NEWS RELEASE

Bristol Myers Squibb Presents New Zeposia (ozanimod) Data on Long-Term Disease Progression and Cognition in Patients with Relapsing Forms of Multiple Sclerosis

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Late-breaking data from the DAYBREAK and RADIANCE trials show similarly low rates of progression independent relapse activity (PIRA) and relapse-associated worsening (RAW) after eight years of follow-up

First interim readout from Phase 3b ENLIGHTEN trial shows almost half of patients with early relapsing multiple sclerosis have clinically meaningful improvement in cognitive functioning compared to baseline after one year of Zeposia treatment

Results add to the growing body of evidence and reinforce the safety and efficacy profile of Zeposia in relapsing forms of multiple sclerosis

PRINCETON, N.J.--(BUSINESS WIRE)-- **Bristol Myers Squibb** (NYSE: BMY) today announced new data showing that after eight years of follow-up, 76% of patients treated with Zeposia for relapsing multiple sclerosis (RMS) were free of six-month confirmed disability progression (CDP). Findings also demonstrated treatment with Zeposia resulted in low rates of progression independent relapse activity (PIRA) and relapse-associated worsening (RAW), key drivers of disease progression and permanent disability in multiple sclerosis. In all participants, PIRA and RAW were observed in 13.2% and 10.7% of participants treated with continuous Zeposia, respectively, after eight years in the open-label extension study. Higher baseline expanded disability status scale (EDSS) scores to assess CDP and lower baseline whole brain, cortical grey matter and thalamic volumes were predictive of RAW but not PIRA. The new late-breaking data (#P368) will be presented on October 11, 2023, at the 9th Joint ECTRIMS-ACTRIMS meeting taking place in

Milan, Italy.

“Even in the absence of relapses, people living with multiple sclerosis may have smoldering neuroinflammation, which is underlying and continuous disease activity occurring simultaneously in different areas of the brain that can start at the earliest stages of multiple sclerosis and cause an irreversible decline in cognitive function, mobility and quality of life,” said Jeffrey Cohen, MD, Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, Ohio and a paid consultant of Bristol Myers Squibb. “Given literature has shown that 25% of people living with multiple sclerosis develop PIRA after approximately seven years, these new analyses are relevant for doctors and patients as they consider early intervention with highly effective therapies to hinder smoldering disease, an important, early driver of long-term disability and relapses, the hallmarks of disease progression.”

The analyses of PIRA and RAW included 363 patients who received continuous Zeposia treatment in the Phase 3 DAYBREAK open-label extension trial, following completion of the Phase 3 RADIANCE trial. Among patients with CDP, 54.5% and 44.3% had PIRA or RAW, respectively, and 8% had both.

Cognitive Functioning Analysis in ENLIGHTEN Trial Shows Clinically Meaningful Improvement with Zeposia Treatment

The Phase 3b ENLIGHTEN study is a trial evaluating patients with early RMS, the majority (70.3%) of whom have not received disease modifying therapies. Interim ad hoc data (poster presentation #P690) showed that after one year of Zeposia treatment, almost half (47.4%, 55/116) of patients living with early RMS showed clinically meaningful improvement in cognitive functioning, defined as an increase of at least four points or 10% from baseline as measured by the symbol digital modalities test (SDMT); 25.9% (30/116) remained stable in their cognitive function as evidenced by a plus or minus four points or 10% change in SDMT versus baseline; and 26.7% (31/116) worsened as evidenced by a decrease of at least four points or 10% in SDMT versus baseline. Additionally, ENLIGHTEN participants had little clinical or radiologic evidence of RMS disease activity during that year, with 91.9% of patients free of gadolinium-enhancing lesions at Month 12 (95% CI: 84.2, 96.0).

Treatment-emergent adverse events (TEAEs) were assessed from the start of the ENLIGHTEN trial (January 16, 2020) through the data cutoff (February 14, 2023) and showed that COVID-19 was the most frequent TEAE, with other common TEAEs largely consistent with those reported in the overall Zeposia clinical development program.

“These new data underscore Zeposia’s potential to delay disease progression and improve cognitive function, especially in individuals with early relapsing multiple sclerosis,” said **Roland Chen, MD**, senior vice president and head, Immunology, Cardiovascular and Neuroscience Development, Bristol Myers Squibb. “With our focus on transformational science, we remain deeply committed to finding solutions to elevate care for the multiple sclerosis

community.”

Bristol Myers Squibb thanks the patients and investigators who participated in the Zeposia clinical trials.

About DAYBREAK

DAYBREAK is a Phase 3, multi-center, long-term open-label extension, randomized, double-blind, double-dummy, active-controlled, parallel group study to evaluate the safety and efficacy of Zeposia (ozanimod) administered orally to patients with relapsing forms of multiple sclerosis (RMS).

