U.S. Food and Drug Administration Approves Augtyro™ (repotrectinib), a Next-Generation Tyrosine Kinase Inhibitor (TKI), for the Treatment of Locally Advanced or Metastatic ROS1-Positive Non-Small Cell Lung Cancer (NSCLC)

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The approval is based on the pivotal TRIDENT-1 trial, in which Augtyro successfully achieved a high objective response rate and durable response[1]

Augtyro adds to Bristol Myers Squibb's growing and differentiated NSCLC portfolio, expanding the company's presence in precision medicine

PRINCETON, N.J.--(BUSINESS WIRE)-- Bristol Myers Squibb (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) approved *Augtyro* ™(repotrectinib) for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).[1] Administered as an oral therapy, *Augtyro* is a tyrosine kinase inhibitor (TKI) targeting *ROS1* oncogenic fusions.[1]

The approval is based on the TRIDENT-1 study, an open-label, single-arm, Phase 1/2 trial that evaluated *Augtyro* in TKI-naïve and TKI-pretreated patients.[2] In TKI-naïve patients (n=71), the primary endpoint of objective response rate (ORR), defined as the percentage of people treated within a certain period of time whose tumor size decreased (partial response) or who no longer have signs of cancer (complete response),was 79% (95% Confidence Interval [CI]: 68 to 88).[1,3] The median duration of response (mDOR) was 34.1 months. Among patients pretreated with one prior *ROS1* TKI and no prior chemotherapy (n=56), the ORR was 38% (95% CI: 25 to 52) and the mDOR was 14.8 months.[1] Among those who had measurable central nervous system (CNS) metastases at baseline, responses in intracranial lesions were observed in 7 of 8 TKI-naïve patients (n=71) and 5 of 12 of those who were TKI-pretreated (n=56).[1]

"New treatment options continue to be needed for patients with *ROS1* fusion-positive NSCLC that support important clinical goals, including achieving durable therapeutic responses," said Jessica J. Lin, MD, TRIDENT-1 primary investigator and attending physician at the Center for Thoracic Cancers at Massachusetts General Hospital and Assistant Professor of Medicine at Harvard Medical School.[4,5,6,7] "Based on the data we have seen in the TRIDENT-1 trial, repotrectinib has the potential to become a new standard of care option for patients with locally advanced or metastatic *ROS1* fusion-positive lung cancer."[1]

Augtyro is associated with the following Warnings & Precautions: central nervous system (CNS) effects, interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, myalgia with creatine phosphokinase elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity.[1] Please see Important Safety Information below.

"While progress has been made in the treatment of NSCLC over the past decade, there is still a need to address this particularly difficult-to-treat form of the disease with innovative science and a targeted approach," said Samit Hirawat, MD, executive vice president, chief medical officer, Global Drug Development, Bristol Myers Squibb.[6,7] "As the only approved next-generation TKI for *ROS1*-positiveNSCLCpatients, *Augtyro* builds on our legacy of delivering transformational therapies for patients with thoracic cancers."[6,8,9]

"*ROS1* -positive NSCLC patients and their families face a stressful journey because our cancer can be difficult to treat, especially when it spreads to the brain," said Janet Freeman-Daily, co-founder and president of The ROS1ders, a patient advocacy organization. [10] "Today's approval brings a new treatment option for the *ROS1*-positive patient community, which gives us hope for more time with loved ones."

Augtyro is designed to minimize interactions that can lead to certain forms of treatment resistance in *ROS1*-positive metastatic NSCLC patients.[6,8,11] Itis expected to be available to patients in the U.S. in mid-December 2023. Bristol Myers Squibb thanks the patients and investigators involved in the TRIDENT-1 clinical trial program.

About TRIDENT-1

TRIDENT-1 is a global, multicenter, single-arm, open-label, multi-cohort Phase 1/2 clinical trial evaluating the safety, tolerability, pharmacokinetics and anti-tumor activity of repotrectinib in patients with advanced solid tumors, including non-small cell lung cancer (NSCLC).[1,2]Phase 1/2 includes patients with locally advanced or metastatic solid tumors harboring *ROS1* fusions.[2] Additional analyses of the trial are still being conducted; asymptomatic central nervous system (CNS) metastases are allowed.[1,2]The trial excludes patients with symptomatic brain metastases, among other exclusion criteria.[1] Phase 1 of the trial included the dose escalation that determined the recommended Phase 2 dose.[2]

