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New IMBRUVICA® (ibrutinib) Data in Fixed-Duration Combination Regimen Presented at EHA 2022 Shows Deep, Durable Response at Three Years in Untreated Chronic Lymphocytic Leukemia

The all-oral, once-daily combination regimen also demonstrates the potential of immune restoration in this patient population

June 10, 2022 (VIENNA) – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced new and updated results from the Phase 2 CAPTIVATE study evaluating IMBRUVICA® (ibrutinib) in combination with venetoclax (I+V) as a potential fixed-duration (FD) treatment in adult patients with previously untreated chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). Updated data from the FD cohort with three years of follow-up shows that I+V continues to demonstrate deep and durable responses and clinically meaningful progression-free survival (PFS) and overall survival (OS) in the first-line treatment setting. New data will be presented from the minimal residual disease (MRD) cohort, which suggests immune restoration with this combination. These data will be presented during the 2022 European Hematology Association (EHA) Annual Congress taking place in Vienna, Austria June 9-12 (Abstracts #S144 and #P669).

"These promising data highlight the complementary mechanism of action between ibrutinib and venetoclax in a fixed-duration combination regimen," said Carol Moreno, M.D., Ph.D., Consultant Hematologist, Hospital de la Santa Creu Sant Pau, Autonomous University of Barcelona, Barcelona, Spain, and study investigator.† "The CAPTIVATE study suggests that this combination may have the potential to provide treatment-free remissions for patients

and effectively eradicate CLL cells and help to restore normal B cells to healthy donor levels in patients with previously untreated CLL/SLL."

The Phase 2 CAPTIVATE (PCYC-1142) study (NCT02910583) – sponsored by Pharmacyclics LLC, an AbbVie Company, and Janssen Biotech, Inc. – enrolled 323 patients with previously untreated CLL/SLL who were younger than 70 years, including patients with high-risk disease, in two cohorts: an FD cohort where all patients stopped therapy after 12 cycles of the combination, regardless of MRD status; and an MRD-guided cohort where treatment duration was guided by the patients' MRD status after 12 cycles of I+V combination (patients who met criteria for confirmed undetectable minimal residual disease [uMRD] were randomized 1:1 to placebo or IMBRUVICA®; patients who did not meet uMRD criteria were randomized to IMBRUVICA® or I+V).[1,2]

Three-Year Follow-Up Data from the FD Cohort of the Phase 2 CAPTIVATE (PCYC-1142) Study of IMBRUVICA®-Based Combination Regimen in Previously Untreated Patients with CLL/SLL (Abstract #P669)[1]

After an additional year of follow-up data from the FD cohort of CAPTIVATE, I+V continues to demonstrate deep, durable responses and clinically meaningful PFS, including in patients with del(17p)/*TP53* mutated or unmutated immunoglobulin heavy chain gene (IGHV).[1] The clinical data underscore the distinct and complementary modes of action of IMBRUVICA® and venetoclax (a BCL-2 inhibitor).[1] IMBRUVICA® has been shown to mobilize CLL cells out of lymph nodes and other lymphoid niches and into peripheral blood where they are more susceptible to venetoclax-induced apoptosis, eliminating dividing and resting CLL cells.[1]

Key findings from the Phase 2 CAPTIVATE FD cohort study include:

- At a median follow-up of 38.7 months, the 36-month PFS rate was 88 percent for all treated patients, 80 percent for patients with del(17p)/*TP53* mutated and 86 percent for unmutated IGHV patients (95 percent Confidence Interval [CI]).[1]
- With an additional year of follow-up, no additional OS events occurred. The 36-month OS rate was 98 percent, overall (95 percent CI).[1]
    - The 36-month OS rates were similar in patients with del(17p)/*TP53* mutated (96 percent) or unmutated IGHV (97 percent).[1]
- The complete response (CR) rate was 57 percent (n=159; 95 percent CI, 50-65) and consistent across high-risk subgroups.[1]

