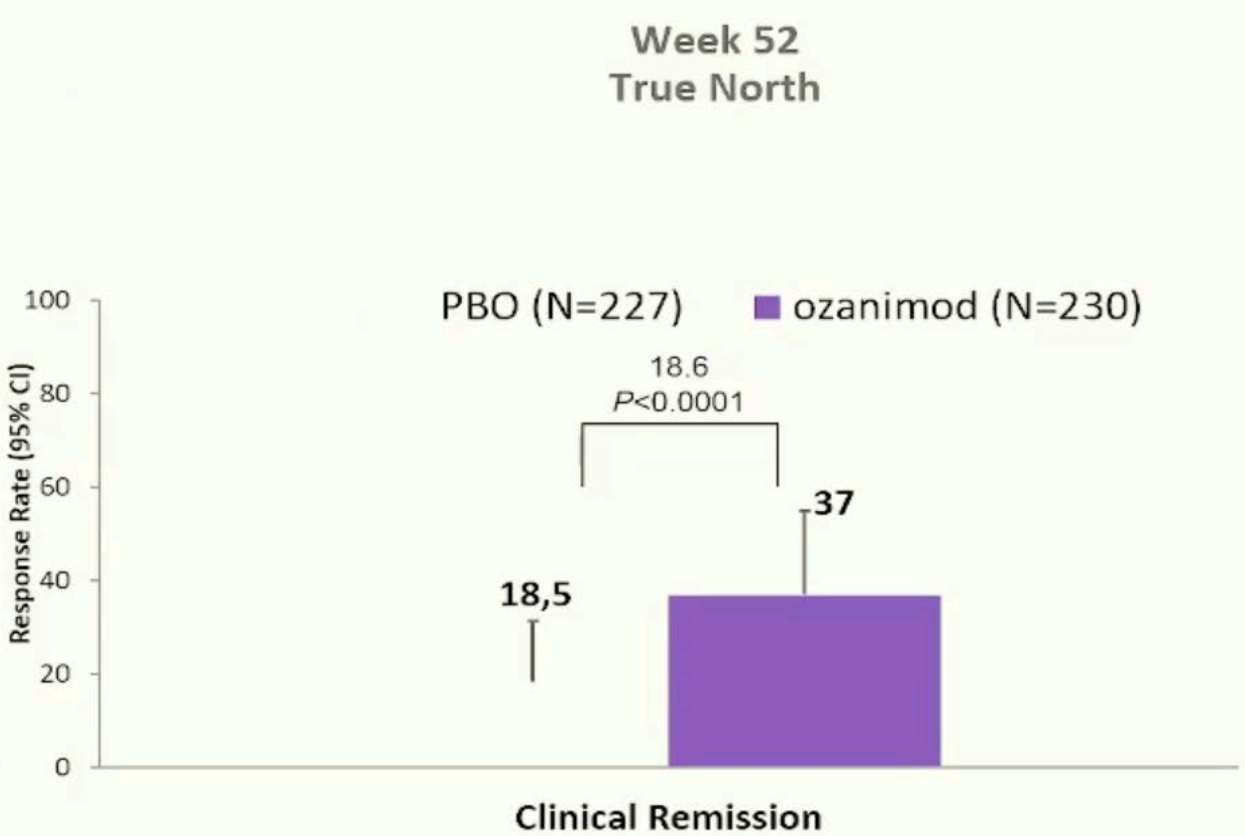
Ozanimod Efficacy Data: True North Trial



Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.

Ozanimod in moderate-to-severe ulcerative colitis





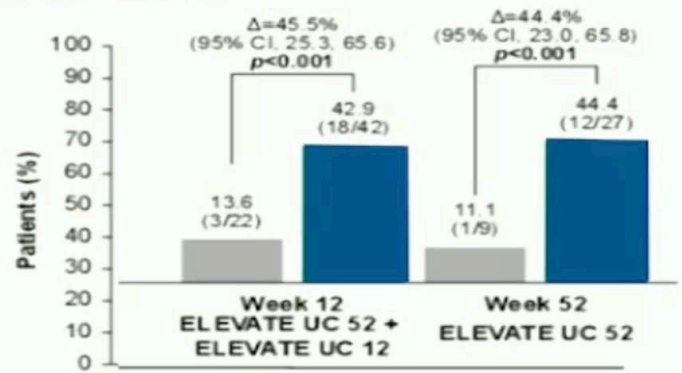
CI=Confidence Interval; ES=Endoscopic Subscore; IV=Intravenous; MIRI=Mirikizumab; PBO=Placebo; RB=Rectal Bleeding; SF=Stool Frequency.
D'Haens G, et al. N Engl J Med. 2022;388:2444-2455.

S1P Receptor Modulators are safe and effective in UC

Etrasimod is effective for induction and maintenance of remission in UC[1]

Etrasimod shows significant corticosteroid-free clinical remission and endoscopic improvement at W52 compared to placebo

Etrasimod works in isolated proctitis[2]



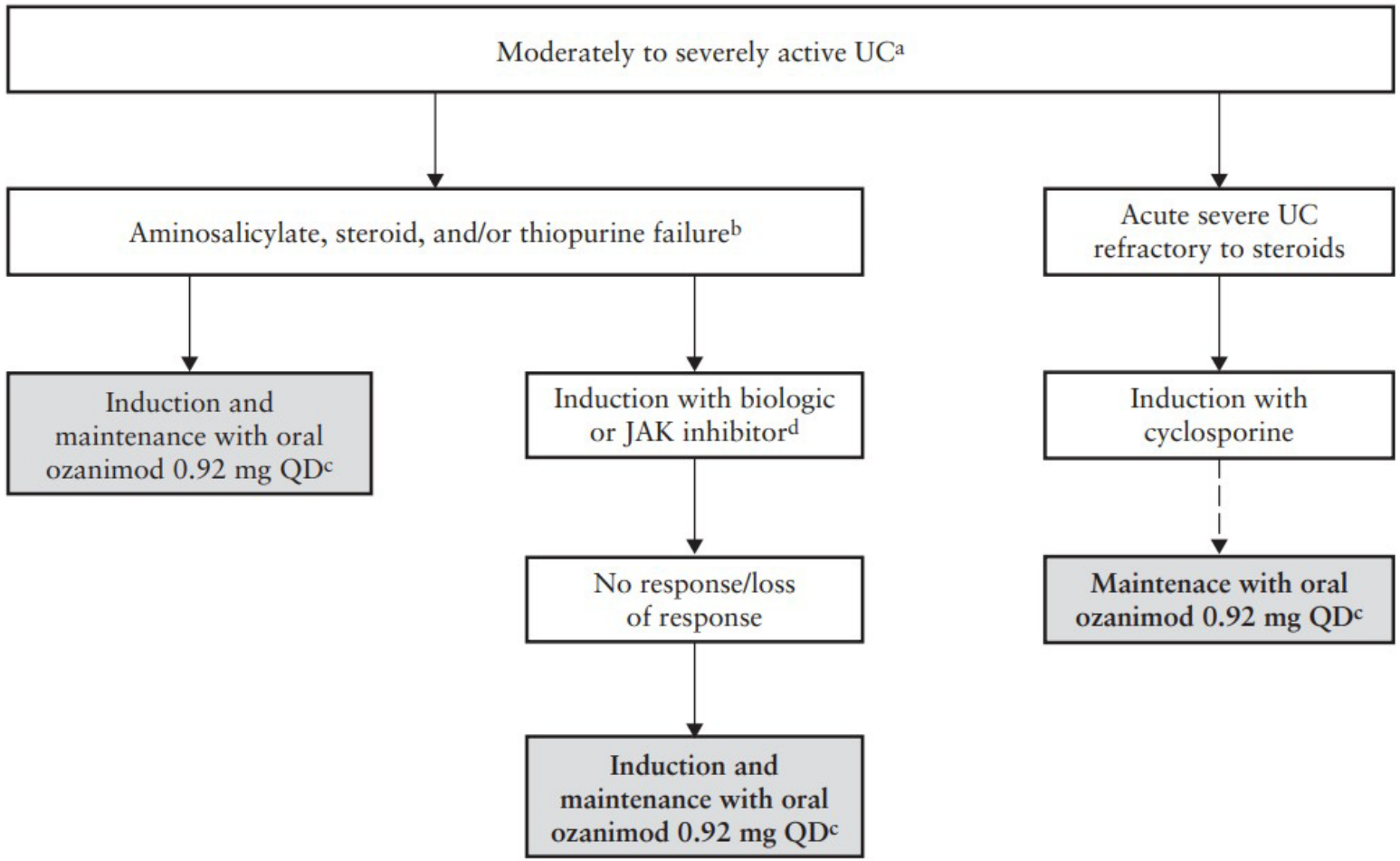
Ozanimod is safe up to 3 years in UC patients[3]





1. Sands B, *et al*. Presented at DDW. May 2023. Tu1702. 2. Dubinsky M, *et al*. Presented at DDW. May 2023. Tu1708. 3. Abreu M, *et al*. Presented at DDW. May 2023. 950.

