Lilly's Jaypirca (pirtobrutinib) recommended by CHMP for approval in the European Union for adults with relapsed or refractory chronic lymphocytic leukemia (CLL) previously treated with a BTK inhibitor

February 28, 2025

The positive opinion is based on results from the Phase 3 BRUIN CLL-321 trial, recently presented at the 2024 American Society of Hematology Annual Meeting

BRUIN CLL-321 is the first randomized Phase 3 study in CLL ever conducted exclusively in patients previously treated with a BTK inhibitor

INDIANAPOLIS, Feb. 28, 2025 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) has issued a positive opinion for Jaypirca (pirtobrutinib), a non-covalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor, for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) who have been previously treated with a BTK inhibitor.

"Results from the BRUIN CLL-321 trial show that Jaypirca delivers clinically meaningful outcomes in a post-BTK inhibitor setting with markedly prolonged time to next treatment, including in those with high-risk characteristics often associated with poor prognosis," said Paolo Ghia, M.D., professor, medical oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy. "Jaypirca allows for continued targeting of the BTK pathway following treatment with a covalent BTK inhibitor and has the potential to be an important new option in a setting with significant unmet need. The CHMP opinion is an important step toward bringing Jaypirca to patients in the European Union."

Following this positive opinion, the application for the use of Jaypirca in patients with relapsed or refractory CLL who have been previously treated with a BTK inhibitor is now referred to the European Commission for final action. The European Commission's decision is expected in the next one to two months. Jaypirca has also previously received a conditional marketing authorization by the EMA for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a BTK inhibitor.

The positive opinion is supported by data from the BRUIN CLL-321 clinical trial, the first randomized Phase 3 study in CLL ever conducted exclusively in patients previously treated with a BTK inhibitor. The study's primary endpoint of progression-free survival (PFS) was met at the prespecified time of final analysis (Aug. 29, 2023), based on independent review committee (IRC) assessment, demonstrating pirtobrutinib was superior to investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR), both global standards of care.[1] At an updated analysis (Aug. 29, 2024), pirtobrutinib reduced the risk of disease progression or death by 46% compared to IdelaR or BR (median PFS: 14.0 vs. 8.7 months), consistent with the primary analysis. PFS results were consistent across key subgroups, including patients who received prior venetoclax and across subgroups associated with poor prognosis, including those with TP53 mutations and/or 17p deletions, unmutated IGHV status and complex karyotype. Additionally, the median time to next treatment or death (TTNT), a prespecified, descriptive secondary endpoint in the trial that can serve as a surrogate marker for disease control outcomes, was 24 months compared to the control arm of 11 months (63% improvement; HR=0.37 [95% CI, 0.25-0.52]). The overall safety profile for patients treated with pirtobrutinib in BRUIN CLL-321 was consistent with safety data from the Phase 1/2 BRUIN study, including adverse events of special interest. The most common adverse reactions of any grade were neutropenia, fatigue, diarrhea, anemia, rash, and contusion.

Results from the BRUIN CLL-321 study were presented at the American Society of Hematology (ASH) Annual Meeting and Exposition in December 2024.

"We are pleased to receive a positive opinion from the CHMP, signaling that the European Union may lead the way in broadening patient access to Jaypirca for those with relapsed or refractory CLL in the post-BTK inhibitor setting," said Jacob Van Naarden, executive vice president and president of Lilly Oncology. "There are currently no treatment options that have been specifically studied in a randomized Phase 3 trial in this patient population, and we are hopeful Jaypirca will be a meaningful new option for patients. We look forward to the European Commission's decision in the coming months."

In addition to this positive opinion in CLL and conditional approval in MCL in the EU, Jaypirca was approved in the U.S. in 2023 under the U.S. Food and Drug Administration's (FDA) Accelerated Approval pathway for the treatment of adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor, and adult patients with CLL or small lymphocytic lymphoma (SLL) who have received at least two prior lines of therapy including a BTK inhibitor and BCL-2 inhibitor. Lilly has submitted supplemental marketing applications for Jaypirca in the post-BTK inhibitor setting for CLL/SLL patients around the globe, including in the U.S.

