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Data at ASH 2016 Show Strong, Lasting Efficacy of Imbruvica® ▼ (ibrutinib) Through Five Years of Treatment for Chronic Lymphocytic Leukaemia (CLL)

89% of study patients, including those with high-risk CLL, responded to therapy.
Durable and improving responses also seen in longer follow-up from Phase 3 RESONATE-2 trial.
This release corresponds to abstracts #233[1] and #234[3]

Beerse, Belgium, 4 December 2016 – Janssen-Cilag International NV today announced the longest follow-up results to date of patients treated with Imbruvica®▼(ibrutinib) for chronic lymphocytic leukaemia (CLL), showing high and lasting responses through five years.[1] These updated Phase 1b/2 data demonstrated an overall response rate (ORR) of 89%,[2] including patients with genetic mutations associated with poor outcomes. A complete response (CR) was observed in 29% of patients treated in the first-line setting.[2] Progression-free survival (PFS) was improved with earlier initiation of therapy across treatment-naïve (TN) and relapsed/refractory (r/r) patients.[2] These data (abstract #233[1]) were presented on Saturday 3 December in an oral presentation[2] at the 58th Annual American Society of Hematology (ASH) Meeting and Exposition in San Diego, CA.

Additional follow-up data in patients with CLL treated with ibrutinib through 29 months from the Phase 3 RESONATE-2 trial were also presented on Saturday (abstract #234[3]). Ibrutinib, a first-in-class Bruton's tyrosine kinase (BTK) inhibitor, is co-developed by Cilag GmbH International (an affiliate of Janssen) and Pharmacyclics/AbbVie. Janssen affiliates market ibrutinib in EMEA (Europe, Middle East and Africa) as well as the rest of the world, except for the United States, where both companies co-market it.

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"These longer-term results demonstrate that ibrutinib can help patients keep chronic lymphocytic leukaemia in a complete or partial remission for an extended period of time, through five years, without chemotherapy," said Susan O'Brien, M.D., Associate Director for Clinical Science, Chao Family Comprehensive Cancer Center at UC Irvine Health, Medical Director, Sue and Ralph Stern Center for Clinical Trials & Research, and an investigator and presenter of the PCYC-1102 and PCYC-1103 trials.* "In addition, these data indicate the time without disease progression is longer for patients when treatment with ibrutinib is started as early as possible in the course of the disease."

Abstract #233: Five-Year Experience With Single-Agent Ibrutinib In Patients With Previously Untreated And Relapsed/Refractory Chronic Lymphocytic Leukaemia[1,2]

In these studies (PCYC-1102 and PCYC-1103), with five years of follow-up, the ORR in patients treated with ibrutinib was 89%,[2] with 14% of patients achieving complete responses (CR)[2] [87% ORR with 29% CR in TN patients (n=31) and 89% ORR with 10% CR in r/r patients (n=101)].[2] Median time on study was 62 months (1-67) for TN patients[2] and 49 months (1-67) for r/r patients.[2] Overall survival (OS) at five years was 92% for TN patients and 57% for r/r patients, with a PFS rate of 92% and 43%, respectively.[2] Median OS and median duration of response (DOR) was not reached. Median PFS was not reached in TN patients and was 52 months for r/r patients.[2]

Findings were consistent in r/r patients with high-risk CLL, and risk factors traditionally associated with poor outcomes[4] including those with deletion 11q (del11q; n=28), deletion 13q (del13q; n=13), deletion 17p (del17p; n=34) and unmutated immunoglobulin heavy-chain variable-region (IGHV; n=79).[2] Median PFS was 55 months (31-NE) for those with del11q, 26 months (95% CI, 18-37) for those with del17p, 43 months (95% CI, 32-not estimable) for those with unmutated IGHV, and was not reached for those with del13q.[2] Results indicated PFS and OS were higher when ibrutinib treatment was started earlier.[2] Median PFS was not reached in TN patients[2] and was 63 months for r/r patients who received one to two prior regimens,[2] 59 months for those who had three prior regimens,[2] and 39 months for those who had four or more prior regimens.[2]

"The resounding evidence in support of ibrutinib's benefits for patients continues to grow, and this longer-term data from five years of CLL treatment provides important reassurance of the lasting effect that can be achieved with ibrutinib over time," said Jane Griffiths, Company Group Chairman, Janssen Europe, Middle East and Africa. "We are so pleased to be altering the treatment landscape

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and changing what a diagnosis means for CLL patients, with these clinically significant improvements."

