NEWS RELEASE

# Additional Efficacy and Safety Data for IMBRUVICA® (Ibrutinib) Submitted to FDA

11/13/2015

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HORSHAM, PA, November 13, 2015 - Janssen Biotech, Inc. announced a supplemental New Drug Application (sNDA) for IMBRUVICA® (ibrutinib) has been submitted to the U.S. Food and Drug Administration (FDA), based on results from the Phase 3 HELIOS (CLL3001) trial evaluating IMBRUVICA® (ibrutinib) plus bendamustine and rituximab (BR) versus placebo plus BR in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

IMBRUVICA is jointly developed and commercialized by Janssen and Pharmacyclics LLC, an AbbVie company. Pharmacyclics is the investigational new drug (IND) holder for IMBRUVICA in the U.S. and submitted the application to the FDA on behalf of the companies. Janssen sponsored this study.

"The Phase 3 HELIOS study provides further efficacy and safety evidence around the potential of IMBRUVICA in combination with BR as an effective and tolerable treatment option within the existing previously treated chronic lymphocytic leukemia treatment landscape: suitable both as a monotherapy, for which it's already approved, and also as a complement to standard chemotherapies for relapsed/refractory CLL patients," said Simon Rule, M.D., Consultant Haematologist, Department of Haematology, and Head of the Lymphoma Service, Derriford Hospital, Plymouth, UK, and HELIOS study investigator.

The interim data were presented and included in the official press program at the American Society of Clinical Oncology (ASCO) Annual Meeting in **June 2015** and showed the combination of ibrutinib+BR significantly reduced the risk of progression or death by 80% (HR=0.203, 95% CI: 0.150-0.276, P< 0.0001) and also significantly improved overall response rate (ORR) in previously treated CLL/SLL patients compared to placebo+BR. The Independent

Review Committee (IRC)-assessed ORR and complete response/complete response with incomplete marrow recovery (CR/CRi) rates were 82.7% and 10.4%, respectively, for patients taking ibrutinib+BR versus 67.8% and 2.8% for people in the placebo+BR arm. At a pre-planned interim analysis **earlier this year**, an Independent Data Monitoring Committee (IDMC) recommended HELIOS be unblinded at that point and patients receiving placebo+BR be offered the option to receive ibrutinib as their next treatment once their CLL or SLL worsened.

"We are committed to a comprehensive and robust development program of IMBRUVICA to fully understand its safety and efficacy profile, alone and as a combination treatment, across a variety of hematologic malignancies," said Sen Zhuang, M.D., Ph.D., Vice President, Clinical Research, Janssen Oncology.

HELIOS is a randomized, double-blind, placebo-controlled, international, multicenter Phase 3 study conducted in 21 countries, which evaluated the safety and efficacy of ibrutinib in combination with BR in 578 patients with relapsed or refractory CLL/SLL who had received at least one prior therapy. Patients were randomized to receive ibrutinib orally once daily and six cycles of BR, with ibrutinib or placebo continued until disease progression or unacceptable toxicity. The primary endpoint was IRC-assessed progression free survival (PFS) and key secondary endpoints included ORR per IRC, overall survival (OS), rate of minimal residual disease negative remissions (MRD- remissions) and safety. More information about the study can be found on **www.clinicaltrials.gov**.

Janssen Research & Development, LLC and Pharmacyclics LLC are continuing an extensive clinical development program for IMBRUVICA, including numerous Phase 3 studies in a variety of patient populations.

## About CLL/SLL

CLL is a slow-growing blood cancer that most commonly arises from B cells, a type of white blood cell (lymphocyte) that originates in the bone marrow.[1,2] CLL is predominantly a disease of the elderly, with a median age of 71 at diagnosis.[3] SLL is a slow-growing lymphoma biologically similar to CLL in which too many immature white blood cells cause lymph nodes to become larger than normal.[4] IMBRUVICA is not approved to treat SLL.

## About IMBRUVICA® (ibrutinib)

IMBRUVICA was one of the first therapies to receive U.S. approval after having received the FDA's Breakthrough Therapy Designation.[5] IMBRUVICA works by blocking a specific protein called Bruton's tyrosine kinase (BTK).[5] The BTK protein transmits important signals that tell B cells to mature and produce antibodies and is needed by specific cancer cells to multiply and spread.[5,6] IMBRUVICA targets and blocks BTK, inhibiting cancer cell survival and spread.[5] For more information, visit **www.IMBRUVICA.com**.

## Additional Information about IMBRUVICA®

### INDICATIONS

IMBRUVICA is indicated to treat people with:

- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy
- Chronic lymphocytic leukemia (CLL) with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Mantle cell lymphoma (MCL) who have received at least one prior therapy
    - Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

## IMPORTANT SAFETY INFORMATION

## WARNINGS AND PRECAUTIONS

Hemorrhage - Fatal bleeding events have occurred in patients treated with IMBRUVICA . Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural hemorrhage) have occurred in up to 6% of patients. Bleeding events of any grade, including bruising and petechiae, occurred in approximately half 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. 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 have occurred with IMBRUVICA therapy. Grade 3 or greater infections occurred in 14% to 26% of patients. Cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with IMBRUVICA . Monitor patients for fever and infections and evaluate promptly.

Cytopenias - Treatment-emergent Grade 3 or 4 cytopenias including neutropenia (range, 19 to 29%), thrombocytopenia (range, 5 to 17%), and anemia (range, 0 to 9%) occurred in patients treated with IMBRUVICA . Monitor complete blood counts monthly.

Atrial Fibrillation - Atrial fibrillation and atrial flutter (range, 6 to 9%) have occurred in patients treated with IMBRUVICA , particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new-onset dyspnea should have an ECG performed. If atrial fibrillation persists, consider the risks and benefits of IMBRUVICA treatment and dose modification.