About BRUIN CLL-321
BRUIN CLL-321 is a Phase 3, randomized, open-label study of pirtobrutinib versus investigator's choice of idelalisib plus rituximab (IdelaR) or bendamustine plus rituximab (BR) in BTK inhibitor pre-treated patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The trial enrolled 238 patients, who were randomized 1:1 to receive pirtobrutinib (200 mg orally, once daily) or investigator's choice of either IdelaR or BR per labeled doses. This trial's primary endpoint is progression-free survival (PFS) per 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria, as assessed by blinded independent review committee (IRC). Secondary endpoints include PFS, as assessed by investigator; overall response rate (ORR) and duration of response (DoR); event-free survival; overall survival (OS) and time to next treatment (TTNT); safety and tolerability; and patient-reported outcomes (PRO).

About Jaypirca (pirtobrutinib)
Jaypirca (pirtobrutinib, formerly known as LOXO-305) (pronounced jay-pihr-kaa) is a highly selective (300 times more selective for BTK versus 98% of

other kinases tested in preclinical studies), non-covalent (reversible) inhibitor of the enzyme BTK.[2] BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL).[3,4] Jaypirca is a U.S. FDA-approved oral prescription medicine, 100 mg or 50 mg tablets taken as a once-daily 200 mg dose with or without food until disease progression or unacceptable toxicity.

About Chronic Lymphocytic Leukemia (CLL)

CLL is a form of slow-growing non-Hodgkin lymphoma that develops from white blood cells known as lymphocytes.[5,6] CLL is one of the most common types of leukemia in adults.[5] There are roughly 100,000 new cases of CLL globally each year, and the overall incidence of CLL in Europe is approximately 4.92 cases per 100,000 persons per year.[7,8] In CLL, the cancer cells are present in the blood.[5]

INDICATIONS FOR JAYPIRCA (pirtobrutinib) (in the United States)

Jaypirca is a kinase inhibitor indicated for the treatment of

- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor.
- Adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

These indications are approved under accelerated approval based on response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

IMPORTANT SAFETY INFORMATION FOR JAYPIRCA (pirtobrutinib)

Infections: Fatal and serious infections (including bacterial, viral, fungal) and opportunistic infections occurred in Jaypirca-treated patients. In a clinical trial, Grade ≥3 infections occurred in 24% of patients with hematologic malignancies, most commonly pneumonia (14%); fatal infections occurred (4.4%). Sepsis (6%) and febrile neutropenia (4%) occurred. In patients with CLL/SLL, Grade ≥3 infections occurred (32%), with fatal infections occurring in 8%. Opportunistic infections included *Pneumocystis jirovecii* pneumonia and fungal infection. Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients at increased risk for infection, including opportunistic infections. Monitor patients for signs and symptoms, evaluate promptly, and treat appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Hemorrhage: Fatal and serious hemorrhage has occurred with Jaypirca. Major hemorrhage (Grade ≥3 bleeding or any central nervous system bleeding) occurred in 3% of patients, including gastrointestinal hemorrhage; fatal hemorrhage occurred (0.3%). Bleeding of any grade, excluding bruising and petechiae, occurred (17%). Major hemorrhage occurred in patients taking Jaypirca with (0.7%) and without (2.3%) antithrombotic agents. Consider risks/benefits of co-administering antithrombotic agents with Jaypirca. Monitor patients for signs of bleeding. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca. Consider benefit/risk of withholding Jaypirca 3-7 days pre- and post-surgery depending on type of surgery and bleeding risk.

