Media Inquiries:
Bernadette King
Phone: 1-215-778-3027

Satu Glawe
Phone: +49-172-294-6264

Investor Relations:
Christopher DelOrefice
Phone: 1-732-524-2955

Lesley Fishman
Phone: 1-732-524-3922

U.S. Medical Inquiries:
Pharmacyclics Medical Information: 1-877-877-3536

IMBRUVICA® (ibrutinib) Long-Term Data from Two Pivotal Phase 3 Studies at ASCO and EHA Demonstrate Sustained Efficacy and Safety in Patients with Chronic Lymphocytic Leukemia (CLL)

With up to six years of follow-up, results from the RESONATE™ study showed patients with previously treated CLL receiving IMBRUVICA monotherapy sustained progression-free survival and overall survival benefits versus ofatumumab

Five-year follow-up data from the RESONATE-2 study showed sustained progression-free survival benefit in patients with previously untreated CLL receiving IMBRUVICA monotherapy versus chlorambucil, with an estimated overall survival rate of 83 percent reported in patients treated with IMBRUVICA

These results add to the robust data supporting IMBRUVICA, a BTK inhibitor with 10 FDA approvals and more than 140,000 patients treated worldwide; IMBRUVICA is the most comprehensively studied BTK inhibitor in CLL

CHICAGO and AMSTERDAM, June 3, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced long-term follow-up results from two pivotal Phase 3 studies of IMBRUVICA® (ibrutinib) in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), a type of non-Hodgkin lymphoma and the most common form of leukemia in adults.[1] One set of data – results from the RESONATE™ study (PCYC-1112) at a median follow-up of 65.3 months – showed treatment with IMBRUVICA

monotherapy sustained progression-free survival (PFS) benefit compared to ofatumumab in patients with previously treated CLL/SLL, with a median PFS of 44.1 months versus 8.1 months, respectively. A consistent PFS benefit with IMBRUVICA was observed across all baseline disease and patient characteristics, including patients with genomic high-risk disease. The median overall survival (OS) was 67.7 months in the IMBRUVICA arm and 65.1 months in the ofatumumab arm, without censoring or adjustment for crossover from ofatumumab to IMBRUVICA. Additionally, no new safety events were identified in this long-term follow-up. The RESONATE results were presented today at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting and selected for the Best of ASCO 2019 Meetings, which highlight cutting-edge science and reflect leading research in oncology (abstract #7510).

The second data set – results from the RESONATE-2 study (PCYC-1115/1116) at a median follow-up of five years – demonstrated durable PFS with IMBRUVICA monotherapy (estimate of 70 percent) versus chlorambucil (estimate of 12 percent) in patients with previously untreated CLL/SLL, including those with genomic high-risk disease. The OS benefit was also sustained in patients treated with IMBRUVICA (estimate of 83 percent) versus chlorambucil (estimate of 68 percent). In addition, no new safety concerns were observed. The RESONATE-2 data will be presented in full during an oral presentation at the 24th European Hematology Association (EHA) Congress in Amsterdam on Friday, June 14 (abstract #S107).

"The follow-up results from the RESONATE and RESONATE-2 studies provide clinicians even more evidence that patients with CLL/SLL across all treatment lines can achieve long-term disease control with IMBRUVICA monotherapy," said Paul M. Barr, M.D., study investigator of the Phase 3 RESONATE and RESONATE-2 trials, and Associate Professor, Director of Medicine, Hematology/Oncology at the Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, New York. "In the RESONATE-2 study, seven of 10 patients with previously untreated CLL who received IMBRUVICA monotherapy were alive and progression-free with five years of follow-up. This is welcome news for people living with CLL."

"The RESONATE and RESONATE-2 pivotal Phase 3 studies served as the basis for FDA approvals of IMBRUVICA monotherapy in CLL. Based on more than five years of follow-up, these studies demonstrate the positive outcomes that many patients have achieved with

IMBRUVICA, including most importantly, extending overall survival," said Craig Tendler, M.D., Vice President, Clinical Development and Global Medical Affairs, Oncology, Janssen Research & Development, LLC. "With the breadth of studies in CLL and broadly B-cell malignancies, IMBRUVICA has become an important, non-chemotherapy treatment option for patients with CLL across all stages of their disease. This is reflected in the National Comprehensive Cancer Network® Guidelines, recommending IMBRUVICA as a preferred regimen for the initial treatment of CLL."

IMBRUVICA, a BTK inhibitor, is jointly developed and commercialized by Janssen Biotech, Inc., and Pharmacyclics LLC, an AbbVie company.

ASCO: RESONATE six-year follow-up of IMBRUVICA monotherapy in patients with previously treated CLL/SLL (abstract #7510)

The RESONATE (PCYC-1112) study evaluated patients with previously treated CLL/SLL who were randomized to receive IMBRUVICA 420 mg orally once daily until disease progression or intravenous ofatumumab for up to 24 weeks (n=391); 86 percent and 79 percent, respectively, were in the genomic high-risk population (17p deletion, 11q deletion, TP53 mutation, and/or unmutated IGHV). Long-term efficacy endpoints were investigator-assessed.

