Bristol Myers Squibb Announces Positive Topline Results from Pivotal Phase 3 True North Trial Evaluating Zeposia (ozanimod) in Patients with Moderate to Severe Ulcerative Colitis

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Study met primary endpoints of clinical remission in induction at Week 10 and in maintenance at Week 52

Zeposia is the first oral sphingosine-1-phosphate (S1P) receptor modulator to demonstrate benefit in moderate to severe ulcerative colitis in a Phase 3 study

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol Myers Squibb (NYSE:BMY) today announced results from True North, a pivotal Phase 3 trial evaluating oral Zeposia (ozanimod) as an induction and maintenance therapy for adult patients with moderate to severe ulcerative colitis. True North met both primary endpoints, demonstrating highly statistically significant (p-value < 0.0001) results for induction of clinical remission at Week 10 and in maintenance at Week 52. The study also met key secondary endpoints of clinical response and endoscopic improvement in induction at Week 10 and in maintenance at Week 52.

The safety profile of Zeposia in the True North trial was consistent with that observed in previously reported trials. The company will complete a full evaluation of the True North data and work with investigators to present detailed results at a future medical meeting, as well as discuss these results with health authorities.

“Patients with ulcerative colitis can struggle to effectively manage this often unpredictable and potentially debilitating disease. The True North results are encouraging for patients living with moderate to severe ulcerative colitis as Zeposia demonstrated consistency across key clinical and endoscopic endpoints, suggesting Zeposia may address the need for new oral therapy options with a favorable benefit to risk profile in the treatment journey,” said Samit Hirawat, M.D., chief medical officer, Bristol Myers Squibb. “At Bristol Myers Squibb, we are committed to researching innovative treatment options that may elevate the standard of care for people living with ulcerative colitis, with a focus on finding solutions that have the potential to transform outcomes for the inflammatory bowel disease community.”

Bristol Myers Squibb is also investigating Zeposia for the treatment of moderately to severely active Crohn’s disease in the ongoing Phase 3 YELLOWSTONE clinical trial program.

About True North

True North is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of Zeposia 1mg in patients with moderate to severe ulcerative colitis who did not adequately respond to prior treatment. In the induction phase, cohort 1 patients were randomized 2:1 to Zeposia or placebo and treated once daily for 10 weeks. Cohort 2 was an open-label arm, and included to allow adequate patient numbers for the maintenance phase of the trial. Cohort 2 patients were treated once daily with Zeposia for 10 weeks.

For the maintenance phase, patients on Zeposia from either cohort 1 or 2 who achieved clinical response in the induction phase at Week 10 were re-randomized 1:1 to Zeposia or placebo through Week 52. Patients on placebo who achieved clinical response in the induction phase at Week 10 remained on placebo during this blinded maintenance phase.

All eligible patients were rolled into an open-label extension trial, which is ongoing and designed to assess the longer-term profile of Zeposia for the treatment of moderate to severe ulcerative colitis.

The primary endpoints are the proportion of patients in clinical remission based on a composite clinical and endoscopic score (3-component Mayo Score) at Week 10 in the induction phase, and at Week 52 for the maintenance phase. Secondary endpoints include the proportion of patients achieving clinical response at Week 10 and Week 52, the proportion of patients...
with endoscopic improvement (endoscopy score ≤1) at Week 10 and Week 52, and clinical remission at Week 52 in patients that were in remission at Week 10. More information can be found on www.clinicaltrials.gov, NCT02435992.

About Ulcerative Colitis

Ulcerative colitis, a chronic inflammatory bowel disease (IBD), is characterized by an abnormal, prolonged immune response that creates long-lasting inflammation and ulcers (sores) in the mucosa (lining) of the large intestine (colon). Symptoms, including bloody stools, severe diarrhea and frequent abdominal pain, usually develop over time rather than suddenly. Ulcerative colitis has a major impact on patients’ health-related quality of life, including physical functioning, social and emotional well-being and ability to work. Many patients have an inadequate response or do not respond at all to currently available therapies. It is estimated that 12.6 million people worldwide have IBD.

About Zeposia (ozanimod)

Zeposia (ozanimod) is an oral, sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Zeposia reduces the capacity of lymphocytes to egress from lymph nodes, reducing the number of circulating lymphocytes in peripheral blood. The mechanism by which Zeposia exerts therapeutic effects in ulcerative colitis is unknown but may involve the reduction of lymphocyte migration into the inflamed intestinal mucosa.

The U.S. Food and Drug Administration (FDA) approved Zeposia for the treatment of adults with relapsing forms of multiple sclerosis (RMS) in March 2020. The European Commission approved Zeposia for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features in May 2020. Zeposia is also in development for additional immune-inflammatory indications, including Crohn’s disease.

U.S. FDA-APPROVED INDICATION FOR ZEPOSIA

ZEPOSIA is 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.

IMPORTANT SAFETY INFORMATION

Contraindications:

- Patients who in the last 6 months, have 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 or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- 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 MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA. 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
- 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.
- Progressive Multifocal Leukoencephalopathy (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. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML has been reported in patients treated with S1P receptor modulators and other MS 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.
- In 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 MS. 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.

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 Ia 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 sinoatrial 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. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease

**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 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

**Severe Increase in Disability After Stopping ZEPOSIA:** Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment so patients should be monitored upon discontinuation

**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%):** upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

For additional safety information, please see the full **Prescribing Information and Medication Guide.**

**About Bristol Myers Squibb**

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at **BMS.com** or follow us on **LinkedIn**, **Twitter**, **YouTube**, **Facebook** and **Instagram**.

Celgene and Juno Therapeutics are wholly owned subsidiaries of Bristol-Myers Squibb Company. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol Myers Squibb company and Juno Therapeutics, a Bristol Myers Squibb company.

**Cautionary Statement Regarding Forward-Looking Statements**

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that Zeposia (ozanimod) may not receive regulatory approval for the additional indication described in this release in the currently anticipated timeframe or at all and, if approved, whether it will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb’s business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made
Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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$BMY announces positive topline results from pivotal Phase 3 trial in moderate to severe #UlcerativeColitis