Cytopenias: Jaypirca can cause cytopenias, including neutropenia, thrombocytopenia, and anemia. In a clinical trial, Grade 3 or 4 cytopenias, including decreased neutrophils (26%), decreased platelets (12%), and decreased hemoglobin (12%), developed in Jaypirca-treated patients. Grade 4 decreased neutrophils (14%) and Grade 4 decreased platelets (6%) developed. Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Cardiac Arrhythmias: Cardiac arrhythmias occurred in patients who received Jaypirca. In a clinical trial of patients with hematologic malignancies, atrial fibrillation or flutter were reported in 3.2% of Jaypirca-treated patients, with Grade 3 or 4 atrial fibrillation or flutter in 1.5%. Other serious cardiac arrhythmias such as supraventricular tachycardia and cardiac arrest occurred (0.5%). Patients with cardiac risk factors such as hypertension or previous arrhythmias may be at increased risk. Monitor for signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea) and manage appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

Second Primary Malignancies: Second primary malignancies, including non-skin carcinomas, developed in 9% of Jaypirca-treated patients. The most frequent malignancy was non-melanoma skin cancer (4.6%). Other second primary malignancies included solid tumors (including genitourinary and breast cancers) and melanoma. Advise patients to use sun protection and monitor for development of second primary malignancies.

Hepatotoxicity, Including Drug-Induced Liver Injury (DILI): Hepatotoxicity, including severe, life-threatening, and potentially fatal cases of DILI, has occurred in patients treated with BTK inhibitors, including Jaypirca. Evaluate bilirubin and transaminases at baseline and throughout Jaypirca treatment. For patients who develop abnormal liver tests after Jaypirca, monitor more frequently for liver test abnormalities and clinical signs and symptoms of hepatic toxicity. If DILI is suspected, withhold Jaypirca. Upon confirmation of DILI, discontinue Jaypirca.

Embryo-Fetal Toxicity: Jaypirca can cause fetal harm in pregnant women. Administration of pirtobrutinib to pregnant rats caused embryo-fetal toxicity, including embryo-fetal mortality and malformations at maternal exposures (AUC) approximately 3-times the recommended 200 mg/day dose. Advise pregnant women of potential fetal risk and females of reproductive potential to use effective contraception during treatment and for one week after last dose.

Adverse Reactions (ARs) in Patients Who Received Jaypirca

The most common (≥20%) ARs in the BRUIN pooled safety population of patients with hematologic malignancies (n=593) were decreased neutrophil count (46%), decreased hemoglobin (39%), fatigue (32%), decreased lymphocyte count (31%), musculoskeletal pain (30%), decreased platelet count (29%), diarrhea (24%), COVID-19 (22%), bruising (21%), cough (20%).

Mantle Cell Lymphoma

Serious ARs occurred in 38% of patients. Serious ARs occurring in ≥2% of patients were pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). **Fatal ARs** within 28 days of last Jaypirca dose occurred in 7% of patients, most commonly due to infections (4.7%), including COVID-19 (3.1% of all patients).

Dose Modifications and Discontinuations: ARs led to dose reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dosage modification in >5% of patients included pneumonia and neutropenia. ARs resulting in permanent discontinuation in >1% of patients included pneumonia.

Most common ARs (≥15%), excluding laboratory terms (all Grades %; Grade 3-4 %): fatigue (29; 1.6), musculoskeletal pain (27; 3.9), diarrhea (19; -), edema (18; 0.8), dyspnea (17; 2.3), pneumonia (16; 14), bruising (16; -).

Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in ≥10% of Patients: hemoglobin decreased (42; 9), platelet count decreased (39; 14), neutrophil count decreased (36; 16), lymphocyte count decreased (32; 15), creatinine increased (30; 1.6), calcium decreased (19; 1.6), AST increased (17; 1.6), potassium decreased (13; 1.6), sodium decreased (13; -), lipase increased (12; 4.4), alkaline phosphatase increased (11; -), ALT increased (11; 1.6), potassium increased (11; 0.8). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (10), platelets decreased (7), lymphocytes decreased (6).

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Serious ARs occurred in 56% of patients. Serious ARs occurring in ≥5% of patients were pneumonia (18%), COVID-19 (9%), sepsis (7%), and febrile neutropenia (7%). **Fatal ARs** within 28 days of last Jaypirca dose occurred in 11% of patients, most commonly due to infections (10%), including sepsis (5%) and COVID-19 (2.7%).