Phase 2 of the trial has a primary endpoint of overall response rate (ORR).[1,2] Key secondary endpoints include duration of response (DOR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as assessed by Blinded Independent Central Review (BICR), progression-free survival (PFS), and intracranial response in six distinct expansion cohorts, including tyrosine kinase inhibitor (TKI)-naïve and TKI-pretreated patients with *ROS1*-positive locally advanced or metastatic NSCLC.[1,2]

In TRIDENT-1, of the 79% (95% Confidence Interval [CI]: 68 to 88) of TKI-naïve patients who responded to treatment, 6% experienced complete

responses and 73% experienced partial responses.[1] The median duration of response (mDOR) was 34.1 months.[1] Of the 38% (95% CI: 25 to 52) of TKI-pretreated patients (n=56) who responded to treatment, 5% experienced complete responses and 32% experienced partial responses and the mDOR was 14.8 months.[1] Among those who had measurable CNS metastases at baseline as assessed by BICR, responses in intracranial lesions were observed in 7 of 8 TKI-naïve patients (n=71) and in 5 of 12 of those who were TKI-pretreated (n=56).[1]

The FDA-approved dosing for *Augtyro*is 160 mg orally once daily for 14 days, then increased to 160 mg twice daily until disease progression or unacceptable toxicity.[1]

Select Safety Profile From TRIDENT-1

Permanent discontinuation of *Augtyro*occurred in 8% of patients.[1] *Augtyro* dosage was interrupted due to an adverse reaction in 48% of patients, and dose reductions due to an adverse event occurred in 35% of patients.[1] Serious adverse reactions occurred in 33% of patients who received *Augtyro.*[1] Serious adverse reactions in ≥2% of patients included pneumonia (5.7%), dyspnea (3.8%), pleural effusion (3.4%) and hypoxia (3%).[1] Fatal adverse reactions occurred in 4.2% of patients who received *Augtyro,* including death, pneumonia, pneumonia aspiration, cardiac arrest, sudden cardiac death, cardiac failure, sudden death, hypoxia, dyspnea, respiratory failure, tremor, and disseminated intravascular coagulation.[1] The most common (≥20%) adverse reactions were dizziness (63%), dysgeusia (48%), peripheral neuropathy (47%), constipation (36%), dyspnea (30%), ataxia (28%), fatigue (24%), cognitive disorders (23%), and muscular weakness (21%).[1] Grade 3 dizziness occurred in 1.9% of patients.[1] The most common and serious adverse reactions and fatal events were evaluated in 264 patients who received the Phase 2 recommended dose of *Augtyro* in TRIDENT-1.[1]

About Lung Cancer

Lung cancer is the leading cause of cancer deaths in the United States.[12] The two main types of lung cancer are non-small cell and small cell.[12] Non-small cell lung cancer (NSCLC) represents up to 85% of diagnoses.[12] Survival rates vary depending on the stage and type of the cancer when diagnosed.[13] *ROS1* fusions are rare and occur in about 1-2% of patients with NSCLC.[10] With a median age of 50, patients with tumors that are *ROS1*-positive tend to be younger than the average lung cancer patient, more often female than male and may have little to no smoking history.[10]*ROS1*-positive lung cancer tends to be aggressive and can often spread to the brain.[10]*ROS1* tyrosine kinase inhibitor (TKI) therapy is the current standard of care for patients with a tumor harboring this gene alteration.[4]

INDICATION

AUGTYRO™ (repotrectinib) is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

Warnings & Precautions

IMPORTANT SAFETY INFORMATION

Central Nervous System Adverse Reactions

- Among the 351 patients who received AUGTYRO in the TRIDENT-1 study, a broad spectrum of central nervous system (CNS) adverse reactions including dizziness, ataxia, and cognitive disorders occurred in 75% with Grade 3 or 4 events occurring in 4%. Dizziness, including vertigo, occurred in 64% and Grade 3 dizziness occurred in 2.8% of patients. The median time to onset was 6 days (1 day to 1.4 years). Dose interruption was required in 9% of patients, and 12% required dose reduction of AUGTYRO due to dizziness.
- Ataxia, including gait disturbance and balance disorder, occurred in 29% of the 351 patients; Grade 3 ataxia occurred in 0.3%. The median time to onset was 15 days (1 day to 1.4 years). Dose interruption was required in 6% of patients, 8% required dose reduction and one patient (0.3%) permanently discontinued AUGTYRO due to ataxia.
- Cognitive disorder, including memory impairment and disturbance in attention, occurred in 23% of the 351 patients. Cognitive disorders included memory impairment (13%), disturbance in attention (11%), and confusional state (2%); Grade 3 cognitive disorders occurred in 0.9% of patients. The median time to onset of cognitive disorders was 37 days (1 day to 1.4 years). Dose interruption was required in 2% of patients, 1.7% required dose reduction and 0.6% permanently discontinued AUGTYRO due to cognitive adverse reactions.
- Mood disorders occurred in 6% of the 351 patients. Mood disorders occurring in >1% of patients included anxiety (2.8%), irritability (1.1%), and depression (1.4%); Grade 4 mood disorders (mania) occurred in 0.3% of patients. Dose interruption was required in 0.3% of patients and 0.3% required a dose reduction due to mood disorders.
- Sleep disorders including insomnia and hypersomnia occurred in 15% of the 351 patients. Sleep disorders observed in >1% of patients were somnolence (8%), insomnia (6%) and hypersomnia (1.1%). Dose interruption was required in 0.9% of patients, and 0.3% required a dose reduction due to sleep disorders.
- The incidences of CNS adverse reactions reported were similar in patients with and without CNS metastases.
- Advise patients not to drive or use machines if they are experiencing CNS adverse reactions. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity.