- Median duration of CR was not reached (n=91); the 24-month landmark estimate for duration of CR was 94 percent. Median duration of response was not reached for responding patients (n=153).[1]
- Seventy-nine percent of patients (n=125) achieved undetectable uMRD at any time in the peripheral blood (PB) and/or bone marrow.[1]
- Of patients with uMRD in PB at three months posttreatment, 78 percent (66/85) of evaluable patients maintained uMRD through 12 months posttreatment.[1]
- All patients are currently off treatment.[1] Frequently occurring treatment-emergent adverse events (TEAEs) (period from first dose until 30 days after the last dose of study treatment) were primarily Grade 1/2 in severity with the exception of neutropenia.[1] Median time to onset of frequently occurring TEAEs generally occurred within four months (87-100 percent).[1] The median time to resolution or improvement ranged from 16.5 days (diarrhea) to 42.5 days (arthralgia).[1] No new serious adverse events or secondary malignancies have been reported since the primary analysis.[1]
- Twelve patients who progressed after FD treatment with I+V have been retreated with single-agent IMBRUVICA®; 11 of the 12 patients were evaluable for response, with 10 responding.[1]

New Data from the MRD-Guided Cohort of the Phase 2 CAPTIVATE (PCYC-1142) Study of IMBRUVICA®-Based Combination Regimen Evaluating Immune Restoration in Previously Untreated Patients with CLL/SLL (Abstract #S144)[2]

Data on the changes over time in the cellular immune profile in patients with CLL/SLL treated with the I+V combination and age-matched healthy donors were featured in an oral presentation at EHA. The FD regimen of I+V in the confirmed uMRD placebo arm effectively eradicated CLL cells to healthy donor levels and enabled sustained regeneration of normal B cell counts.[2]

Immune restoration was evaluated in 79 previously untreated patients with CLL/SLL enrolled in the MRD cohort by monitoring changes over time in the cellular immune profile of patients treated with I+V combination regimen and compared to 20 age-matched healthy donors.[2]

Key findings from this analysis include:

- Patients with confirmed uMRD (n=40) had a significantly more pronounced decrease in circulating CLL cell count than patients with uMRD not confirmed (n=39).[2]

    - At Cycles seven and 16 the p-value was <0.0001 with I+V combination therapy.[2]
- From Cycle 16 – 29, patients with Confirmed uMRD (n=40) had cell counts similar to those of healthy donors (≤0.8 cell/μL).[2]
- Normalization of critical immune cells, including T-cell subsets, classical monocytes, and dendritic cell counts was observed in this population.[2]

"These new clinical and immune results from the CAPTIVATE study add further evidence of the promise of IMBRUVICA in a fixed-duration regimen for previously untreated CLL patients," said Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Janssen Research & Development, LLC. "IMBRUVICA has become a standard of care in CLL treatment, and we continue to explore novel combinations such as I+V which may offer the option of off-treatment, disease-free intervals for patients with B-cell malignancies."

The CAPTIVATE study is part of a comprehensive development program exploring the potential of IMBRUVICA®-based FD therapy. Janssen continues to evaluate the I+V combination regimen and its potential to provide a FD treatment option for patients living with CLL/SLL. Recently, *The New England Journal of Medicine Evidence* published the primary analysis from the Phase 3 GLOW study, which evaluated the safety and efficacy of the I+V combination in older or unfit patients with CLL/SLL, and showed that the combination demonstrated superior PFS and deeper sustained responses compared to chemoimmunotherapy in first-line CLL.[3]

About IMBRUVICA®

IMBRUVICA® (ibrutinib) is a once-daily oral medication that is jointly developed and commercialized by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company. IMBRUVICA® blocks the Bruton's tyrosine kinase (BTK) protein, which is needed by normal and abnormal B cells, including specific cancer cells, to multiply and spread. By blocking BTK, IMBRUVICA® may help move abnormal B cells out of their nourishing environments and inhibits their proliferation.[4,5,6]

IMBRUVICA® is approved in more than 100 countries and has been used to treat more than 250,000 patients worldwide. There are more than 50 company-sponsored clinical trials, including 18 Phase 3 studies, over 11 years evaluating the efficacy and safety of IMBRUVICA®.

