BeiGene, Ltd.
百濟神州有限公司
(incorporated in the Cayman Islands with limited liability)
(Stock Code: 06160)

VOLUNTARY ANNOUNCEMENT - UPDATE REGARDING RECENT BUSINESS DEVELOPMENTS

Health Canada Approves BRUKINSA® (Zanubrutinib) for the Treatment of Waldenström's Macroglobulinemia

- *Approval is based on the Phase 3 ASPEN trial of BRUKINSA compared to ibrutinib*
- *This marks the first regulatory approval for BRUKINSA in Waldenström's macroglobulinemia, and BeiGene's first approval in Canada*

On February 26, 2021 (U.S. Eastern Time), BeiGene, Ltd. ("**BeiGene**" or the "**Company**") announced that BRUKINSA® (zanubrutinib) has been approved by Health Canada for the treatment of adult patients with Waldenström's macroglobulinemia (WM).

"BRUKINSA is a highly selective BTK inhibitor designed to provide deep and durable response for patients with hematologic malignancies while reducing the frequency of certain side effects. With today's approval, we are looking forward to bringing this potentially best-in-class BTK inhibitor to Canadians affected by WM," said Josh Neiman, Chief Commercial Officer for North America and Europe at BeiGene. "We are committed to working to ensure access for patients in Canada and to making BRUKINSA available to patients in more markets worldwide."

"WM is a rare disease with significant morbidity. BTK inhibitors have brought advancements in the treatment of WM, yet not all patients respond and intolerability due to side effects remains an issue, particularly for the elderly patient population," said Christine Chen, M.D., Med, FRCPC, Associate Professor at University of Toronto and Clinical Investigator at Princess Margaret Cancer Centre. "The ASPEN trial results underscore the potential that zanubrutinib has to provide clinical benefit with advantages in safety, offering new hope for WM patients."

"The Waldenström's Macroglobulinemia Foundation of Canada (WMFC) is delighted with Health Canada's approval of BRUKINSA (zanubrutinib) as a WM treatment. This marks an important step forward in providing a variety of quality options for Canadian patients. As the study results from ASPEN demonstrated, BRUKINSA presents the possibility of improved outcomes for Canadian patients," commented Paul Kitchen, Chair of Board at WMFC.

Following the previously granted priority review in September 2020, the Health Canada approval for BRUKINSA is based on efficacy results from the ASPEN clinical trial, a Phase 3 randomized, open-label, multicenter trial (NCT03053440) that evaluated BRUKINSA compared to ibrutinib in patients with relapsed/refractory (R/R) or treatment-naïve (TN) WM who harbor a MYD88 mutation (*MYD88*^{MUT}). In the ASPEN trial, BRUKINSA demonstrated numerically higher very good partial response (VGPR) rate and a favorable safety profile over ibrutinib, although the primary endpoint of statistical superiority related to deep response (VGPR or better) was not met.

As assessed by independent review committee (IRC) per adaptation of the response criteria updated at the Sixth International Workshop on Waldenström's Macroglobulinemia (IWWM), the combined complete response (CR) + VGPR rate in the overall intention-to-treat (ITT) population was 28.4% with BRUKINSA (95% CI: 20, 38), compared to 19.2% with ibrutinib (95% CI: 12, 28).[1]

In the ASPEN trial, of the 101 patients with WM randomized and treated with BRUKINSA, four percent of patients discontinued due to adverse events, including cardiomegaly, neutropenia, plasma cell myeloma, and subdural hemorrhage. Adverse events leading to dose reduction occurred in 14% of patients, with the most common being neutropenia (3.0%) and diarrhea (2.0%).[1]

The overall safety profile of BRUKINSA is based on pooled data from 779 patients with B-cell malignancies treated with BRUKINSA in clinical trials. The most common adverse reactions (≥10%) with BRUKINSA were neutropenia, thrombocytopenia, upper respiratory tract infection, anemia, rash, musculoskeletal pain, diarrhea, cough, contusion, pneumonia (grouped terms), urinary tract infection, hemorrhage (grouped terms), and hematuria. The most frequent serious adverse reactions (≥2%) were pneumonia (10.0%) and hemorrhage (2.1%).[1]

The recommended total daily dose of BRUKINSA is 320mg. BRUKINSA is expected to be available in Canada in the coming weeks.