Interstitial Lung Disease (ILD)/Pneumonitis

- Among the 351 patients treated with AUGTYRO, ILD/pneumonitis (pneumonitis [2.6%] and interstitial lung disease [0.3%]) occurred in 2.9%; Grade 3 ILD/pneumonitis occurred in 1.1%. The median time to onset was 45 days (19 days to 0.9 years). Dose interruption was required in 1.4% of patients, 0.6% required dose reduction, and 1.1% permanently

discontinued AUGTYRO due to ILD/pneumonitis.
- Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. Immediately withhold AUGTYRO in patients with suspected ILD/pneumonitis and permanently discontinue AUGTYRO if ILD/pneumonitis is confirmed.

Hepatotoxicity

- Among the 351 patients treated with AUGTYRO, increased alanine transaminase (ALT) occurred in 35%, increased aspartate aminotransferase (AST) occurred in 40%, including Grade 3 or 4 increased ALT in 2% and increased AST in 2.6%. The median time to onset of increased ALT or AST was 15 days (range: 1 day to 1.9 years). Increased ALT or AST leading to dose interruptions or reductions occurred in 2.8% and 1.4% of patients, respectively. Hyperbilirubinemia leading to dose interruptions occurred in 0.6%.
- Monitor liver function tests, including ALT, AST and bilirubin, every 2 weeks during the first month of treatment, then monthly thereafter and as clinically indicated. Withhold and then resume at same or reduced dose upon improvement or permanently discontinue AUGTYRO based on the severity.

Myalgia with Creatine Phosphokinase (CPK) Elevation

- Among the 351 patients treated with AUGTYRO, myalgia occurred in 13% of patients, with Grade 3 in 0.6%. Median time to onset of myalgia was 19 days (range: 1 day to 2 years). Concurrent increased CPK within a 7-day window was observed in 3.7% of patients. AUGTYRO was interrupted in one patient with myalgia and concurrent CPK elevation.
- Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor serum CPK levels during AUGTYRO treatment and monitor CPK levels every 2 weeks during the first month of treatment and as needed in patients reporting unexplained muscle pain, tenderness, or weakness. Initiate supportive care as clinically indicated. Based on severity, withhold and then resume AUGTYRO at same or reduced dose upon improvement.

Hyperuricemia

- Among the 351 patients treated with AUGTYRO, 18 patients (5%) experienced hyperuricemia reported as an adverse reaction, 0.9% experienced Grade 3 or 4 hyperuricemia. One patient without pre-existing gout required urate-lowering medication.
- Monitor serum uric acid levels prior to initiating AUGTYRO and periodically during treatment. Initiate treatment with urate-lowering medications as clinically indicated. Withhold and then resume at same or reduced dose upon improvement, or permanently discontinue AUGTYRO based on severity.

Skeletal Fractures

- Among 351 adult patients who received AUGTYRO, fractures occurred in 2.3%. Fractures involved the ribs (0.6%), feet (0.6%), spine (0.3%), acetabulum (0.3%), sternum (0.3%), and ankles (0.3%). Some fractures occurred at sites of disease and prior radiation therapy. The median time to fracture was 71 days (range: 31 days to 1.4 years). AUGTYRO was interrupted in 0.3% of patients.
- Promptly evaluate patients with signs or symptoms (e.g., pain, changes in mobility, deformity) of fractures. There are no data on the effects of AUGTYRO on healing of known fractures and risk of future fractures.

Embryo-Fetal Toxicity

- Based on literature reports in humans with congenital mutations leading to changes in tropomyosin receptor tyrosine kinase (TRK) signaling, findings from animal studies, and its mechanism of action, AUGTYRO can cause fetal harm when administered to a pregnant woman.
- Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with AUGTYRO and for 2 months following the last dose, since AUGTYRO can render some hormonal contraceptives ineffective.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with AUGTYRO and for 4 months after the last dose.