Placement of Ozanimod Within the Treatment Armamentarium for UC



Ozanimod for Crohn disease

- **The positive, preliminary phase 2 findings suggest that ozanimod is likely to become an option for Crohn's disease in addition to UC.**

Treatment Paradigm for a Durable Remission with Ozanimod: **Iran IBD Expert Opinions + world evidence**

Moderate-to-severe UC

Patients with MS & UC

Induction and maintenance with
Ozanimod 0.92 Once Daily







Systemic Treatment with 5-ASA, Oral steroid failure

Induction and maintenance with
Ozanimod 0.92 Once Daily

- **Tofacitinib**
- **Upadacitinib**

Induction with biologic/ TNFi
(Adalimumab, Infliximab. Vedolizumab)
(**On Remission**)

Ozanimod 0.92 Once Daily
Maintenance

On TNFi (Immunogenicity): Add Azathioprine
Safety Concern/Non-adherence to Bio

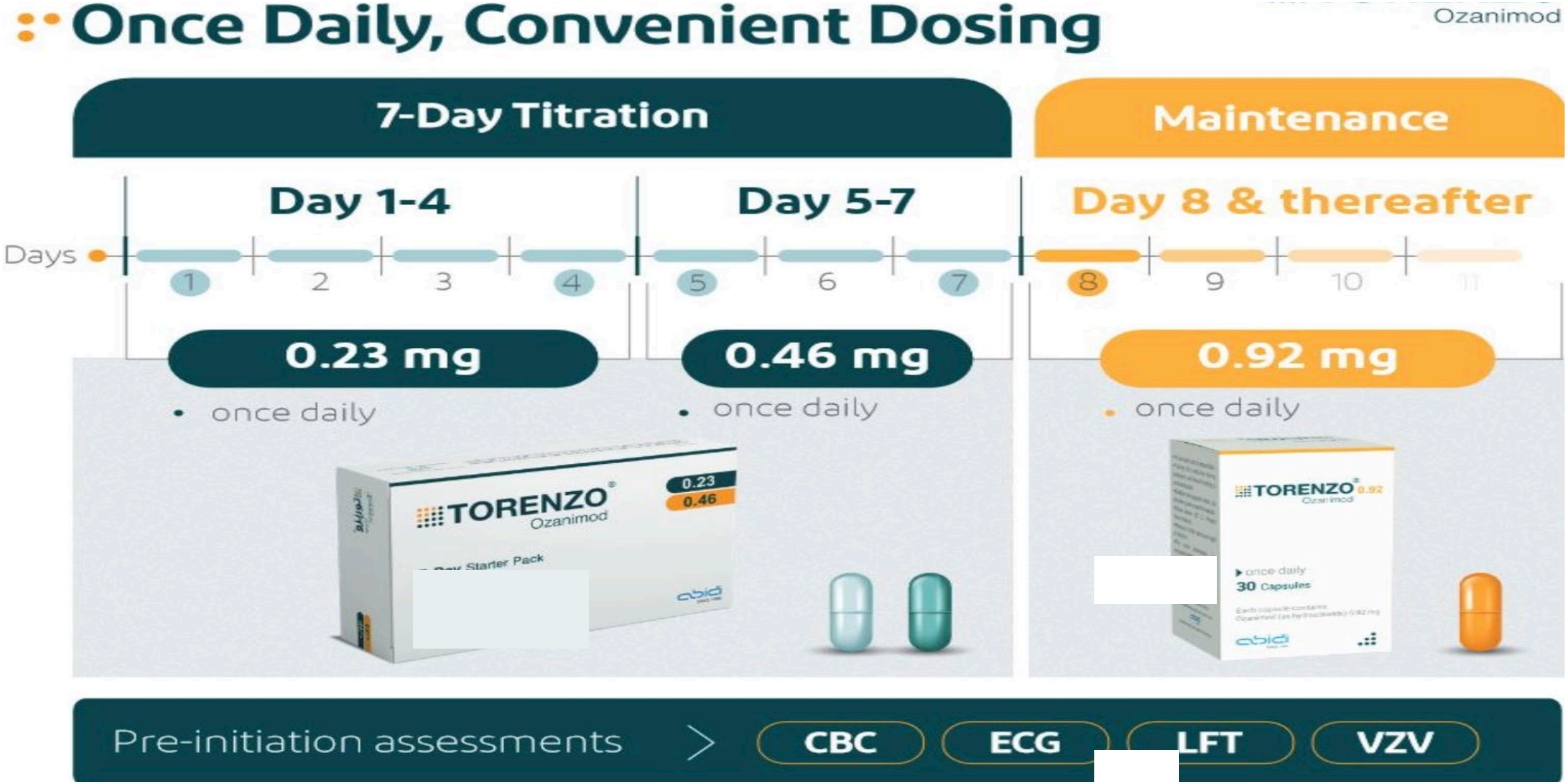
TNFi-refractory

- **Tofacitinib**
- **Upadacitinib**

*** **TNFi:** Tumor necrosis factor Inhibitor

Clin Gastroenterol Hepatol . **2024** 13:S1542-3565(24)00728-6.
Clin Gastroenterol Hepatol . **2024** 13:S1542-3565(24)00728-6.
Journal of Crohn's and Colitis, 2023, 17, 2012–2025
Nat Rev Gastroenterol Hepatol 20, 411–412 (2023).

Expert opinion (Dr. Daryani) & Dr. Vahedi Update: 06/2024



-The induction and maintenance dose for etrasimod is 2 mg orally once daily


•To be used only by prescription.
•Taking this medicine during pregnancy and breast-feeding is contraindicated.
•Swallow the capsule whole. Do not chew, crush or open the capsule.
•Store below 30° C. Protect from moisture.
•Keep out of the reach and sight of children.
•For more information, see enclosed leaflet.
Marketing Authorization Holder:
Dr. Abidi Pharmaceuticals Tehran - Iran
abidi
Manufacturing Site: Sobhan Oncology
TORENZO® 0.92
Ozanimod
once daily
30 Capsules
Each capsule contains:
Ozanimod (as hydrochloride) 0.92 mg
abidi
SINCE 1946

Dosing Considerations

Recommended Dosage in Patients With Hepatic Impairment

• In patients with **mild or moderate** hepatic impairment (Child-Pugh class A or B)

✓ Initiate Ozanimod with a 7-day titration. After initial titration, the recommended dosage of Ozanimod in these patients is 0.92 mg taken orally once every other day, starting on Day 8.

•Use of Ozanimod in patients with **severe** hepatic impairment (Child-Pugh class C) is **not recommended**

Recommended Dosage in Patients With Renal Impairment

- **No dose adjustment** is necessary for patients with renal impairment.