No new safety signals emerged in the study.[2] The onset of most grade three or higher treatment-emergent adverse events (TEAEs) among all patients was highest in the first year and decreased over time. The most frequent adverse events (AEs) were hypertension (26%), pneumonia (22%), neutropenia (17%) and atrial fibrillation (9%).[2]

The Phase 1b/2 PCYC-1102 trial evaluated safety and efficacy of single-agent ibrutinib in 132 patients with CLL: 31 patients were TN: 101 were r/r.[2] Patients received either 420 mg or 840 mg once daily until disease progression or unacceptable toxicity.[2] Among r/r patients, 34% had del17p, 35% del11q, 47% had del13q and 78% unmutated IGHV.[2] Primary endpoint was ORR, with secondary endpoints of DOR and PFS in addition to safety. PCYC-1103 is the long-term extension study. Primary results from this trial were published in *The New England Journal of Medicine* in June 2013[5] and were the basis for the initial approval of ibrutinib in the US in CLL in February 2014 via the Breakthrough Therapy Designation pathway.[6]

Abstract #234: Updated Efficacy and Safety From The Phase 3 RESONATE-2 Study: Ibrutinib as First-Line Treatment Option in Patients 65 Years and Older With Chronic Lymphocytic Leukaemia[3]

Updated findings from the pivotal Phase 3 RESONATE-2 trial (PCYC-1115) demonstrated that at a median of 29 months of follow-up, ibrutinib continued to have substantial efficacy as first-line therapy in CLL. The study found ibrutinib reduced the risk of progression or death by 88% compared with commonly used chemotherapy agent chlorambucil. At 24 months, PFS was 89% for patients taking ibrutinib and 34% for chlorambucil [HR, 0.121; 95% CI 0.074-0.198; p<0.0001). Investigator-assessed ORR with this longer follow up was 92% with ibrutinib and 36% with chlorambucil; in the ibrutinib arm, CR or CR with incomplete bone marrow recovery (Cri) improved from 15% at 24 months to 18% with longer follow-up of 29 months.

Safety findings were in line with the primary analysis of the study and found that most Grade 3 or higher AEs decreased over time. Most AEs that led to discontinuation occurred in the first year of treatment. The most frequent (≥5%) Grade ≥ 3 AEs were neutropenia (12%), pneumonia (7%), anemia (7%) and hypertension (5%).

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About RESONATE-2[7]

RESONATE-2 is a continuing Pharmacyclics-sponsored, randomised multi-centre, open-label, Phase 3 study which enrolled 269 treatment-naïve patients with CLL aged 65 years or older in the EU, U.S. and other regions. Patients were randomised to receive ibrutinib 420 mg orally, once daily until progression or unacceptable toxicity, or chlorambucil on days 1 and 15 of each 28-day cycle for up to 12 cycles. The starting dose for chlorambucil in Cycle 1 was 0.5 mg/kg and was increased based on tolerability in Cycle 2 by increments of 0.1 mg/kg to a maximum of 0.8 mg/kg. The study met its primary endpoint, demonstrating improved PFS, as assessed by an independent review committee (IRC).

Initial RESONATE-2 results were presented in an oral session at the American Society of Hematology (ASH) meeting in December 2015[8] and simultaneously published in *The New England Journal of Medicine*.[7]

About ibrutinib

Ibrutinib is a first-in-class Bruton's tyrosine kinase (BTK) inhibitor, which works by forming a strong covalent bond with BTK to block the transmission of cell survival signals within the malignant B cells.[9] By blocking this BTK protein, ibrutinib helps kill and reduce the number of cancer cells, thereby delaying progression of the cancer.[10]

Ibrutinib is currently approved in Europe for the following uses:[11]

- As a single agent for the treatment of adult patients with previously untreated CLL, adult patients with relapsed or refractory mantle cell lymphoma (MCL), or adult patients with Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy or in first line treatment for patients unsuitable for chemo-immunotherapy.
- As a single agent or in combination with bendamustine and rituximab (BR) for the treatment of adult patients with CLL who have received at least one prior therapy.

Please see the ibrutinib summary of product characteristics for further information.[11]

About CLL

CLL is a chronic disease; median overall survival ranges between 18 months and more than 10 years, according to the stage of disease.[12] The disease eventually progresses in the majority of patients, and patients are faced with fewer treatment options each time. Patients are often prescribed multiple lines of therapy as they relapse or become resistant to treatments.

About the Janssen Pharmaceutical Companies

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us on www.twitter.com/janssenEMEA for our latest news.

Cilag GmbH International; Janssen Biotech, Inc.; and Janssen-Cilag International NV are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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-Cilag International NV and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges inherent in product research and development, including the uncertainty of clinical success and obtaining regulatory approvals; uncertainty of commercial success for new products or new indications; 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 January 3, 2016, 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.

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**Disclaimer: Dr. O'Brien served as an investigator of this Pharmacyclics-sponsored clinical study. Dr. O'Brien does not have a financial interest in the company.*

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