About Waldenström's Macroglobulinemia

Waldenström's macroglobulinemia (WM) is a rare indolent B-cell lymphoma that occurs in less than two percent of patients with non-Hodgkin's lymphoma (NHL). The disease usually affects older adults and is primarily found in the bone marrow, although lymph nodes and the spleen may be involved.[2] In Canada and the United States, the incidence rate of WM is about five cases per million people per year.[3]

About the ASPEN trial

The Phase 3 randomized, open-label, multicenter ASPEN clinical trial (NCT03053440) evaluated zanubrutinib versus ibrutinib in people with relapsed/refractory (R/R) or treatment-naïve (TN) Waldenström's macroglobulinemia. The primary objective was to establish superiority of zanubrutinib compared to ibrutinib as demonstrated by the proportion of people achieving complete response (CR) or very good partial response (VGPR). Secondary endpoints included major response rate, duration of response and progression-free survival, and safety, measured by incidence, timing and severity of treatment-emergent adverse events. The pre-specified analysis populations for the trial included the overall population (n=201) and R/R patients (n=164). Exploratory endpoints included quality of life measures.

The study includes two cohorts, a randomized cohort (cohort 1) consisting of 201 patients with a MYD88 mutation and a non-randomized cohort (cohort 2) in which 28 patients with MYD88 wild-type ($MYD88^{WT}$) received zanubrutinib because they have historically responded poorly to ibrutinib therapy.

The randomized cohort 1 enrolled 102 patients (including 83 relapsed or refractory (R/R) patients and 19 treatment-naïve (TN) patients) in the zanubrutinib arm and 99 patients (including 81 R/R patients and 18 TN patients) in the ibrutinib arm. Patients in the zanubrutinib arm were assigned to receive zanubrutinib 160 mg twice daily (BID) and patients in the ibrutinib arm received 420 mg of ibrutinib once daily (QD).

Results of cohort 2 were previously presented at the 24th Congress of European Hematology Association (EHA) and showed an overall response rate (ORR) of 80.8%, a major response rate (MRR; partial response or better) of 53.8% and a VGPR rate of 23.1%.

About BRUKINSA® (zanubrutinib)

BRUKINSA (zanubrutinib) is a small molecule inhibitor of Bruton's tyrosine kinase (BTK), discovered by BeiGene scientists, that is currently being evaluated globally in a broad pivotal clinical program as a monotherapy and in combination with other therapies to treat various B-cell malignancies.

BRUKINSA is approved in the following indications and regions:

- For the treatment of mantle cell lymphoma (MCL) in adult patients who have received at least one prior therapy (United States, November 2019)*;
- For the treatment of MCL in adult patients who have received at least one prior therapy (China, June 2020)**;
- For the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) in adult patients who have received at least one prior therapy (China, June 2020)**;
- For the treatment of relapsed or refractory MCL (United Arab Emirates, February 2021); and
- For the treatment of Waldenström's macroglobulinemia (WM) in adult patients (Canada, March 2021).

In Canada, a new drug submission for BRUKINSA for the treatment of patients with MCL who have received at least one prior therapy has been accepted and is currently under review. Currently, more than 20 marketing applications for BRUKINSA have been submitted, covering more than 40 countries and regions globally, including the United States, China, and European Union.

IMPORTANT U.S. SAFETY INFORMATION FOR BRUKINSA (ZANUBRUTINIB)

Warnings and Precautions

Hemorrhage

Fatal and serious hemorrhagic events have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher bleeding events including intracranial and gastrointestinal hemorrhage, hematuria and hemothorax have been reported in 2% of patients treated with BRUKINSA monotherapy. Bleeding events of any grade, including purpura and petechiae, occurred in 50% of patients treated with BRUKINSA monotherapy.