Factor	1 point	2 points	3 points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

	Class A	Class B	Class C
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

Pregnancy & Lactation

Women of Childbearing Potential / Contraception

- **Ozanimod is contraindicated in women of childbearing potential not using effective contraception.**
- **A negative pregnancy test result required before initiation.**
- **Women of childbearing potential must use effective contraception during ozanimod treatment and for 3 months after treatment discontinuation.**



- **S1-P is known to be involved in vascular formation during embryogenesis. Ozanimod should be stopped 3 months before planning a pregnancy.**
- **If a woman becomes pregnant during treatment, ozanimod must be discontinued.**

Breast-feeding

- **Ozanimod/metabolites are excreted in milk of treated animals during lactation.**

- **Due to the potential for serious adverse reactions to ozanimod/metabolites in nursing infants, women receiving ozanimod should not breastfeed.**

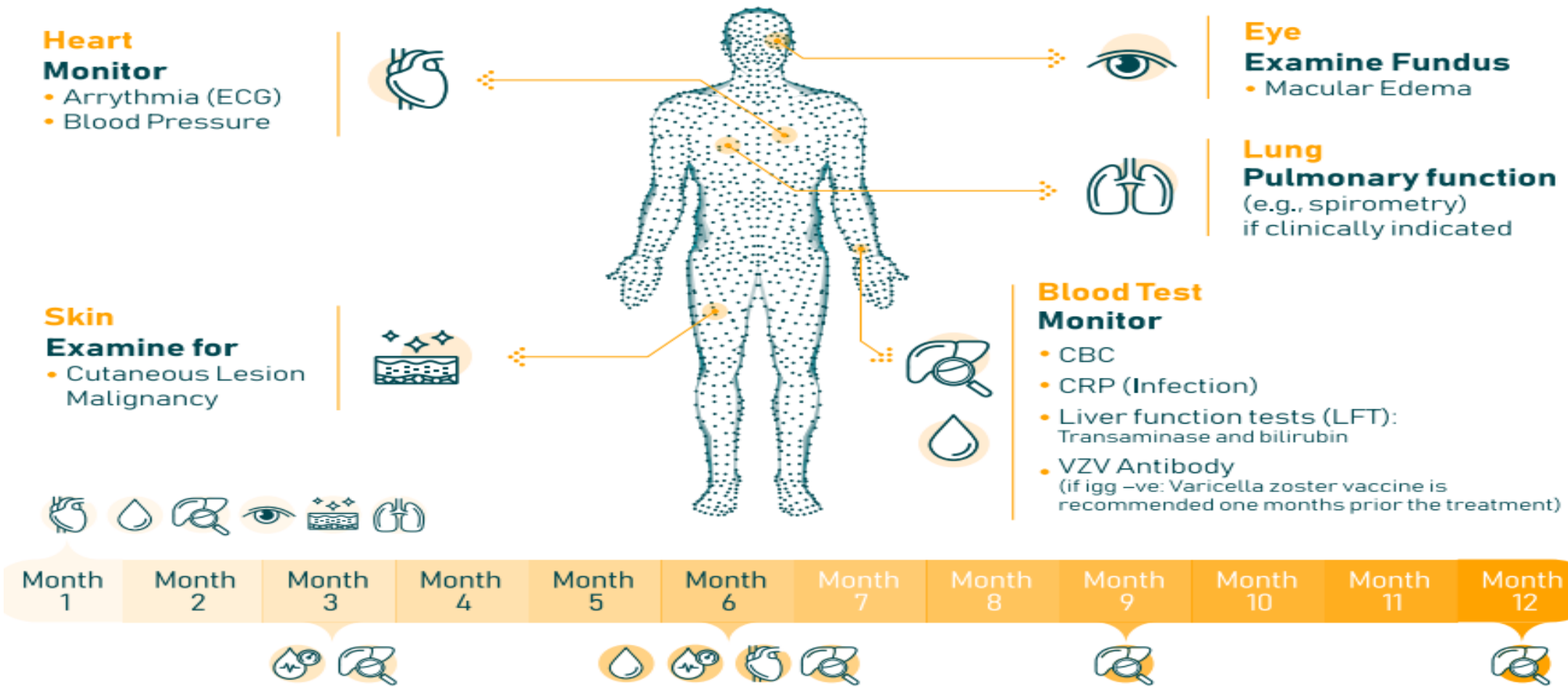


Fertility

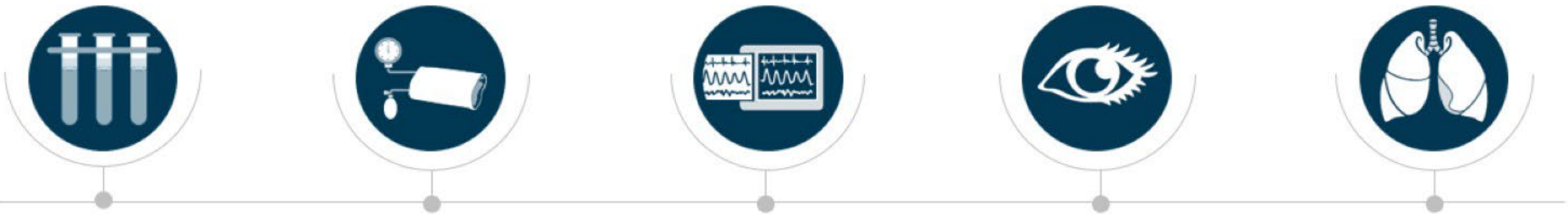
- **No fertility data are available in humans.**

- **In animal studies, no adverse effects on fertility were observed.**

Baseline exams and Routine Monitoring



Safety Monitoring With Ozanimod



- Lab monitoring before and during treatment
  - CBC with differential
  - CMP
- Monitor BP during treatment
- ECG recommended at baseline
- Ophthalmic evaluation in patients with history of uveitis or macular edema
- Spirometry if clinically indicated

VZ IgG+ or Varicella-Zoster Vaccination > 30 days

BP, blood pressure; CBC, complete blood count; CMP, comprehensive metabolic panel; ECG, electrocardiogram; IgG, immunoglobulin G; VZ, varicella zoster.
Ozanimod [PI]. Approved 2020. Revised November 2022.

Contraindications[10,11]

- Myocardial infarction, unstable angina, stroke, transient ischaemic attack, decompensated heart failure requiring hospitalisation, or New York Heart Association class III/IV heart failure in the past 6 months
- Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker
- Severe untreated sleep apnoea
- Concomitant use of an MAO inhibitor [eg, selegiline, phenelzine, linezolid]

Additional contraindications per the EU SmPC

- Immunodeficient state
- Severe active infection or active chronic infection [eg, hepatitis, tuberculosis]
- Active malignancy
- Severe hepatic impairment [Child-Pugh class C]
- Current pregnancy or lack of effective contraception use

