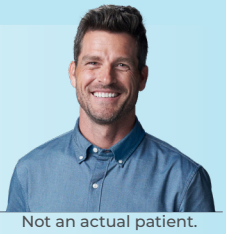
ZEPOSIA® (ozanimod) 0.92 mg capsules

THE FIRST ORAL ADVANCED THERAPY[a] THAT CAN BE USED BEFORE BIOLOGICS IN MODERATE-TO-SEVERE UC PATIENTS[1-4]

WHEN 5-ASAs NO LONGER PROVIDE RELIEF

PATIENT NAME: STEPHEN

- **Age:** 35
- **Sex:** male
- **Diagnosis:** left-sided moderately to severely active UC
- **Time since diagnosis:** 1 year



Not an actual patient.

BACKGROUND

- Stephen is a husband, father of 2 young children, and business owner with a busy professional and personal life

INITIAL CLINICAL SITUATION AT DIAGNOSIS (1 YEAR AGO)

- 7 loose stools per day with occasional urgency
- Frequent blood in stools
- Abdominal pain and cramping

Initial endoscopic findings:

- Marked erythema and friability (Mayo endoscopy subscore=2)

Medications prescribed at diagnosis:

- Started 5-ASA and an 8-week tapering course of corticosteroid

CURRENT CLINICAL SITUATION

- 6 loose stools per day with frequent blood present
- Nocturnal stools
- Fatigue

Current medications:

- 5-ASA (4.8 g daily)
- Two tapering courses of corticosteroids (in 1 year)

CURRENT ENDOSCOPIC AND LAB FINDINGS

- **Vitals:** within limits of normal
- **Comorbidities:** none

Current endoscopic evaluation:

- Diffuse erythematous inflammation, friability, and superficial erosions (Mayo endoscopy subscore=2)
- **Fecal calprotectin:** 540 µg/g
- **CRP:** 9 mg/L

REASON FOR MOST RECENT VISIT

To discuss treatment options:

- He is still experiencing symptoms

Clinical Trial: the efficacy and safety of ZEPOSIA were evaluated in 2 multicenter, randomized, double-blind, placebo-controlled clinical studies (UC Study 1 [induction] and UC Study 2 [maintenance]) in adult patients with moderately to severely active UC, defined as a Mayo score of 6 to 12 at baseline.[1]

Primary Endpoint of Clinical Remission Is Defined as: RBS=0, SFS=0 or 1 (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore=0 or 1 without friability.[1]

Secondary Endpoint of Clinical Response Is Defined as: a reduction from baseline in the 3-component Mayo score of ≥2 and ≥35%, and a reduction from baseline in the RBS of ≥1 or an absolute RBS of 0 or 1.[1]

UC Study 1 (10-week induction): 645 patients were randomized 2:1 to either ZEPOSIA 0.92 mg given orally once daily or placebo for 10 weeks, beginning with a dosage titration. The trial included patients who had an inadequate response or were intolerant to any of the following: oral aminosalicylates, corticosteroids, immunomodulators, or a biologic. Patients were required to be on stable doses of oral aminosalicylates and/or corticosteroids.[1]

UC Study 2 (42-week maintenance): 457 patients who received ZEPOSIA in either UC Study 1 or in an open-label arm and achieved clinical response at Week 10 were re-randomized 1:1 and were treated with either ZEPOSIA 0.92 mg (n=230) or placebo (n=227) for 42 weeks (UC Study 2), for a total of 52 weeks of treatment. Corticosteroid tapering was required upon entering this study for patients who were receiving corticosteroids during the induction period.[1]

[a]Advanced therapies include S1P, biologics, and JAKi.

5-ASA=5-aminosalicylic acid; CRP=C-reactive protein; JAKi=Janus kinase inhibitor; RBS=rectal bleeding subscore; S1P=sphingosine 1-phosphate; SFS=stool frequency subscore; UC=ulcerative colitis.

INDICATION

ZEPOSIA® (ozanimod) is indicated for the treatment of moderately to severely active ulcerative colitis (UC) in adults.