With up to six years of follow-up (median 65.3 months, range, 0.3-71.6 months), extended IMBRUVICA treatment showed sustained efficacy in patients with previously treated CLL, including patients with high-risk genomic features, with no new safety signals over long-term therapy.

Of the patients receiving ofatumumab, 68 percent crossed over to receive IMBRUVICA. A statistically significant PFS benefit was sustained with IMBRUVICA versus ofatumumab, with median PFS of 44.1 months versus 8.1 months (hazard ratio [HR]=0.15; 95 percent confidence interval [CI], 0.11-0.20, P<0.0001), and was consistent across baseline subgroups. Median PFS in the genomic high-risk population was 44.1 months versus 8.0 months on IMBRUVICA versus ofatumumab (HR=0.11; 95 percent CI, 0.08-0.15).

The median OS was 67.7 months in the IMBRUVICA arm and 65.1 months in the ofatumumab arm, without censoring or adjustment for crossover from ofatumumab to

IMBRUVICA (HR=0.81; 95 percent CI, 0.60-1.09). Sensitivity analysis adjusting for crossover based on the rank-preserving structural failure time (RPSFT) method also showed continued OS benefit with IMBRUVICA compared with ofatumumab (HR=0.24; 95 percent CI, 0.11-0.55). The overall response rate (ORR) with IMBRUVICA was 91 percent, with 11 percent achieving a complete response (CR)/CR with incomplete blood recovery (CRi). Median treatment duration of IMBRUVICA was 41 months; 40 percent of patients received IMBRUVICA for longer than four years.

The adverse event (AE) profile with IMBRUVICA remained consistent with prior studies. The prevalence of any Grade 3 or higher AEs with IMBRUVICA decreased after the first year and remained stable thereafter. All-Grade and Grade 3 or higher AEs, respectively, included hypertension (21 percent; 9 percent) and atrial fibrillation (12 percent; 6 percent); major hemorrhage occurred in 10 percent. The most common reasons for IMBRUVICA discontinuation prior to study closure were progressive disease (37 percent) and AEs (16 percent).

EHA: RESONATE-2 five-year follow-up of IMBRUVICA monotherapy in patients with previously untreated CLL/SLL (abstract #S107)

The RESONATE-2 (PCYC-1115/1116) study evaluated patients 65 years or over with previously untreated CLL/SLL, without 17p deletion, who received IMBRUVICA 420 mg orally once daily continuously until disease progression or unacceptable toxicity, or chlorambucil 0.5-0.8 mg/kg orally for up to 12 cycles (n=269).

Results from this five-year follow-up showed IMBRUVICA monotherapy sustained PFS and OS benefits for patients with CLL/SLL versus chlorambucil, including those with high-risk genomic features. More than half of patients remain on long-term continuous treatment with IMBRUVICA. Additionally, no new safety concerns were identified.

At 60 months (range, 0.1-66 months) of follow-up, the PFS benefits were sustained in patients treated with IMBRUVICA (estimate of 70 percent) versus chlorambucil (estimate of 12 percent) (HR=0.15; 95 percent CI, 0.10-0.22). The OS benefits were also sustained in patients treated with IMBRUVICA (estimate of 83 percent) versus chlorambucil (estimate of 68 percent). IMBRUVICA improved PFS compared with chlorambucil in patients with unmutated IGHV (HR=0.11; 95 percent CI, 0.06-0.19) and in patients with 11q deletion

(HR=0.03; 95 percent CI, 0.01-0.11). Additionally, 57 percent of patients crossed over from chlorambucil to IMBRUVICA after progression.

As a composite, patients with high-risk genomics (unmutated IGHV, 11q deletion, and/or TP53 mutation) had superior outcomes with IMBRUVICA compared with chlorambucil (PFS: HR=0.08; 95 percent CI, 0.05-0.15; OS: HR=0.37; 95 percent CI, 0.18-0.74). With IMBRUVICA, the ORR including partial response with lymphocytosis was 92 percent and the CR/CRi rate increased over time to 30 percent (increased from 11 percent CR/CRi at primary analysis at median follow-up of 18 months).

The most common Grade 3 or higher AEs included neutropenia (13 percent), pneumonia (12 percent), hypertension (8 percent), anemia (7 percent), hyponatremia (6 percent), atrial fibrillation (5 percent) and cataract (5 percent), with rates of most events decreasing over time. Dose reductions due to Grade 3 or higher AEs decreased over time. Benefit with IMBRUVICA treatment continued in 58 percent of patients who remained on therapy at the time of this analysis.