Food limitation

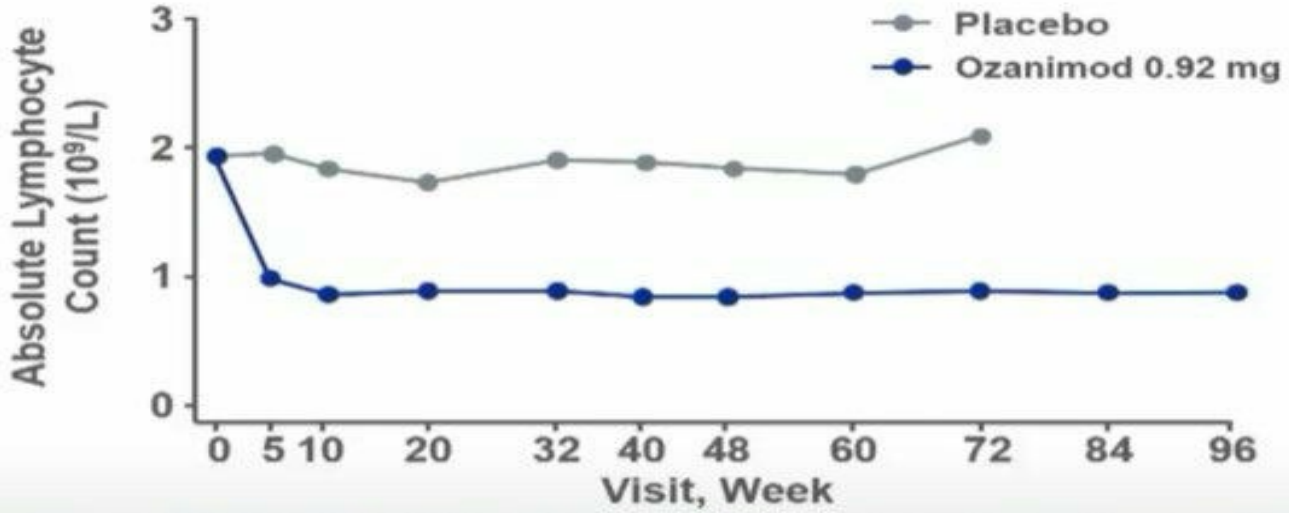
- **Low quality evidence but the US prescribing information advises that patients should be counselled about consuming foods or drinks containing high amounts of tyramine [ie, more than 150 mg].**

Lymph count consideration

Physicians and patients should be made aware that reduction of absolute lymphocyte count [ALC]

Absolute Lymphocyte Counts

- Reductions in ALC at week 5 and sustained
- 60 patients (5.3%) had ALC <200 at least once
- 59/60 (98%) returned to >200 continuing treatment



Placebo, n=	508	261	258	307	242	180	136	36	1	0	0
Ozanimod 0.92 mg n=	1157	1034	1005	781	736	442	572	724	610	460	411

ALC = absolute lymphocyte count.

Adapted from: Tran JQ, et al. *J Clin Pharmacol.* 2017;57(8):988-996. Colombel JF, et al. *Am J Gastroenterol.* 2021;116:S9.

Lymphopenia

- **Immunosuppressant should be avoided or used with caution during treatment and up to 4 weeks after the last dose of ozanimod.**
- **There is no specific guidance on lymphocyte counts considered unsuitable for ozanimod treatment initiation, but the EU summary of product characteristics does recommend discontinuing treatment when ALC is <0.2 × 10 log**

Infection consideration

- Ozanimod initiation should be delayed in patients with an active infection and those without confirmed varicella zoster virus [VZV] antibodies.

- VZV vaccination is recommended for antibody-negative preferably 1 month before initiating ozanimod.

Ophthalmic considerations

- **S1P receptor modulators have been associated with increased risk for macular edema, especially in patients with pre-existing risk factors.**

- **Patients with a history of uveitis, macular oedema, or diabetes may use ozanimod, but an ophthalmic evaluation should be performed before treatment initiation to minimize the risk of macular edema.**
- **Ophthalmic examinations should already be performed regularly in patients in high-risk groups.**

Cutaneous malignancies

- **Modest increased risk of cutaneous malignancy.**

- **Prior to initiating an oral S1P receptor modulator, patients should undergo dermatologic evaluation to screen for skin cancer.**

- **Ozanimod clinical trial data demonstrated a low incidence of malignancy [~1%] with long-term treatment in patients with UC for up to 142 weeks in the phase 3 True North.**

Pulmonary effects

- Ozanimod may affect pulmonary function and should be used with caution in patients with severe respiratory disease, pulmonary fibrosis, or COPD.

- Contraindicated in patients with severe, untreated sleep apnea per the US prescribing information.

Elderly

- **Safe and efficacious in patients with UC aged ≥60 years**
- **Should be monitored, particularly for adverse hepatic and cardiac reactions, because of the greater frequency of hepatic and cardiac abnormalities .**

Drug interactions

Table 2. Potential drug-drug interactions with concomitant ozanimod treatment.[16,17]

Drug class	Drug examples	Potential interaction
Antineoplastic, non-corticosteroid immuno-suppressive, or immune-modulating therapies[a]	Ciclosporin, tacrolimus, sirolimus, methotrexate, alemtuzumab, beta interferon, glatiramer acetate, azathioprine, 6-mercaptopurine	Additive immunosuppressive effect with concomitant ozanimod use
Anti-arrhythmic drugs, QT-prolonging drugs, or drugs that may de-crease heart rate	Quinidine, procainamide, disopyramide [Class Ia anti-arrhythmic]; amiodarone, sotalol [Class III anti-arrhythmic]	Additive effect on heart rate with con-comitant ozanimod use Anti-arrhythmic drugs have been associated with Torsades de Pointes in patients with bradycardia
Beta blockers	Propranolol, metoprolol, carvedilol, atenolol	Additive effect on heart rate if used in combination with a calcium channel blocker and ozanimod
Calcium channel block-ers	Verapamil, diltiazem, amlodipine, felodipine, nifedipine	Additive effect on heart rate if used in combination with a beta blocker and ozanimod
Opioid drugs	Meperidine, methadone, tramadol, oxycodone, hydrocodone, morphine, codeine, fentanyl	Serious adverse reactions, including hypertensive crisis, with concomitant ozanimod use due to potential MAO inhibition by ozanimod metabolites
Serotonergic/adrenergic drugs	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline [SSRI]; desvenlafaxine, duloxetine, levomilnacipran, venlafaxine [SNRI]; amitriptyline, amoxapine, desipramine, doxepin, im-ipramine, nortriptyline, protriptyline, trimipramine [tricyclic]	Serious adverse reactions, including hypertensive crisis, with concomitant ozanimod use due to potential MAO inhibition by ozanimod metabolites
Sympathomimetic drugs[b]	Pseudoephedrine, phenylephrine, amphetamines, midodrine, clonidine, albuterol, salmeterol, terbutaline	Serious adverse reactions, including hypertensive crisis, with concomitant ozanimod use due to potential MAO inhibition by ozanimod metabolites
MAO inhibitors	Selegiline, phenelzine, linezolid, isocarboxazid, tranylcypromine	Reduced exposure to active metab-

Opioid drugs	Meperidine, methadone, tramadol, oxycodone, hydrocodone, morphine, codeine, fentanyl	Serious adverse reactions, including hypertensive crisis, with concomitant ozanimod use due to potential MAO inhibition by ozanimod metabolites
Serotonergic/adrenergic drugs	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline [SSRI]; desvenlafaxine, duloxetine, levomilnacipran, venlafaxine [SNRI]; amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine [tricyclic]	Serious adverse reactions, including hypertensive crisis, with concomitant ozanimod use due to potential MAO inhibition by ozanimod metabolites
Sympathomimetic drugs[b]	Pseudoephedrine, phenylephrine, amphetamines, midodrine, clonidine, albuterol, salmeterol, terbutaline	Serious adverse reactions, including hypertensive crisis, with concomitant ozanimod use due to potential MAO inhibition by ozanimod metabolites
MAO inhibitors	Selegiline, phenelzine, linezolid, isocarboxazid, tranylcypromine	Reduced exposure to active metabolites of ozanimod with concomitant ozanimod use, which may decrease the efficacy of ozanimod Risk of hypertensive crisis with concomitant ozanimod use due to potential MAO inhibition by ozanimod metabolites
CYP2C8 inhibitors	Gemfibrozil, clopidogrel	Increased exposure to active metabolites of ozanimod with concomitant ozanimod use, which may increase the risk of adverse reactions to ozanimod
CYP2C8 inducers	Rifampin	Reduced exposure to active metabolites of ozanimod with concomitant ozanimod use, which may decrease the efficacy of ozanimod

AV, atrioventricular; MAO, monoamine oxidase; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VZV, varicella zoster virus.
[a]Ozanimod has only been studied with ciclosporin, which had no pharmacokinetic interaction.
[b]Ozanimod [which inhibits MAO-B *in vitro*] has only been studied with pseudoephedrine, which did not result in any potentiated effects on blood pressure, but hypertensive crisis has been reported with concomitant use of other MAO inhibitors and sympathomimetic drugs.