IMPORTANT SAFETY INFORMATION

Contraindications:

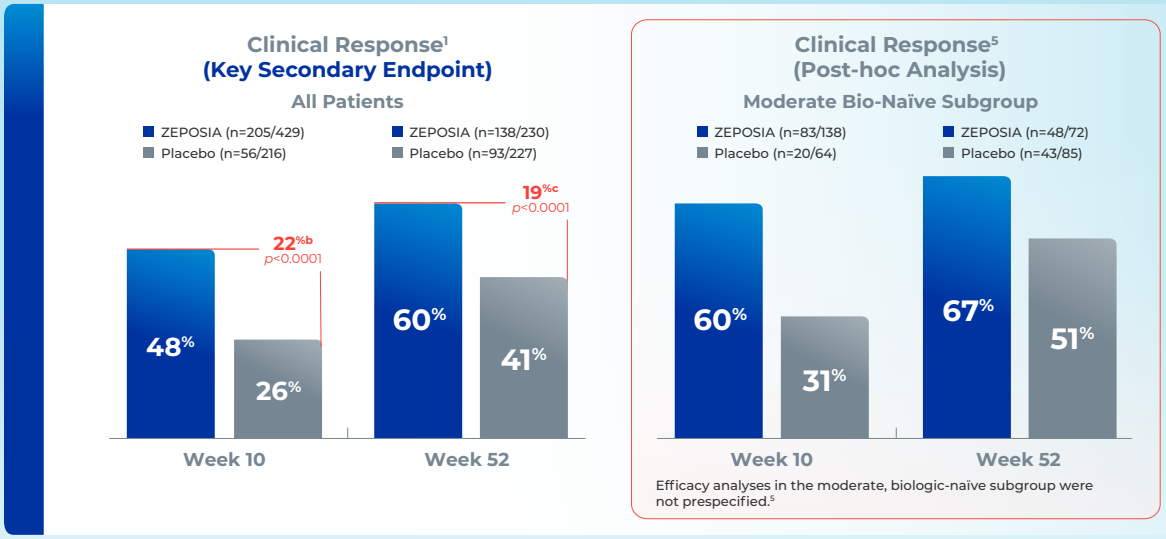
- Patients who in the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure or have a presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker

Please see additional Important Safety Information throughout and the full Prescribing Information and Medication Guide.

TAKE THE NEXT STEP WITH ZEPOSIA—THE FIRST ORAL ADVANCED THERAPY[a] THAT CAN BE USED BEFORE BIOLOGICS[1-4]

Rapid Clinical Response at Week 10[1]

Rapid clinical response was observed at Week 10, and increased at Week 52 in the all-patients group[1,5]

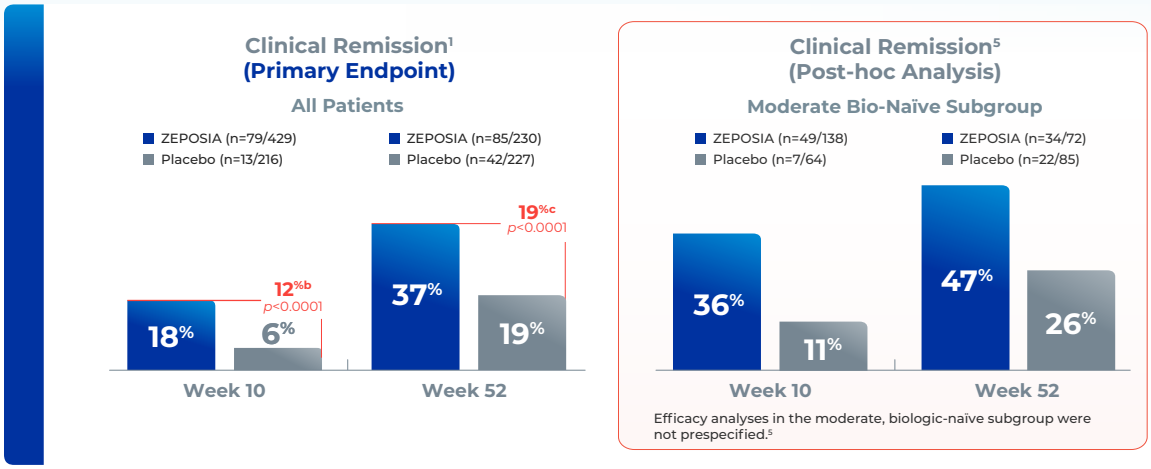


Not an actual patient.