Bleeding events have occurred in patients with and without concomitant antiplatelet or anticoagulation therapy. Co-administration of BRUKINSA with antiplatelet or anticoagulant medications may further increase the risk of hemorrhage.

Monitor for signs and symptoms of bleeding. Discontinue BRUKINSA if intracranial hemorrhage of any grade occurs. Consider the benefit-risk of withholding BRUKINSA for 3-7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections

Fatal and serious infections (including bacterial, viral, or fungal) and opportunistic infections have occurred in patients with hematological malignancies treated with BRUKINSA monotherapy. Grade 3 or higher infections occurred in 23% of patients treated with BRUKINSA monotherapy. The most common Grade 3 or higher infection was pneumonia. Infections due to hepatitis B virus (HBV) reactivation have occurred.

Consider prophylaxis for herpes simplex virus, pneumocystis jiroveci pneumonia and other infections according to standard of care in patients who are at increased risk for infections. Monitor and evaluate patients for fever or other signs and symptoms of infection and treat appropriately.

Cytopenias

Grade 3 or 4 cytopenias, including neutropenia (27%), thrombocytopenia (10%), and anemia (8%) based on laboratory measurements, were reported in patients treated with BRUKINSA monotherapy.

Monitor complete blood counts during treatment and treat using growth factor or transfusions, as needed.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinoma, have occurred in 9% of patients treated with BRUKINSA monotherapy. The most frequent second primary malignancy was skin cancer (basal cell carcinoma and squamous cell carcinoma of skin), reported in 6% of patients. Advise patients to use sun protection.

Cardiac Arrhythmias

Atrial fibrillation and atrial flutter have occurred in 2% of patients treated with BRUKINSA monotherapy. Patients with cardiac risk factors, hypertension, and acute infections may be at increased risk. Grade 3 or higher events were reported in 0.6% of patients treated with BRUKINSA monotherapy. Monitor signs and symptoms for atrial fibrillation and atrial flutter and manage as appropriate.

Embryo-Fetal Toxicity

Based on findings in animals, BRUKINSA can cause fetal harm when administered to a pregnant woman. Administration of zanubrutinib to pregnant rats during the period of organogenesis caused embryo-fetal toxicity, including malformations at exposures that were 5 times higher than those reported in patients at the recommended dose of 160 mg twice daily. Advise women to avoid becoming pregnant while taking BRUKINSA and for at least 1 week after the last dose. Advise men to avoid fathering a child during treatment and for at least 1 week after the last dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Adverse Reactions

The most common adverse reactions in >10% of patients who received BRUKINSA were neutrophil count decreased (53%), platelet count decreased (39%), upper respiratory tract infection (38%), white blood cell count decreased (30%), hemoglobin decreased (29%), rash (25%), bruising (23%), diarrhea (20%), cough (20%), musculoskeletal pain (19%), pneumonia (18%), urinary tract infection (13%), hematuria (12%), fatigue (11%), constipation (11%), and hemorrhage (10%). The most frequent serious adverse reactions were pneumonia (11%) and hemorrhage (5%).

Of the 118 patients with MCL treated with BRUKINSA, 8 (7%) patients discontinued treatment due to adverse reactions in the trials. The most frequent adverse reaction leading to treatment discontinuation was pneumonia (3.4%). One (0.8%) patient experienced an adverse reaction leading to dose reduction (hepatitis B).

Drug Interactions

CYP3A Inhibitors: When BRUKINSA is co-administered with a strong CYP3A inhibitor, reduce BRUKINSA dose to 80 mg once daily. For co-administration with a moderate CYP3A inhibitor, reduce BRUKINSA dose to 80 mg twice daily.

CYP3A Inducers: Avoid co-administration with moderate or strong CYP3A inducers.

Specific Populations

Hepatic Impairment: The recommended dose of BRUKINSA for patients with severe hepatic impairment is 80 mg orally twice daily.

U.S. INDICATION

BRUKINSA is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Please see full U.S. Prescribing Information at www.beigene.com/PDF/BRUKINSAUSPI.pdf and Patient Information at www.beigene.com/PDF/BRUKINSAUSPPI.pdf.