Janus kinase (JAK) inhibitors in IBD

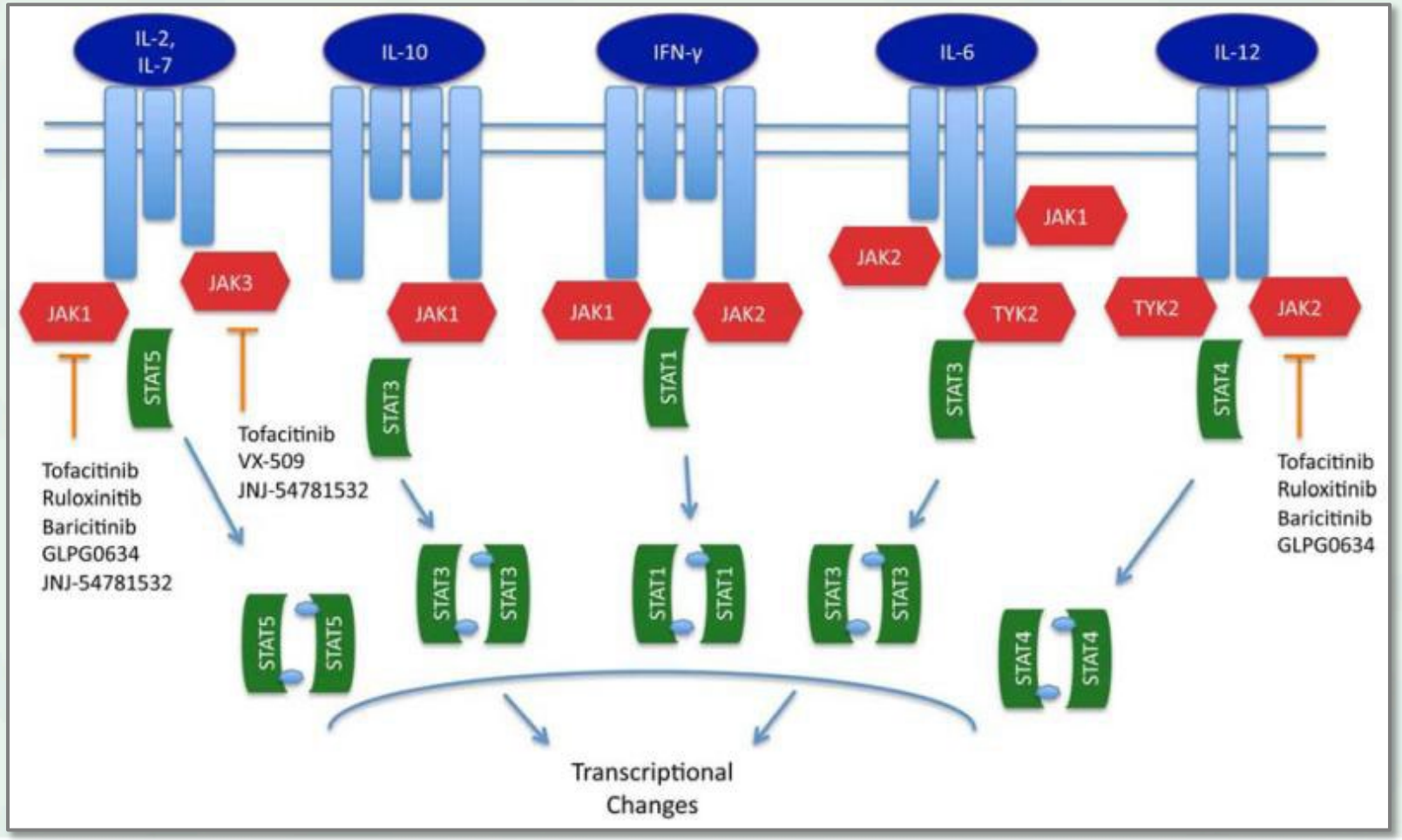
Rationale for Targeting JAK-STAT Signaling

- JAKs play a role in regulating cellular proliferation, differentiation, and immune cell functions
- JAK-STAT is the major signaling cascade downstream from cytokine and growth factor receptors
  - JAK family = JAK1, JAK2, JAK3
  - STAT family = 7 transcription factors
- JAKs serve to transduce signals from cytokine receptors
- JAK inhibitors interfere with JAK-STAT signaling
  - Compete with ATP for binding to the kinase domain of JAKs and inhibit JAK1, JAK2, JAK3
- JAK inhibitors are used effectively in other chronic inflammatory conditions (eg, rheumatoid arthritis, psoriasis)
- JAK inhibition is a potential therapeutic target in IBD
  - JAK1/JAK3 involved in transduction processes of IL-2R and IL-6R (including IL-12 and IL-23)

JAK, Janus kinase family; STAT, signaling transducers and activators of transcription; IBD, inflammatory bowel disease.

Boland BS, et al. *Gastroenterol Clin North Am.* 2014;43:603-17.
Villarino AV, et al. *J Immunol.* 2015;194:21-27.
Patterson H, et al. *Clin Exp Immunol.* 2014;176(1):1-10.

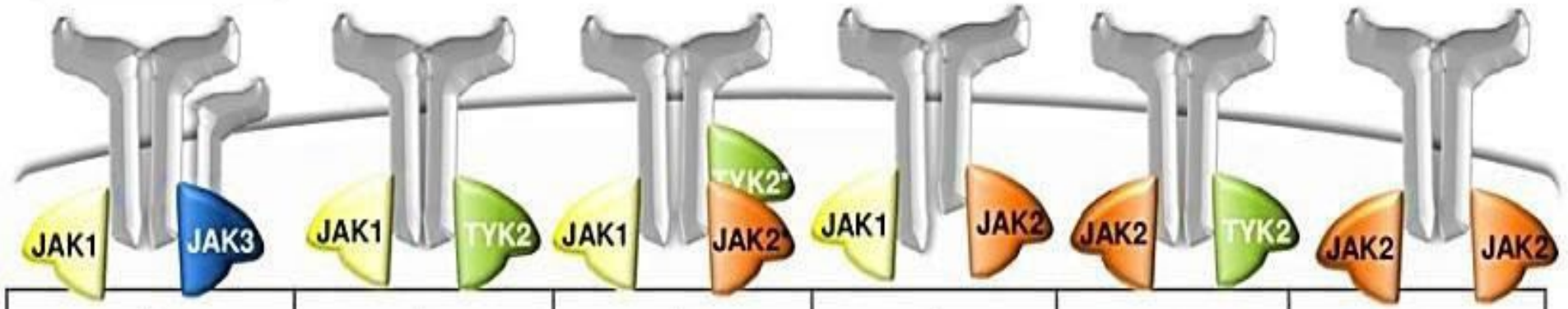
JAK Signaling Pathways in IBD and Therapeutic Targets of JAK Inhibitors



Reprinted from *Gastroenterology Clinics of North America*, Vol 43, Boland BS, Sanborn WJ, Chang JT, Update on Janus Kinase Antagonists in Inflammatory Bowel Disease, Pages 603-617, Copyright 2014, with permission from Elsevier.