- Clinical response is defined as a reduction from baseline in the 3-component Mayo score of ≥2 points and ≥35%, and a reduction from baseline in the RBS of ≥1 point or an absolute RBS of 0 or 1[1,5]
- Moderate biologic-naïve subgroup included patients with a Mayo endoscopy subscore of 2[5]

Sustained Clinical Remission at Week 52[1]

Clinical remission observed at Week 10 was sustained at Week 52 in the all-patients group[1,5]



- Clinical remission is defined as: RBS=0, SFS=0 or 1 (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore=0 or 1 without friability[1,5]
- Moderate biologic-naïve subgroup included patients with a Mayo endoscopy subscore of 2[5]

[a]Advanced therapies include S1P, biologics, and JAKi.
[b]Treatment difference (adjusted for stratification factors of prior TNFi exposure and corticosteroid use at baseline).[1]
[c]Treatment difference (adjusted for stratification factors of clinical remission and concomitant corticosteroid use at Week 10).[1]
TNFi=tumor necrosis factor inhibitor.

IMPORTANT SAFETY INFORMATION (cont'd)

Contraindications: (cont'd)

- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior UC therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA.

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A DEMONSTRATED SAFETY PROFILE[1]

Adverse Reactions With an Incidence of at Least 2% in ZEPOSIA-Treated Patients and at Least 1% Greater Than Placebo in Patients With UC[1]

Induction Periods (UC Study 1 and Study 3)[a]		
Adverse Reaction	**ZEPOSIA 0.92 mg (n=496)[de]**	**Placebo (n=281)[e]**
Upper Respiratory Infection[b]	5%	4%
Liver Test Increased[c]	5%	0%
Headache	4%	3%
Pyrexia	3%	2%
Nausea	3%	2%
Arthralgia	3%	1%

[a]Additional data from the induction period of a randomized, double-blind, placebo-controlled study (TOUCHSTONE or UC Study 3) included 67 patients who received ZEPOSIA 0.92 mg once daily.[1]

[b]Includes the following terms: streptococcal pharyngitis, pharyngotonsillitis, bacterial pharyngitis, nasopharyngitis, upper respiratory tract infection, pharyngitis, sinusitis, tonsillitis, viral upper respiratory tract infection, laryngitis, acute sinusitis, catarrh, chronic sinusitis, upper respiratory tract inflammation, chronic tonsillitis, viral pharyngitis, viral sinusitis, bacterial sinusitis, bacterial upper respiratory tract infection, viral labyrinthitis, laryngeal inflammation, and pharyngeal inflammation.[1]

[c]Includes the following terms: gamma-glutamyl transferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hyperbilirubinemia, liver function test increased, blood alkaline phosphatase increased, and transaminases increased.[1]

[d]ZEPOSIA was initiated with a 7-day titration.[1]

[e]Percentages were calculated as the sum of each individual study percentage multiplied by its Cochran-Mantel-Haenszel weight.[1]

Adverse Reactions With an Incidence of at Least 4% in ZEPOSIA-Treated Patients and at Least 1% Greater Than Placebo in Patients With UC[1]

Maintenance (UC Study 2)		
Adverse Reaction	**ZEPOSIA 0.92 mg (n=230)**	**Placebo (n=227)**
Liver Test Increased[a]	11%	2%
Headache	5%	<1%

[a]Includes the following terms: gamma-glutamyl transferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hyperbilirubinemia, blood bilirubin increased, liver function test increased, blood alkaline phosphatase increased.[1]

In patients treated with ZEPOSIA, rates of thromboembolic events (PE, venous and arterial thrombosis) or major adverse cardiac events (CV death, MI, stroke) were similar to patients treated with placebo in TRUE NORTH.[6a]

[a]In the TRUE NORTH phase 3 studies, 1 case of ischemic stroke (0.2%) was reported in ZEPOSIA-treated patients vs no reports in patients treated with placebo.[6]

CV=cardiovascular; MI=myocardial infarction; PE=pulmonary embolism.