Adverse Reactions

- Among 351 patients who received AUGTYRO for *ROS1*-positive NSCLC and other solid tumors in the TRIDENT-1 trial, the most common (>20%) adverse reactions were dizziness (64%), dysgeusia (50%), peripheral neuropathy (47%), constipation (37%), dyspnea (30%), ataxia (29%), fatigue (29%), cognitive disorders (23%), and nausea (20%).
- In a subset of 264 patients who received AUGTYRO for *ROS1*-positive NSCLC, the most common (≥20%) adverse reactions were dizziness (63%), dysgeusia (48%), peripheral neuropathy (47%), constipation (36%), dyspnea (30%), ataxia (28%), fatigue (24%), cognitive disorders (23%), and muscular weakness (21%).

Drug Interactions

Effects of Other Drugs on AUGTYRO

Strong and Moderate CYP3A Inhibitors

- Avoid concomitant use with strong or moderate CYP3A inhibitors. Concomitant use of AUGTYRO with a strong or a moderate CYP3A inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO. Discontinue CYP3A inhibitors for 3 to 5 elimination half-lives of the CYP3A inhibitor prior to initiating AUGTYRO.

P-gp Inhibitors

- Avoid concomitant use with P-gp inhibitors. Concomitant use of AUGTYRO with a P-gp inhibitor may increase repotrectinib exposure, which may increase the incidence and severity of adverse reactions of AUGTYRO.

Strong and Moderate CYP3A Inducers

- Avoid concomitant use with strong or moderate CYP3A inducers. Concomitant use of AUGTYRO with a strong or moderate CYP3A inducer may decrease repotrectinib plasma concentrations, which may decrease efficacy of AUGTYRO.

Effects of AUGTYRO on other Drugs

Certain CYP3A4 Substrates

- Avoid concomitant use unless otherwise recommended in the Prescribing Information for CYP3A substrates, where minimal concentration changes can cause reduced efficacy. If concomitant use is unavoidable, increase the CYP3A4 substrate dosage in accordance with approved product labeling.
- Repotrectinib is a CYP3A4 inducer. Concomitant use of repotrectinib decreases the concentration of CYP3A4 substrates, which can reduce the efficacy of these substrates.

Contraceptives

- Repotrectinib is a CYP3A4 inducer, which can decrease progestin or estrogen exposure to an extent that could reduce the effectiveness of hormonal contraceptives.
- Avoid concomitant use of AUGTYRO with hormonal contraceptives. Advise females to use an effective nonhormonal contraceptive.

Please see U.S. Full Prescribing Information for AUGTYRO

Bristol Myers Squibb: Creating a Better Future for People with Cancer

Bristol Myers Squibb is inspired by a single vision — transforming patients' lives through science. The goal of the company's cancer research is to deliver medicines that offer each patient a better, healthier life and to make cure a possibility. Building on a legacy across a broad range of cancers that have changed survival expectations for many, Bristol Myers Squibb researchers are exploring new frontiers in personalized medicine and, through innovative digital platforms, are turning data into insights that sharpen their focus. Deep understanding of causal human biology, cutting-edge capabilities and differentiated research programs uniquely position the company to approach cancer from every angle.

Cancer can have a relentless grasp on many parts of a patient's life, and Bristol Myers Squibb is committed to taking actions to address all aspects of care, from diagnosis to survivorship. As a leader in cancer care, Bristol Myers Squibb is working to empower all people with cancer to have a better future.

About Bristol Myers Squibb's Patient Access Support

Bristol Myers Squibb remains committed to providing assistance so that cancer patients who need our medicines can access them and expedite time to therapy.

BMS Access Support®, the Bristol Myers Squibb patient access and reimbursement program, is designed to help appropriate patients initiate and maintain access to BMS medicines during their treatment journey. BMS Access Support offers benefit investigation, prior authorization assistance, as well as co-pay assistance for eligible, commercially insured patients. More information about our access and reimbursement support can be obtained by calling BMS Access Supportat 1-800-861-0048 or by visiting www.bmsaccesssupport.com.

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, whether Augtyro™ (repotrectinib) for the indication described in this release will be commercially successful, that any marketing approvals, if granted, may have significant limitations on their use, and that continued approval of Augtyro™ (repotrectinib) for such indication described in this release may be contingent upon verification and description of clinical benefit in 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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Bristol Myers Squibb

M edia Inquiries:
media@bms.com

Investors:
investor.relations@bms.com

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