Broad Cytokine Inhibition Profile

Receptors sharing γ-chain[1]	Type I IFNR[1]	IL-10R family[1]	Receptors sharing gp130 subunit[1,2*]	Type II IFNR[1]	IL-12R family sharing p40 subunit[1]	Hormone receptors[1]	IL-3R family[1]
IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	IFN-α/β/κ/ω/ε	IL-10[†], IL-20, IL-22	IL-6, IL-11, IL-27, G-CSF	IFN-γ	IL-12, IL-23	EPO, TPO, GH, PRL	IL-3, IL-5



JAK1 inhibitor	+	+	+	+	-	-
JAK2 inhibitor	-	-	+	+	+	+
JAK3 inhibitor	+	-	-	-	-	-
TYK2 inhibitor	-	+	+	-	+	-

Pharmacology and use

The oral JAK inhibitors that are available for treating moderate to severe UC(who have not responded or are intolerant to anti-TNF agent-based therapy) include tofacitinib and upadacitinib. JAK inhibitors decrease signaling by a number of cytokine and growth factor receptors:

- Tofacitinib is a nonselective JAK inhibitor that inhibits JAK1, JAK2, and JAK3 enzymes

- Upadacitinib is a selective JAK inhibitor that inhibits JAK1 enzyme

The onset of action of JAK inhibitors varies greatly. For example, some patients have a relatively rapid response (within one week), while for other patients, response may take up to 16 weeks.

Pretreatment screening

- Prior to starting a JAK inhibitor, we review each patient's vaccination and exposure history , and we check total cholesterol and high density lipoprotein levels because JAK inhibition has been associated with increased cholesterol levels.

- Pretreatment screening includes documenting immunity to varicella (eg, varicella zoster virus [VZV] IgG, clinician diagnosis of disease). For patients with evidence of immunity who are ≥19 years old, we assess the need for and timing of zoster (shingles) vaccination, because JAK inhibition is associated with higher rates of herpes zoster infection.

- We check total cholesterol and high-density lipoprotein cholesterol levels within four to 8 weeks after initiating tofacitinib and within 12 weeks after initiating upadacitinib because both are associated with increased cholesterol .However, whether the increase in lipids is clinically significant is uncertain.

Contraindications

- We do not use JAK inhibitors in patients with active serious infections (eg, tuberculosis) or severe liver impairment.
- In addition, for patients with a history of thromboembolic disease (eg, history of PTE, DVT), JAK inhibitors should be used with caution because of concern for increased risk of thromboembolic events and mortality in patients with rheumatoid arthritis treated with tofacitinib.

- However, studies in patients with inflammatory bowel disease (IBD) suggested that tofacitinib and upadacitinib were not associated with an increased risk of venous thromboembolism or major cardiovascular events.

Dosing and administration

- **Tofacitinib** – We use a tofacitinib induction dose of 10 mg twice daily (or tofacitinib XR 22 mg once daily) for eight weeks, followed by a maintenance dose of 5 mg twice daily (or tofacitinib XR 11 mg once daily) . For patients with inadequate response to initial therapy after eight weeks, induction dosing may be extended for a total of 16 weeks.

- **Upadacitinib** – We use an upadacitinib induction dose of 45 mg once daily for eight weeks, followed by a maintenance dose of 15 mg once daily . For patients with refractory, severe, or extensive disease, a maintenance dose of 30 mg once daily may be appropriate.

ALPAMONT®
Tofacitinib 5 mg

COBEL DAROU

Tofacitinib (Alpamont)

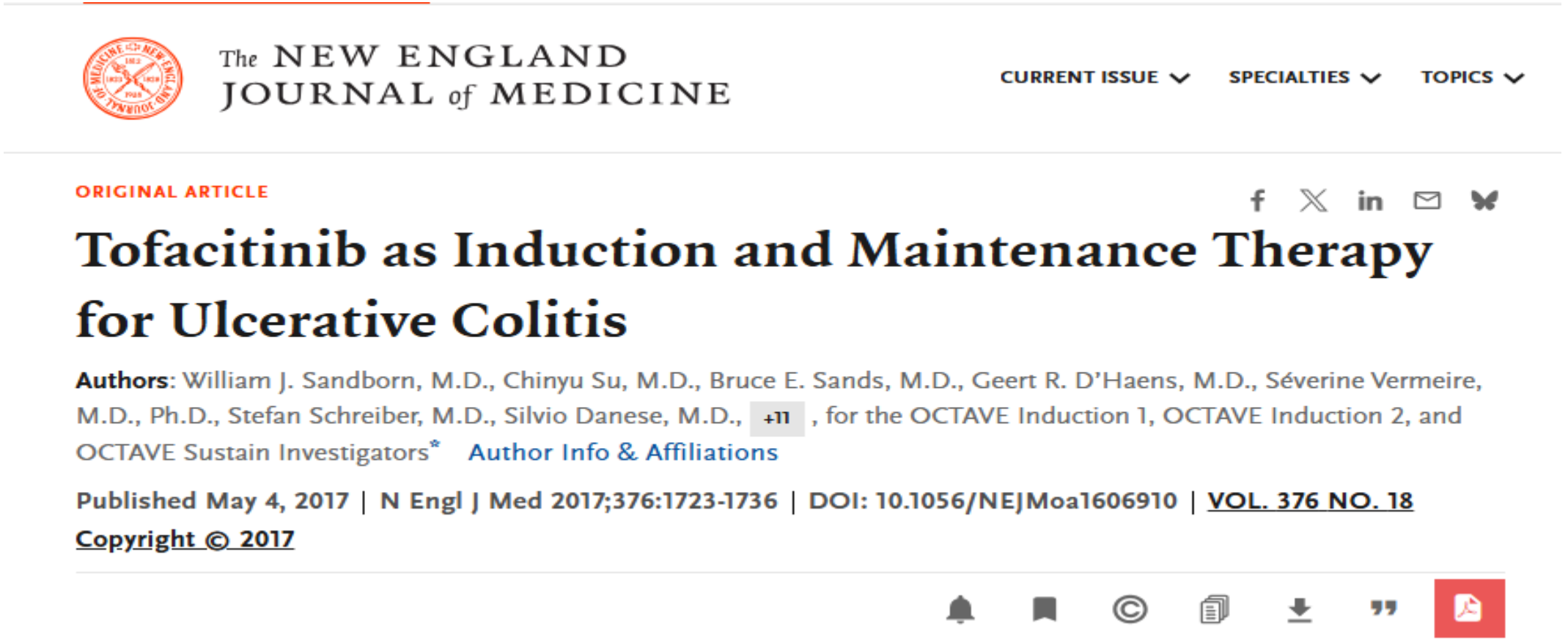
Approved for moderate to severely active UC patients who did not improve with conventional therapy or anti-TNF failure patients

Advantage include;

- -Lack Immunogenicity
- -Short half life
- -Oral administration
- -Low manufacturing cost



Tofacitinib as induction and maintenance therapy in UC_OCTAVE studies



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ORIGINAL ARTICLE

Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

Authors: William J. Sandborn, M.D., Chinyu Su, M.D., Bruce E. Sands, M.D., Geert R. D'Haens, M.D., Séverine Vermeire, M.D., Ph.D., Stefan Schreiber, M.D., Silvio Danese, M.D., +11 , for the OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators* Author Info & Affiliations

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Study Summary

OCTAVE induction 1, 2:

•**Study design:** three phase 3, randomized, double-blind, placebo-controlled trials of tofacitinib therapy in adults with ulcerative colitis.
•**Study population:** In the OCTAVE Induction 1 and 2 trials, 598 and 541 patients, respectively, who had moderately to severely active ulcerative colitis despite previous conventional therapy or therapy with a tumor necrosis factor antagonist
•**Study intervention:** induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks.
•**Study endpoints:** The primary end point was remission at 8 weeks.