Eligible patients from the RADIANCE, SUNBEAM and RPC01-1001 trials diagnosed with RMS are enrolled to receive treatment until the end of the DAYBREAK trial or until the development program is discontinued. Patients in the trial are receiving Zeposia 0.92 mg (equivalent to 1 mg).

About RADIANCE

RADIANCE Part B was a pivotal, Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled trial evaluating the efficacy, safety and tolerability of oral Zeposia 0.92 mg (equivalent to 1 mg) against weekly intramuscular Avonex® (interferon beta-1a) over a 24-month treatment period. The study included 1,320 people living with RMS across 150 sites in 21 countries.

The primary endpoint of the trial was annualized relapse rates over 24 months. The secondary MRI endpoints included the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months.

About SUNBEAM

SUNBEAM was a pivotal, Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled trial evaluating the efficacy, safety and tolerability of two doses of oral Zeposia (0.92 mg and 0.46 mg, equivalent to 1 mg and 0.5 mg, respectively) against weekly intramuscular Avonex® for at least a 12-month treatment period. The study included 1,346 people living with RMS across 152 sites in 20 countries.

The primary endpoint of the trial was annualized relapse rates during the treatment period. The secondary MRI endpoints included the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months, number of gadolinium-enhanced brain MRI lesions at Month 12 and percent change from baseline in whole brain volume at Month 12. Cortical grey and thalamic volume changes were also prospectively assessed versus active comparator.

About ENLIGHTEN

ENLIGHTEN is a Phase 3b, multicenter, single-arm, open-label study evaluating the change from baseline in cognitive processing speed, measured by the symbol digital modalities test, in patients with RMS treated with oral Zeposia (0.92 mg, equivalent to 1mg) at three years.

The primary efficacy endpoint is the proportion of patients with a clinically meaningful increase in raw score of greater than or equal to four points or 10% from baseline (improved at three years). The secondary MRI endpoints include the number of new or enlarging hyperintense T2-weighted brain MRI and their volumes from baseline to three years.

About Multiple Sclerosis

Multiple sclerosis (MS) is a disabling, unpredictable disease in which the immune system attacks the protective myelin sheath that covers the nerves. The myelin damage disrupts communication between the brain and the rest of the body. Ultimately, the nerves themselves may deteriorate—a process that's currently irreversible. MS affects 700,000 people in Europe and approximately 2.5 million people worldwide.

RMS, including clinically isolated syndrome, relapsing remitting disease and active secondary progressive disease, is characterized by clearly defined attacks of worsening neurologic function. These attacks—often called relapses, flare-ups or exacerbations—are followed by partial or complete recovery periods. During these recovery periods, also called remissions, symptoms improve partially or completely with no apparent progression of disease. However, smoldering neuroinflammation can be present from the earliest stages of MS, which is underlying and continuous disease activity occurring simultaneously in different areas of the brain that contributes to disability accumulation. Since MS relapses are unpredictable, patients can feel frustrated, stressed or scared when they occur. RMS is the most common disease course at the time of diagnosis. Approximately 85% of patients are initially diagnosed with RMS, compared with 10%-15% diagnosed with progressive forms of the disease.

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 blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which Zeposia exerts therapeutic effects in multiple sclerosis (MS) is unknown but may involve the reduction of lymphocyte migration into the central nervous system.

Zeposia is approved in numerous countries around the world for the treatment of adults with relapsing forms of MS and adults with moderately to severely active ulcerative colitis.

U.S. FDA APPROVED INDICATIONS

ZEPOSIA® (ozanimod) is indicated for the treatment of:

1. Relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.
2. 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
- 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 or UC 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.
- In the MS and 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 MS and 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 MS and 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. Women who become pregnant while taking ZEPOSIA for MS may enroll in the ZEPOSIA pregnancy registry by calling 1-877-301-9314 or visiting **www.zeposiapregnancyregistry.com.**

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.

Severe Increase in Multiple Sclerosis (MS) Disability After Stopping ZEPOSIA: In MS, 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. After stopping ZEPOSIA in the setting of PML, monitor for development of immune reconstitution inflammatory syndrome (PML-IRIS).

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 that occurred in the MS clinical trials of ZEPOSIA-treated patients (≥4%): upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

In the UC clinical trials, the most common adverse reactions that occurred in ≥4% of ZEPOSIA-treated patients and greater than in patients who received placebo were upper respiratory infection, liver test increased, 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.

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**.

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 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 results of future post-marketing studies may not be consistent with the results of this study, that Zeposia, for the indication described in this release, may not be commercially successful, that any marketing approvals, if granted, may have significant limitations on their use, and that continued approval of such product candidate for such indication described in this release may be contingent upon verification and description of clinical benefit in additional confirmatory trials. 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, 2022, 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 only as of the date of this document and except as otherwise required by applicable law, 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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