IMBRUVICA® was first approved by the U.S. Food and Drug Administration (FDA) in November 2013, and today is indicated for adult patients in six disease areas, including five hematologic cancers. These include indications to treat adults with CLL/SLL with or without 17p deletion (del17p), and adults with Waldenström's macroglobulinemia (WM), and adult patients with previously treated mantle cell lymphoma (MCL)*, as well as to treat adult patients with previously treated marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy*, and adult patients with previously treated chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.[7]

**Accelerated approval was granted for MCL and MZL based on overall response rate. Continued approval for MCL and MZL may be contingent upon verification and description of clinical benefit in confirmatory trials.*

Since 2019, the National Comprehensive Cancer Network® (NCCN®), recommends ibrutinib (IMBRUVICA®) as a preferred regimen for the initial treatment of CLL/SLL and has Category 1 treatment status for treatment-naïve patients without deletion 17p/*TP53* mutation and as a preferred treatment for treatment-naïve patients with deletion 17p/*TP53* mutation. The NCCN Guidelines® also recommend IMBRUVICA®, with or without rituximab, as a preferred regimen for the treatment of relapsed/refractory MCL, as a Category 1 preferred regimen for both untreated and previously treated WM patients, and as a preferred regimen for relapsed/refractory MZL.[8]

For more information, visit www.IMBRUVICA.com.

IMBRUVICA® IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients who received IMBRUVICA®. Major hemorrhage (≥ Grade 3, serious, or any central nervous system events; e.g., intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) occurred in 4.2% of patients, with fatalities occurring in 0.4% of 2,838 patients who received IMBRUVICA® in 27 clinical trials. Bleeding

events of any grade including bruising and petechiae occurred in 39%, and excluding bruising and petechiae occurred in 23% of patients who received IMBRUVICA®, respectively.

The mechanism for the bleeding events is not well understood.

Use of either anticoagulant or antiplatelet agents concomitantly with IMBRUVICA® increases the risk of major hemorrhage. Across clinical trials, 3.1% of 2,838 patients who received IMBRUVICA® without antiplatelet or anticoagulant therapy experienced major hemorrhage. The addition of antiplatelet therapy with or without anticoagulant therapy increased this percentage to 4.4%, and the addition of anticoagulant therapy with or without antiplatelet therapy increased this percentage to 6.1%. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with IMBRUVICA®. Monitor for signs and symptoms of bleeding.

Consider the benefit-risk of withholding IMBRUVICA® for at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections: Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with IMBRUVICA® therapy. Grade 3 or greater infections occurred in 21% of 1,476 patients who received IMBRUVICA® in clinical trials. Cases of progressive multifocal leukoencephalopathy (PML) and *Pneumocystis jirovecii* pneumonia (PJP) have occurred in patients treated with IMBRUVICA®. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections. Monitor and evaluate patients for fever and infections and treat appropriately.

Cardiac Arrhythmias, Cardiac Failure and Sudden Death: Fatal and serious cardiac arrhythmias and cardiac failure have occurred with IMBRUVICA®. Deaths due to cardiac causes or sudden deaths occurred in 1% of 4,896 patients who received IMBRUVICA® in clinical trials, including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These adverse reactions occurred in patients with and without preexisting hypertension or cardiac comorbidities. Patients with cardiac comorbidities may be at greater risk of these events.

Grade 3 or greater ventricular tachyarrhythmias were reported in 0.2%, Grade 3 or greater atrial fibrillation and atrial flutter were reported in 3.7%, and Grade 3 or greater cardiac failure was reported in 1.3% of 4,896 patients who received IMBRUVICA® in clinical trials,

including in patients who received IMBRUVICA® in unapproved monotherapy or combination regimens. These events have occurred particularly in patients with cardiac risk factors including hypertension and diabetes mellitus, a previous history of cardiac arrhythmias, and in patients with acute infections.

Evaluate cardiac history and function at baseline, and monitor patients for cardiac arrhythmias and cardiac function. Obtain further evaluation (e.g., ECG, echocardiogram) as indicated for patients who develop symptoms of arrhythmia (e.g., palpitations, lightheadedness, syncope, chest pain), new onset dyspnea, or other cardiovascular concerns. Manage cardiac arrhythmias and cardiac failure appropriately, follow dose modification guidelines, and consider the risks and benefits of continued IMBRUVICA® treatment.

Hypertension: Hypertension occurred in 19% of 1,476 patients who received IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 8% of patients. Based on data from 1,124 of these patients, the median time to onset was 5.9 months (range, 0.03 to 24 months). Monitor blood pressure in patients treated with IMBRUVICA®, initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate, and follow dosage modification guidelines for Grade 3 or higher hypertension.

Cytopenias: In 645 patients with B-cell malignancies who received IMBRUVICA® as a single agent, grade 3 or 4 neutropenia occurred in 23% of patients, grade 3 or 4 thrombocytopenia in 8% and grade 3 or 4 anemia in 2.8%, based on laboratory measurements. Monitor complete blood counts monthly.