In the OCTAVE Sustain trial:

593 patients who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. The primary end point was remission at 52 weeks

- **In the OCTAVE Induction 1 trial;**

remission at 8 weeks; 18.5% in the tofacitinib group vs 8.2% in the placebo group (P=0.007)

- **In the OCTAVE Induction 2 trial;**

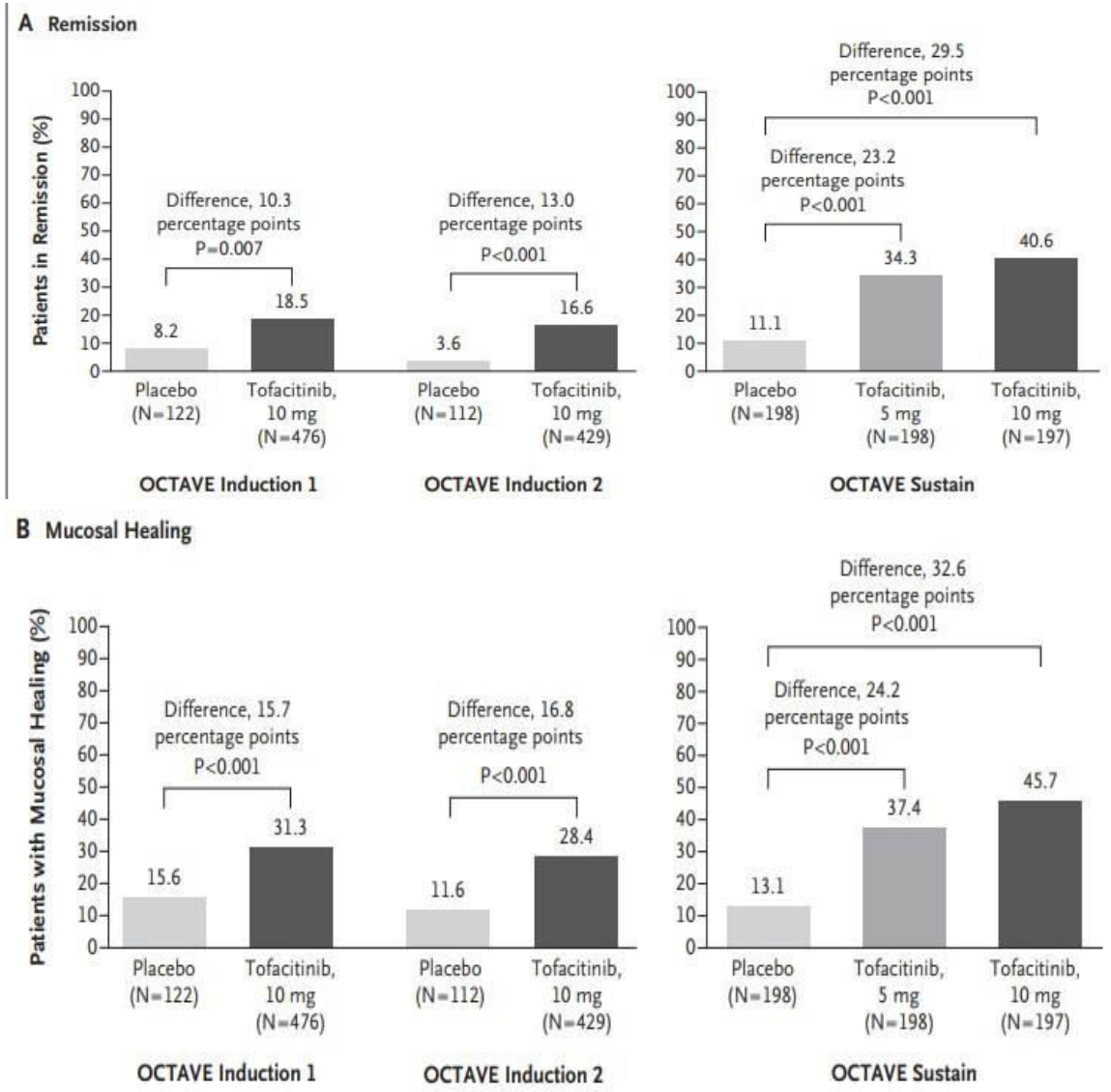
remission occurred in 16.6% versus 3.6% (P<0.001)

- **In the OCTAVE Sustain trial;**

remission at 52 weeks occurred in:

- 34.3% of the patients in the 5-mg tofacitinib group
- 40.6% in the 10-mg tofacitinib group
- 11.1% in the placebo group

(P<0.001 for both comparisons with placebo)



Study Results

Table 2. Efficacy Outcomes in the OCTAVE Induction 1 and OCTAVE Induction 2 Trials.*

End Point	OCTAVE Induction 1				OCTAVE Induction 2			
	Placebo (N=122)	Tofacitinib, 10 mg (N=476)	Difference (95% CI)	P Value	Placebo (N=112)	Tofacitinib, 10 mg (N=429)	Difference (95% CI)	P Value
			percentage points				*percentage points*	
Based on Mayo score†								
Primary end point: remission at wk 8 — no. (%)	10 (8.2)	88 (18.5)	10.3 (4.3 to 16.3)	0.007	4 (3.6)	71 (16.6)	13.0 (8.1 to 17.9)	<0.001
Mucosal healing at wk 8 — no. (%)	19 (15.6)	149 (31.3)	15.7 (8.1 to 23.4)	<0.001	13 (11.6)	122 (28.4)	16.8 (9.5 to 24.1)	<0.001
Clinical response at wk 8 — no. (%)	40 (32.8)	285 (59.9)	27.1 (17.7 to 36.5)	<0.001	32 (28.6)	236 (55.0)	26.4 (16.8 to 36.0)	<0.001
Clinical remission at wk 8 — no. (%)	10 (8.2)	88 (18.5)	10.3 (4.3 to 16.3)	0.007	4 (3.6)	72 (16.8)	13.2 (8.3 to 18.1)	<0.001
Endoscopic remission at wk 8 — no. (%)	2 (1.6)	32 (6.7)	5.1 (1.9 to 8.3)	0.04	2 (1.8)	30 (7.0)	5.2 (1.8 to 8.6)	0.04
Symptomatic remission at wk 8 — no. (%)	7 (5.7)	56 (11.8)	6.0 (1.0 to 11.1)	0.06	3 (2.7)	46 (10.7)	8.0 (3.9 to 12.2)	0.009
Deep remission at wk 8 — no. (%)	0	31 (6.5)	6.5 (4.3 to 8.7)	0.004	2 (1.8)	22 (5.1)	3.3 (0.1 to 6.6)	0.14
Change from baseline in total Mayo score at wk 8	−1.8±0.3	−3.8±0.1	−1.9 (−2.5 to −1.4)	<0.001	−2.1±0.3	−3.7±0.1	−1.6 (−2.2 to −1.0)	<0.001
Based on IBDQ score‡								
Remission at wk 4 — no. (%)	27 (22.1)	167 (35.1)	13.0 (4.4 to 21.5)	0.008	9 (8.0)	124 (28.9)	20.9 (14.3 to 27.5)	<0.001
Remission at wk 8 — no. (%)	32 (26.2)	206 (43.3)	17.0 (8.1 to 26.0)	<0.001	20 (17.9)	173 (40.3)	22.5 (14.0 to 30.9)	<0.001
Treatment response at wk 4 — no. (%)	55 (45.1)	299 (62.8)	17.7 (7.9 to 27.6)	<0.001	44 (39.3)	266 (62.0)	22.7 (12.6 to 32.9)	<0.001
Treatment response at wk 8 — no. (%)	56 (45.9)	307 (64.5)	18.6 (8.8 to 28.4)	<0.001	54 (48.2)	288 (67.1)	18.9 (8.7 to 29.2)	<0.001

* Plus–minus values are least-squares means ±SE.
† Definitions of all efficacy end points that are based on the Mayo score are provided in Table S1 in the Supplementary Appendix. The total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.
‡ The Inflammatory Bowel Disease Questionnaire (IBDQ) score ranges from 32 to 224, with higher scores indicating better quality of life. An IBDQ score of 170 or higher is indicative of remission, and an IBDQ score at least 16 points higher than the baseline score in the induction trial is indicative of a treatment response.