IMPORTANT SAFETY INFORMATION (cont'd)

Infections: (cont'd)

Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA.

- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA.

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IMPORTANT SAFETY INFORMATION (cont'd)

Infections: (cont'd)

- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another S1P receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.
- In the UC clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of UC. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects.
- Use of live attenuated vaccines should be avoided during and for 3 months after treatment with ZEPOSIA. If live attenuated vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA.

Progressive Multifocal Leukoencephalopathy (PML): PML is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability.

PML has been reported in patients treated with S1P receptor modulators, including ZEPOSIA, and other UC therapies and has been associated with some risk factors.

If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation.

If confirmed, treatment with ZEPOSIA should be discontinued.

Immune reconstitution inflammatory syndrome (IRIS) has been reported in MS patients treated with S1P receptor modulators who developed PML and subsequently discontinued treatment. IRIS presents as a clinical decline in the patient's condition that may be rapid, can lead to serious neurological complications or death, and is often associated with characteristic changes on MRI. The time to onset of IRIS in patients with PML was generally within a few months after S1P receptor modulator discontinuation. Monitoring for development of IRIS and appropriate treatment of the associated inflammation should be undertaken.

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- with significant QT prolongation
- with arrhythmias requiring treatment with Class 1a or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick sinus syndrome, or sino-atrial heart block

Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed.

Fetal Risk: There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA.

Increased Blood Pressure: Increase in systolic pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA.

Respiratory Effects: ZEPOSIA may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy, if clinically indicated.

Macular Edema: S1P modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued.

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a S1P receptor modulator. If a ZEPOSIA-treated patient develops unexpected neurological or psychiatric symptoms or any symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued.

Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation. Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended.

Immune System Effects After Stopping ZEPOSIA: After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA.

Most Common Adverse Reactions (≥4%): liver test increased, upper respiratory infection, and headache.

Use in Specific Populations: Hepatic Impairment: Dosage adjustment in patients with mild or moderate hepatic impairment (Child-Pugh class A or B) is required, and use of ZEPOSIA in patients with severe hepatic impairment (Child-Pugh class C) is not recommended.

Please see additional Important Safety Information throughout and the full Prescribing Information and Medication Guide.

References: 1. ZEPOSIA. Prescribing Information. Bristol-Myers Squibb Company; 2023. **2.** Press Release. U.S. Food and Drug Administration approves Bristol Myers Squibb's ZEPOSIA® (ozanimod), an oral treatment for adults with moderately to severely active ulcerative colitis. Princeton, NJ: Bristol-Myers Squibb Company; 2021. **3.** Rinvoq [package insert]. North Chicago, Illinois: AbbVie Biotechnology Ltd; 2022. **4.** Xeljanz [package insert]. New York, New York: Pfizer Inc; 2021. **5.** BMS-REF-OZA-0042. Princeton, NJ: Bristol-Myers Squibb Company; 2023. **6.** Long M, Cross RK, Lichtenstein GR, et al. Long-term cardiac safety of ozanimod in phase 3 clinical program of ulcerative colitis and relapsing multiple sclerosis. Presented at: Digestive Disease Week (DDW); San Diego, CA, and Virtual, May 21–24, 2022. Presentation 15.

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Bristol Myers Squibb is committed to transparency. For information on the list price of ZEPOSIA, as well as information regarding average out-of-pocket costs and assistance programs, please visit our pricing information page at ZEPOSIA.com/ulcerative-colitis/cost.

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