Second Primary Malignancies: Other malignancies (10%), including non-skin carcinomas (3.9%), occurred among the 1,476 patients who received IMBRUVICA® in clinical trials. The most frequent second primary malignancy was non-melanoma skin cancer (6%).

Tumor Lysis Syndrome: Tumor lysis syndrome has been infrequently reported with IMBRUVICA®. Assess the baseline risk (e.g., high tumor burden) and take appropriate precautions. Monitor patients closely and treat as appropriate.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA® 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 contraception during

treatment with IMBRUVICA® and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥30%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (54.5%)*, diarrhea (43.8%), fatigue (39.1%), musculoskeletal pain (38.8%), neutropenia (38.6%)*, rash (35.8%), anemia (35.0%)*, and bruising (32.0%).

The most common Grade ≥ 3 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (20.7%)*, thrombocytopenia (13.6%)*, pneumonia (8.2%), and hypertension (8.0%).

Approximately 9% (CLL/SLL), 14% (MCL), 14% (WM) and 10% (MZL) of patients had a dose reduction due to adverse reactions. Approximately 4-10% (CLL/SLL), 9% (MCL), and 7% (WM [5%] and MZL [13%]) of patients discontinued due to adverse reactions.

cGVHD: The most common adverse reactions (≥20%) in patients with cGVHD were fatigue (57%), bruising (40%), diarrhea (36%), thrombocytopenia (33%)*, muscle spasms (29%), stomatitis (29%), nausea (26%), hemorrhage (26%), anemia (24%)*, and pneumonia (21%).

The most common Grade 3 or higher adverse reactions (≥5%) reported in patients with cGVHD were pneumonia (14%), fatigue (12%), diarrhea (10%), neutropenia (10%)*, sepsis (10%), hypokalemia (7%), headache (5%), musculoskeletal pain (5%), and pyrexia (5%).

Twenty-four percent of patients receiving IMBRUVICA® in the cGVHD trial discontinued treatment due to adverse reactions. Adverse reactions leading to dose reduction occurred in 26% of patients.

*Treatment-emergent decreases (all grades) were based on laboratory measurements.

DRUG INTERACTIONS

CYP3A Inhibitors: Co-administration of IMBRUVICA® with strong or moderate CYP3A inhibitors may increase ibrutinib plasma concentrations. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of IMBRUVICA® are recommended when used concomitantly with posaconazole, voriconazole, and moderate CYP3A inhibitors. Avoid concomitant use of other strong CYP3A inhibitors. Interrupt IMBRUVICA® if strong inhibitors are used short-term (e.g., for ≤ 7 days). Avoid grapefruit and Seville oranges during IMBRUVICA® treatment, as these contain strong or moderate inhibitors of CYP3A. See dose modification guidelines in USPI sections 2.3 and 7.1.

CYP3A Inducers: Avoid coadministration with strong CYP3A inducers.

SPECIFIC POPULATIONS

Hepatic Impairment (based on Child-Pugh criteria): Avoid use of IMBRUVICA® in patients with severe hepatic impairment. In patients with mild or moderate impairment, reduce recommended IMBRUVICA® dose and monitor more frequently for adverse reactions of IMBRUVICA®.

Please click here to see the full Prescribing Information.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular, Metabolism, & Retina; Immunology; Infectious Diseases & Vaccines; Neuroscience; Oncology; and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at @JanssenGlobal and @JanssenUS. Janssen Research & Development, LLC and Janssen Biotech, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

[†]Dr. Moreno has served as a paid consultant to Janssen; she has not been paid for any media work.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding product development and the potential benefits and treatment impact of IMBRUVICA® (ibrutinib). The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC or any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 2, 2022, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in Johnson & Johnson's subsequent Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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[2] Soloman I., et al. Immune Restoration and Synergistic Activity With First-Line Ibrutinib Plus Venetoclax: Translational Analyses of CAPTIVATE Patients with CLL. 2022 European Hematology Association Annual Congress. June 9-12, 2022.

[3] Kater, A., et al. Fixed-Duration Ibrutinib-Venetoclax in Patients with Chronic Lymphocytic Leukemia and Comorbidities. *NEJM Evidence.* 2022. Accessed June 2022 https://doi.org/10.1056/evidoa2200006

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