Study Results

Table 4. Safety Outcomes at 8 Weeks in the OCTAVE Induction 1 and 2 Trials and at 52 Weeks in the OCTAVE Sustain Trial.*

End Point	OCTAVE Induction 1		OCTAVE Induction 2		OCTAVE Sustain		
	Placebo (N=122)	Tofacitinib, 10 mg (N=476)	Placebo (N=112)	Tofacitinib, 10 mg (N=429)	Placebo (N=198)	Tofacitinib, 5 mg (N=198)	Tofacitinib, 10 mg (N=196)
Adverse events — no. (%)	73 (59.8)	269 (56.5)	59 (52.7)	232 (54.1)	149 (75.3)	143 (72.2)	156 (79.6)
Serious adverse events — no. (%)	5 (4.1)	16 (3.4)	9 (8.0)	18 (4.2)	13 (6.6)	10 (5.1)	11 (5.6)
Most frequent adverse events — no. (%)†							
Worsening ulcerative colitis	5 (4.1)	11 (2.3)	6 (5.4)	13 (3.0)	71 (35.9)	36 (18.2)	29 (14.8)
Nasopharyngitis	9 (7.4)	34 (7.1)	4 (3.6)	21 (4.9)	11 (5.6)	19 (9.6)	27 (13.8)
Arthralgia	6 (4.9)	14 (2.9)	6 (5.4)	11 (2.6)	19 (9.6)	17 (8.6)	17 (8.7)
Headache	8 (6.6)	37 (7.8)	9 (8.0)	33 (7.7)	12 (6.1)	17 (8.6)	6 (3.1)
Infections — no. (%)							
Any infection	19 (15.6)	111 (23.3)	17 (15.2)	78 (18.2)	48 (24.2)	71 (35.9)	78 (39.8)
Serious infection‡	0	6 (1.3)	0	1 (0.2)	2 (1.0)	2 (1.0)	1 (0.5)
Herpes zoster	1 (0.8)	3 (0.6)	0	2 (0.5)	1 (0.5)	3 (1.5)	10 (5.1)
Adverse events of special interest — no.							
Intestinal perforation§	0	1	1	0	0	0	0
Cancer other than nonmelanoma skin cancer¶	0	0	0	0	1‖	0	0
Nonmelanoma skin cancer¶	0	1	0	1	1	0	3
Cardiovascular events¶	0	2	0	2	0	1	1
Adverse events leading to discontinuation — no. (%)**	2 (1.6)	18 (3.8)	8 (7.1)	17 (4.0)	37 (18.7)	18 (9.1)	19 (9.7)
Abnormal laboratory test results — no./total no. (%)††							
Total cholesterol >1.3× ULN	11/122 (9.0)	80/471 (17.0)	6/111 (5.4)	73/424 (17.2)	16/198 (8.1)	54/198 (27.3)	44/195 (22.6)
Low-density lipoprotein >1.2× ULN	11/122 (9.0)	91/471 (19.3)	12/111 (10.8)	92/424 (21.7)	37/198 (18.7)	62/198 (31.3)	55/195 (28.2)
High-density lipoprotein <0.8× LLN	2/122 (1.6)	6/471 (1.3)	1/111 (0.9)	7/424 (1.7)	12/198 (6.1)	9/198 (4.5)	3/195 (1.5)
Triglycerides >1.3× ULN	1/122 (0.8)	15/471 (3.2)	2/111 (1.8)	12/424 (2.8)	7/198 (3.5)	9/198 (4.5)	15/195 (7.7)
Creatine kinase >2× ULN	2/122 (1.6)	45/474 (9.5)	10/112 (8.9)	40/425 (9.4)	14/198 (7.1)	37/198 (18.7)	54/195 (27.7)
Addition or increase in dose of lipid-lowering agent — no. (%)	0	4 (0.8)	1 (0.9)	2 (0.5)	3 (1.5)	2 (1.0)	8 (4.1)

Conclusion

Among patients with moderately to severely active ulcerative colitis, therapy with tofacitinib at a dose of 10 mg twice daily was more effective than placebo for induction of remission and mucosal healing.

Maintenance therapy with tofacitinib at a dose of either 5 mg or 10 mg twice daily was more effective than placebo in sustaining remission and mucosal healing.

Tofacitinib in acute severe UC

Tofacitinib, 10 mg, 3 times daily for 3 days followed by 10 mg twice daily had lower rates of colectomy at 90 days (tofacitinib, 8.3% vs control, 20.4%; hazard ratio, 0.11 [95% CI, 0.02-0.56])

However, randomized trials are required to establish the role of

JAK inhibitors in the treatment of ASUC

JAMA September 12, 2023 Volume 330, Number 10

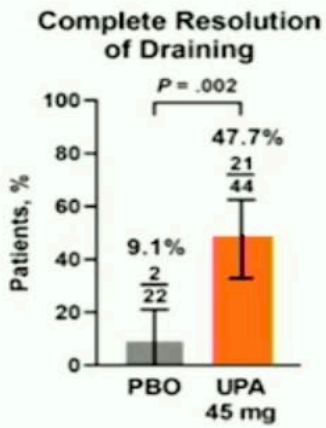
***Gastroenterol Hepatol*. 2021;19(10):2112-2120**

***J Crohns Colitis*. March 1, 2023**

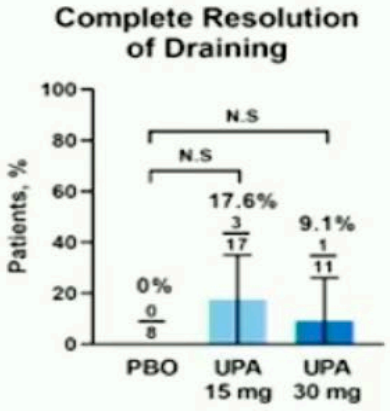
Upa(dacitinib) Updates

Treats fistulizing disease

Induction



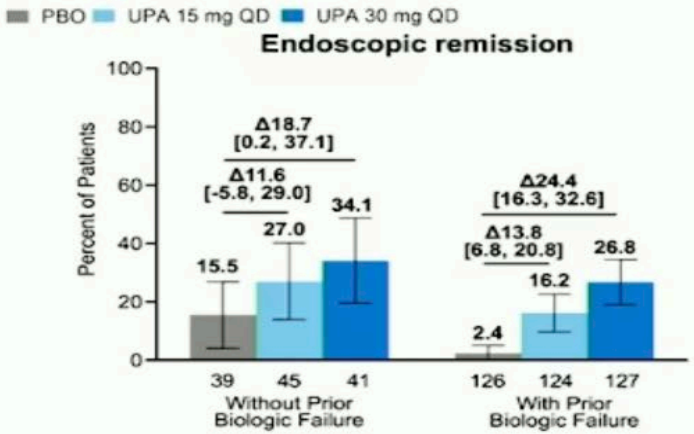
Maintenance



Colombel JF, *et al*. Presented at DDW. May 2023. 947.

Endoscopic remission in CD

U-ENDURE, Week 52 of Maintenance



D'Haens G, *et al*. Presented at DDW. May 2023. Tu1705.

Severe hospitalized UC



Berinstein J, *et al*. Presented at DDW. May 2023. Tu1769.

Clinical Scenario	JAK1-3 Inhibitor	JAK1 Inhibitor		S1P Receptor Modulator	
	Tofacitinib (IR: 10 mg BID, 5 mg BID) (ER: 11, 22 mg QD)	Upadacitinib (45 mg PO QD for 8 weeks, then 15 mg or 30 mg QD)	Filgotinib (200 mg daily)	Ozanimod (titration in week 1, then 1 mg daily)	Etrasimod (2mg daily)
New UC, failing 5-ASA	X	X	Not available in the U.S.	✓	In development
Moderate to severe UC, failing anti-TNF	✓	✓		✓	
Low albumin	✓	✓		probably	
Concomitant MS and UC	X	X		✓	
Peripheral arthropathy	✓	✓		probably	
Axial spondyloarthropathy	✓	✓		unknown	
Inpatient acute severe UC	maybe	unknown		unknown	
History of heart disease	Not if atherosclerotic	Not if atherosclerotic		Not if type 2 heart block	
History of eye disease, specifically uveitis or DM-related	✓	✓		Not recommended	


Thank you for your attention
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