[1] BRUKINSA (zanubrutinib) Canadian Product Monograph. March 2021.

[2] Lymphoma Research Foundation. Available at https://lymphoma.org/aboutlymphoma/nhl/wm/. Accessed December 2020.

[3] Waldenström's Macroglobulinemia Foundation of Canada. https://wmfc.ca/what-we-do/what-is-wm/.

* This indication was approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

** This indication was approved under conditional approval. Complete approval for this indication may be contingent upon results from one or more ongoing randomized, controlled confirmatory clinical trials.

About BeiGene

BeiGene is a global, commercial-stage biotechnology company focused on discovering, developing, manufacturing, and commercializing innovative medicines to improve treatment outcomes and access for patients worldwide. Our 5,400+ employees around the world are committed to expediting the development of a diverse pipeline of novel therapeutics. We currently market two internally discovered oncology medicines: BTK inhibitor BRUKINSA® (zanubrutinib) in the United States and China, and anti-PD-1 antibody tislelizumab in China. We also market or plan to market in China additional oncology products licensed from Amgen Inc., Celgene Logistics Sàrl, a Bristol Myers Squibb (BMS) company, and EUSA Pharma; and have entered a collaboration with Novartis Pharma AG for Novartis to develop and commercialize tislelizumab in North America, Europe and Japan. To learn more about BeiGene, please visit www.beigene.com and follow us on Twitter at @BeiGeneUSA.

Forward-Looking Statements

This announcement contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws, including statements regarding future development and potential commercialization of BRUKINSA in Canada and other markets, plans for making BRUKINSA accessible to patients in Canada and to making it available to more patients globally, the potential for BRUKINSA to be a best-in-class BTK inhibitor, the potential for zanubrutinib to provide improved clinical benefit with advantages in safety, and the potential commercial opportunity for BRUKINSA. Actual results may differ materially from those indicated in the forward-looking statements as a result of various important factors, including the possibility that the closing conditions set forth in the Collaboration and License Agreement, including, those related to antitrust clearance, will not be met and that the parties will be unable to consummate the proposed transaction; the possibility that BeiGene will not realize the expected benefits of the transaction; the possibility that BeiGene or Novartis will fail to fully perform their respective obligations under the Collaboration and License Agreement; BeiGene's ability to demonstrate the efficacy and safety of its drug candidates; the clinical results for its drug candidates, which may not support further development or marketing approval; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials and marketing approval; BeiGene's ability to achieve commercial success for its marketed products and drug candidates, if approved; BeiGene's ability to obtain and maintain protection of intellectual property for its technology and drugs; BeiGene's reliance on third parties to conduct drug development, manufacturing and other services; BeiGene's limited operating history and BeiGene's ability to obtain additional funding for operations and to complete the development and commercialization of its drug candidates; and the impact of the COVID-19 pandemic on the Company's clinical development, commercial and other operations, as well as those risks more fully discussed in the section entitled "Risk Factors" in BeiGene's most recent annual report on Form 10-K, as well as discussions of potential risks, uncertainties, and other important factors in BeiGene's subsequent filings with the U.S. Securities and Exchange Commission and the Stock Exchange of Hong Kong Limited. All information in this announcement is as of the date of this announcement, and BeiGene undertakes no duty to update such information unless required by law.

By order of the Board
BeiGene, Ltd.
Mr. John V. Oyler
Chairman

Hong Kong, March 3, 2021

As at the date of this announcement, the Board of Directors of the Company comprises Mr. John V. Oyler as Chairman and Executive Director, Dr. Xiaodong Wang and Mr. Anthony C. Hooper as Non-executive Directors, and Mr. Timothy Chen, Mr. Donald W. Glazer, Mr. Michael Goller, Mr. Ranjeev Krishana, Mr. Thomas Malley, Dr. Corazon (Corsee) D. Sanders, Mr. Jing-Shyh (Sam) Su and Mr. Qingqing Yi as Independent Non-executive Directors.