About IMBRUVICA

IMBRUVICA® (ibrutinib) is a once-daily oral medicine that works differently than chemotherapy as it blocks the Bruton's tyrosine kinase (BTK) protein. The BTK protein sends important signals that tell B cells to mature and produce antibodies. BTK signaling is needed by specific cancer cells to multiply and spread.[2,3] By blocking BTK, IMBRUVICA may help move abnormal B cells out of their nourishing environments in the lymph nodes, bone marrow, and other organs.[4]

IMBRUVICA is approved in more than 95 countries, and, to date, has been used to treat more than 140,000 patients worldwide across approved indications. It was first approved by the U.S. Food and Drug Administration (FDA) in November 2013, and today is indicated in six disease areas, including five hematologic cancers – chronic lymphocytic leukemia (CLL) with or without 17p deletion (del17p), small lymphocytic lymphoma (SLL) with or without del17p, Waldenström's macroglobulinemia (WM), previously-treated patients with mantle cell lymphoma (MCL)*, previously-treated patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy* – and previously-treated patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.[5]

** 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.*

As of early 2019, the National Comprehensive Cancer Network® (NCCN®), a not-for-profit alliance of 28 leading cancer centers devoted to patient care, research, and education, recommends ibrutinib (IMBRUVICA®) as a preferred regimen for the initial treatment of CLL/SLL and it is the only Category 1 single-agent regimen for patients without deletion 17p. IMBRUVICA is the only FDA-approved medicine in WM and cGVHD. IMBRUVICA has been granted four Breakthrough Therapy Designations by the FDA, and it was one of the first medicines to receive U.S. approval with the Breakthrough Therapy Designation.

IMBRUVICA is a comprehensively studied molecule, with more than 150 active clinical trials studying IMBRUVICA alone and in combination with other medicines in several blood cancers and other serious diseases. For more information, visit www.IMBRUVICA.com.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hemorrhage: Fatal bleeding events have occurred in patients treated with IMBRUVICA®. Grade 3 or higher bleeding events (intracranial hemorrhage [including subdural hematoma], gastrointestinal bleeding, hematuria, and post procedural hemorrhage) have occurred in 3% of patients, with fatalities occurring in 0.3% of 1,124 patients exposed to IMBRUVICA® in clinical trials. Bleeding events of any Grade, including bruising and petechiae, occurred in 44% of patients treated with IMBRUVICA®.

The mechanism for the bleeding events is not well understood.

IMBRUVICA® may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs 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 24% of 1,124 patients exposed to 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.

Cytopenias: Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (23%), thrombocytopenia (8%), and anemia (3%) based on laboratory measurements occurred in patients with B-cell malignancies treated with single agent IMBRUVICA®.

Monitor complete blood counts monthly.

Cardiac Arrhythmias: Fatal and serious cardiac arrhythmias have occurred with IMBRUVICA® therapy. Grade 3 or greater ventricular tachyarrhythmias occurred in 0.2% of patients, and Grade 3 or greater atrial fibrillation and atrial flutter occurred in 4% of 1,124 patients exposed to IMBRUVICA® in clinical trials. These events have occurred particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Periodically monitor patients clinically for cardiac arrhythmias. Obtain an ECG for patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Manage cardiac arrhythmias appropriately, and if it persists, consider the risks and benefits of IMBRUVICA® treatment and follow dose modification guidelines**.**

Hypertension: Hypertension of any Grade occurred in 12% of 1,124 patients treated with IMBRUVICA® in clinical trials. Grade 3 or greater hypertension occurred in 5% of patients with a median time to onset of 5.9 months (range, 0.03 to 24 months).

Monitor blood pressure in patients treated with IMBRUVICA® and initiate or adjust anti-hypertensive medication throughout treatment with IMBRUVICA® as appropriate.

Second Primary Malignancies: Other malignancies (10%) including non-skin carcinomas (4%) have occurred in 1,124 patients treated with 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® therapy. 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 women to avoid becoming pregnant while taking IMBRUVICA® and for 1 month after cessation of therapy. 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. Advise men to avoid fathering a child during the same time period.

ADVERSE REACTIONS

B-cell malignancies: The most common adverse reactions (≥20%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were thrombocytopenia (58%)*, diarrhea (41%), anemia (38%)*, neutropenia (35%)*, musculoskeletal pain (32%), rash (32%), bruising (31%), nausea (26%), fatigue (26%), hemorrhage (24%), and pyrexia (20%).

The most common Grade 3 or 4 adverse reactions (≥5%) in patients with B-cell malignancies (MCL, CLL/SLL, WM and MZL) were neutropenia (18%)*, thrombocytopenia (16%)*, and pneumonia (14%).

Approximately 7% (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: Modify IMBRUVICA® dose as described in USPI sections 2.4 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 baseline hepatic impairment. In patients with mild or moderate impairment, reduce IMBRUVICA® dose.

Please click here for 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, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

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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 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, 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 December 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent 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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[1] American Cancer Society. What Is Chronic Lymphocytic Leukemia? https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/what-is-cll.html. Accessed May 2019.

[2] Genetics Home Reference. Isolated growth hormone deficiency. http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency. Accessed May 2019.

[3] Turetsky, A, et al. Single cell imaging of Bruton's Tyrosine Kinase using an irreversible inhibitor. Scientific Reports. volume 4, Article number: 4782 (2014).
[4] de Rooij MF, Kuil A, Geest CR, et al. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. *Blood*. 2012;119(11):2590-2594.
[5] IMBRUVICA U.S. Prescribing Information, January 2019.