Dose Modifications and Discontinuations: ARs led to dose reductions in 3.6%, treatment interruption in 42%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dose reductions in >1% included neutropenia; treatment interruptions in >5% of patients included pneumonia, neutropenia, febrile neutropenia, and COVID-19; permanent discontinuation in >1% of patients included second primary malignancy, COVID-19, and sepsis.

Most common ARs (≥20%), excluding laboratory terms (all Grades %; Grade 3-4 %): fatigue (36; 2.7), bruising (36; -), cough (33; -), musculoskeletal pain (32; 0.9), COVID-19 (28; 7), pneumonia (27; 16), diarrhea (26; -), abdominal pain (25; 2.7), dyspnea (22; 2.7), hemorrhage (22; 2.7), edema (21; -), nausea (21; -), pyrexia (20; 2.7), headache (20; 0.9).

Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in ≥20% of Patients: neutrophil count decreased (63; 45), hemoglobin decreased (48; 19), calcium decreased (40; 2.8), platelet count decreased (30; 15), sodium decreased (30; -), lymphocyte count decreased (23; 8), ALT increased (23; 2.8), AST increased (23; 1.9), creatinine increased (23; -), lipase increased (21; 7), alkaline phosphatase increased (21; -). Grade 4 laboratory abnormalities in >5% of patients included neutrophils decreased (23).

Drug Interactions

Strong CYP3A Inhibitors: Concomitant use with Jaypirca increased pirtobrutinib systemic exposure, which may increase risk of Jaypirca ARs. Avoid use of strong CYP3A inhibitors with Jaypirca. If concomitant use is unavoidable, reduce Jaypirca dosage according to approved labeling.

Strong or Moderate CYP3A Inducers: Concomitant use with Jaypirca decreased pirtobrutinib systemic exposure, which may reduce Jaypirca efficacy. Avoid concomitant use of Jaypirca with strong or moderate CYP3A inducers. If concomitant use with moderate CYP3A inducers is unavoidable, increase Jaypirca dosage according to approved labeling.

Sensitive CYP2C8, CYP2C19, CYP3A, P-gp, or BCRP Substrates: Concomitant use with Jaypirca increased their plasma concentrations, which may increase risk of adverse reactions related to these substrates for drugs that are sensitive to minimal concentration changes. Follow recommendations for these sensitive substrates in their approved labeling.

Use in Special Populations

Pregnancy and Lactation: Due to potential for Jaypirca to cause fetal harm, verify pregnancy status in females of reproductive potential prior to starting Jaypirca and advise use of effective contraception during treatment and for one week after last dose. Presence of pirtobrutinib in human milk is unknown. Advise women not to breastfeed while taking Jaypirca and for one week after last dose.

Geriatric Use: In the pooled safety population of patients with hematologic malignancies, patients aged ≥65 years experienced higher rates of Grade ≥3 ARs and serious ARs compared to patients <65 years of age.

Renal Impairment: Severe renal impairment increases pirtobrutinib exposure. Reduce Jaypirca dosage in patients with severe renal impairment according to approved labeling.

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Please see Prescribing Information and Patient Information for Jaypirca.

About Lilly
Lilly is a medicine company turning science into healing to make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help tens of millions of people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges: redefining diabetes care; treating obesity and curtailing its most devastating long-term effects; advancing the fight against Alzheimer's disease; providing solutions to some of the most debilitating immune system disorders; and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit Lilly.com and Lilly.com/news, or follow us on Facebook, Instagram, and LinkedIn. P-LLY

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Cautionary Statement Regarding Forward-Looking Statements
This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Jaypirca (pirtobrutinib), as a potential treatment for adults with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have been previously treated with a BTK inhibitor and as a treatment for adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor and the timeline for future readouts, presentations, and other milestones relating to Jaypirca and its clinical trials, and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, that Jaypirca will receive regulatory approval, or that Lilly will execute its strategy as expected. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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