U.S. Food and Drug Administration Accepts for Priority Review Bristol Myers Squibb's Application for Augtyro™ (repotrectinib) for the Treatment of Patients with NTRK-Positive Locally Advanced or Metastatic Solid Tumors

February 15, 2024

Application based on results from the TRIDENT-1 and CARE trials, in which Augtyro demonstrated clinically meaningful response rates

If approved, Augtyro will provide a new, next-generation option for patients with NTRK-positive locally advanced or metastatic solid tumors who have high unmet medical needs

The U.S. Food and Drug Administration assigned a target action date of June 15, 2024

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol Myers Squibb (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) has accepted the supplemental New Drug Application (sNDA) for *Augtyro*™(repotrectinib) for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a *neurotrophic tyrosine receptor kinase (NTRK)* gene fusion, and are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity. The filing acceptance is based on results from the registrational Phase 1/2 TRIDENT-1 trial (adult patients with *NTRK*-positive solid tumors) and CARE study (pediatric patients with *NTRK*-positive solid tumors). The FDA granted the application Priority Review status and assigned a Prescription Drug User Fee Act (PDUFA) goal date of June 15, 2024.

"While great advancements have been made over the last decade, patients with *NTRK*-positive locally advanced or metastatic solid tumors still experience significant unmet needs. New and effective treatment options that may improve durability of response and address resistance to existing tyrosine kinase inhibitors are critical to helping patients with these aggressive tumors," said Joseph Fiore, vice president, global program lead, *Augtyro*, Bristol Myers Squibb. "We look forward to working closely with the FDA on the review of our application for *Augtyro* for this tumor-agnostic indication and potentially offering patients with *NTRK*-positive disease a new, durable treatment option."

The filing was based on the results from the TRIDENT-1 and CARE trials. In the TRIDENT-1 study, *Augtyro* demonstrated clinically meaningful response rates in patients with *NTRK*-positive locally advanced or metastatic solid tumors. Durability of response was robust, including among patients whose tumors harbor common resistance mutations, and intracranial responses were observed. *Augtyro* showed a safety profile that was well tolerated and generally manageable. The study remains ongoing to assess long-term outcomes and additional endpoints. Results from TRIDENT-1 were supported by data from the CARE study, which evaluates *Augtyro* in pediatric and young adult patients with locally advanced or metastatic solid tumors harboring *ALK*, *ROS1* or *NTRK1-3* gene alterations. Additionally, in November 2023 the U.S. Food and Drug Administration approved *Augtyro* for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer NSCLC.

Bristol Myers Squibb thanks the patients and investigators involved with the TRIDENT-1 and CARE clinical trials.

Turning Point Therapeutics is a wholly owned subsidiary of the Bristol-Myers Squibb Company. As of August 2022, Bristol Myers Squibb acquired the company, including its asset *repotrectinib*.

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 *Augtyro* in patients with advanced solid tumors, including non-small cell lung cancer (NSCLC). Phase 1/2 includes patients with locally advanced or metastatic solid tumors harboring *ROS1* or NTRK fusions. Additional analyses of the trial are still being conducted; asymptomatic central nervous system (CNS) metastases are allowed. The trial excludes patients with symptomatic brain metastases, among other exclusion criteria. Phase 1 of the trial included the dose escalation that determined the recommended Phase 2 dose.

Phase 2 of the trial has a primary endpoint of overall response rate (ORR). 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 and *NTRK*-positive locally advanced or metastatic solid tumors.

About CARE

CARE is a Phase 1/2 open-label, safety, tolerability, pharmacokinetics and anti-tumor activity clinical trial evaluating *Augtyro* in pediatric and young adult patients with locally advanced or metastatic solid tumors harboring *ALK*, *ROS1* or *NTRK1-3* gene alterations.

Phase 1 of the study aims to evaluate the safety and tolerability at different dose levels. Phase 1 of the trial has primary endpoints of dose limiting toxicities (DLTs) and pediatric recommended Phase 2 dose (RP2D). Secondary endpoints include overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), duration of response (DOR) and intracranial ORR (IC-ORR). Phase 2 of the study will seek to demonstrate the efficacy and anti-tumor activity of *Augtyro* in pediatric and young adult patients. The primary endpoint of Phase 2 is ORR and secondary endpoints include CBR, TTR, DOR, IC-ORR, progression-free survival (PFS), central nervous system PFS (CNS-PFS) and overall survival (OS).

About *NTRK*-Positive Solid Tumors

Neurotrophic tropomyosin kinase receptors (NTRK) are a family of receptors involved in neural development. *NTRK* gene fusions can play a role in the development of cancer. They are rare in patients with solid tumors with less than 1% of patients testing positive, though may be more frequent in patients with secretory breast cancer, infantile fibrosarcoma, thyroid cancer, gastrointestinal stromal tumors, spitzoid tumors and infantile fibrosarcoma, among other cancers. Per international treatment guidelines, targeted agents are part of the treatment armamentarium for patients with a tumor harboring this gene alteration.

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 platforms 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 *Augtyro*

Augtyro (TPX-0005, BMS-986472) is a next-generation tyrosine kinase inhibitor (TKI) targeting *ROS1*-positive or *NTRK*-positive locally advanced or metastatic solid tumors, including non-small cell lung cancer (NSCLC), where there remain significant unmet medical needs for patients. *Augtyro* was designed to improve durability of response and with favorable properties for human brain penetration to enhance intracranial activity. It is being studied in a registrational Phase 1/2 trial in adults (TRIDENT-1) and a Phase 1/2 trial in pediatric patients (CARE).

Augtyro has demonstrated clinically meaningful results and was granted three Breakthrough Therapy Designations (BTDs) by the FDA for the treatment of patients with: *ROS1*-positive metastatic NSCLC who have not been treated with a ROS1 TKI; *ROS1*-positive metastatic NSCLC who have been previously treated with one ROS1 TKI and who have not received prior platinum-based chemotherapy; and advanced solid tumors that have an *NTRK* gene fusion who have progressed following treatment with one or two prior tropomyosin receptor kinase (TRK) TKIs (with or without prior chemotherapy) and have no satisfactory alternative treatments.

Augtyro was also previously granted four fast-track designations in patients with: *ROS1*-positive advanced NSCLC who have been treated with disease progression following one prior line of platinum-based chemotherapy and one prior line of a ROS1 TKI; *ROS1*-positive advanced NSCLC who have not been treated with a ROS1 TKI; *ROS1*-positive advanced NSCLC who have been previously treated with one ROS1 TKI and who have not received prior platinum-based chemotherapy; and advanced solid tumors that have an *NTRK* gene fusion who have progressed following treatment with at least one prior line of chemotherapy and one or two prior TRK TKIs and have no satisfactory alternative treatments. *Augtyro* was also granted an Orphan Drug designation by the U.S. Food and Drug Administration (FDA).

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

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 Augtyro *(repotrectinib) may not receive regulatory approval for the additional indication described in this release in the currently anticipated timeline or at all, that any marketing approvals, if granted, may have significant limitations on their use, and, if approved, whether such treatment for such additional indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. It should be noted that acceptance of the application does not change the standards for FDA approval. 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, 2023 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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