Second Primary Malignancies - Other malignancies (range, 5 to 14%) including non-skin carcinomas (range, 1 to 3%) have occurred in patients treated with IMBRUVICA . The most frequent second primary malignancy was non-

melanoma skin cancer (range, 4 to 11%).

Tumor Lysis Syndrome - Tumor lysis syndrome has been reported with IMBRUVICA therapy. Monitor patients closely and take appropriate precautions in patients at risk for tumor lysis syndrome (e.g., high tumor burden).

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 . 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 (?25%) in patients with B-cell malignancies (MCL, CLL, WM) were thrombocytopenia* (57%, 52%, 43%), neutropenia* (47%, 51%, 44%), diarrhea (51%, 48%, 37%), anemia* (41%, 36%, 13%), fatigue (41%, 28%, 21%), musculoskeletal pain (37%, 28%?, NA?), bruising (30%, 12%?, 16%?), nausea (31%, 26%, 21%), upper respiratory tract infection (34%, 16%, 19%), and rash (25%, 24%?, 22%?).

*Based on adverse reactions and/or laboratory measurements (noted as platelets, neutrophils, or hemoglobin decreased).

†Includes multiple ADR terms.

‡Not applicable; no associated ADRs.

The most common Grade 3 or 4 non-hematological adverse reactions (≥5%) in MCL patients were pneumonia (7%), abdominal pain (5%), atrial fibrillation (5%), diarrhea (5%), fatigue (5%), and skin infections (5%). Approximately 6% (CLL), 14% (MCL), and 11% (WM) of patients had a dose reduction due to adverse events. Approximately 5% (CLL), 9% (MCL), and 6% (WM) of patients discontinued due to adverse events. Most frequent adverse events leading to discontinuation were infections, subdural hematomas, and diarrhea in CLL patients and subdural hematoma (1.8%) in MCL patients.

## DRUG INTERACTIONS

CYP3A Inhibitors - Avoid co-administration with strong and moderate CYP3A inhibitors. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose.

CYP3A Inducers - Avoid co-administration with strong CYP3A inducers.

## SPECIFIC POPULATIONS

**Hepatic Impairment** - Avoid use in patients with moderate or severe baseline hepatic impairment. In patients with mild impairment, reduce IMBRUVICA® dose.

## Please see full Prescribing Information:

**http://www.imbruvica.com/downloads/Prescribing_Information.pdf**

## About Janssen Biotech, Inc.

Janssen Biotech, Inc. redefines the standard of care in immunology, oncology, urology and nephrology. Built upon a rich legacy of innovative firsts, Janssen Biotech has delivered on the promise of new treatments and ways to improve the health of individuals with serious disease. Beyond its innovative medicines, Janssen Biotech is at the forefront of developing education and public policy initiatives to ensure patients and their families, caregivers, advocates and health care professionals have access to the latest treatment information, support services and quality care.

Janssen Biotech, Inc. and Janssen Research & Development, LLC are part of the Janssen Pharmaceutical Companies of Johnson & Johnson. For more information on Janssen Biotech, Inc. or its products, visit **http://www.janssenbiotech.com**. Follow us on Twitter at **www.twitter.com/JanssenUS**.

## Janssen in Oncology

In oncology, our goal is to fundamentally alter the way cancer is understood, diagnosed and managed, reinforcing our commitment to the patients who inspire us. In looking to find innovative ways to address the cancer challenge, our primary efforts focus on several treatment and prevention solutions. These include a focus on hematologic malignancies, prostate cancer and lung cancer; cancer interception with the goal of developing products that interrupt the carcinogenic process; biomarkers that may help guide targeted, individualized use of our therapies; as well as safe and effective identification and treatment of early changes in the tumor microenvironment. Please visit **http://www.janssen.com**.

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. 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 Biotech, Inc., Janssen Research & Development, LLC and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in new product development, including the uncertainty of clinical success and of obtaining regulatory approvals; competition,

including technological advances, new products and patents attained by competitors; challenges to patents; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and description 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 28, 2014, including in Exhibit 99 thereto, 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 or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

## References:

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[1] American Cancer Society. Detailed guide: what is chronic lymphocytic leukemia. Available from: **http://www.cancer.org/acs/groups/cid/documents/webcontent/003111-pdf.pdf Accessed November 2015**.

[2] Shaffer AL, Rosenwald A, Staudt LM. Lymphoid malignancies: the dark side of B-cell differentiation. Nat Rev Immunol. 2002;2(12):920-932.

[3] American Cancer Society. What are the key statistics for chronic lymphocytic leukemia? Available from: **http://www.cancer.org/cancer/leukemia-chroniclymphocyticcll/detailedguide/leukemia-chronic-lymphocytic-key-statistics**. Accessed: November 2015

[4] American Cancer Society. Leukemia - Chronic Lymphocytic. Available from: **http://www.cancer.org/acs/groups/cid/documents/webcontent/003111-pdf.pdf**. Accessed November 2015.

[5] IMBRUVICA Prescribing Information, January 2015.

[6] Genetics Home Reference. Isolated growth hormone deficiency. Available from: **http://ghr.nlm.nih.gov/condition/isolated-growth-hormone-deficiency**. Accessed November 2015.


## Media Inquiries:


Bernadette King
Phone: 1-215-325-2158
Mobile: 1-215-778-3027

Kellie McLaughlin
Phone: 1-908-927-7477
Mobile: 1-609-468-8356

Satu Kaarina Glawe
Mobile: +49 172 294 6264

## Investor Relations:

Lesley Fishman

Phone: 1-732-524-3922

## U.S. Medical Inquiries:

Pharmacyclics Medical Information:

1-877-877-3536