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Ibrutinib (IMBRUVICA®) Significantly Improved Progression-Free and Overall Survival Versus Chlorambucil in Treatment-Naïve Patients with Chronic Lymphocytic Leukaemia

Ibrutinib was associated with a 24-month survival rate of 98 percent [1]

Data published in The New England Journal of Medicine

Phase 3 data also featured in the official press programme of the 2015 American Society of Hematology Annual Meeting & Exposition (Abstract #495)

BEERSE, BELGIUM, December 6, 2015 – Data from the investigational, randomised, multi-centre, open-label Phase 3 RESONATE™-2 (PCYC-1115) trial show ibrutinib (IMBRUVICA®) was superior to chlorambucil in all efficacy endpoints measured in patients with treatment-naïve chronic lymphocytic leukaemia or small lymphocytic lymphoma (CLL/SLL) aged 65 or older, Janssen-Cilag International NV announced today. Ibrutinib significantly prolonged progression-free survival (PFS), the study's primary endpoint, and overall survival (OS), a key secondary endpoint, and also improved other haematologic measures. Notably, ibrutinib was associated with a 98 percent OS rate versus 85 percent for chlorambucil at 24 months. These data will be included in a presentation today during the official press programme at the 2015 American Society of Hematology (ASH) meeting in Orlando, FL, U.S. and simultaneously published in *The New England Journal of Medicine*.[1] IMBRUVICA is co-developed by Cilag GmbH International, a member of the Janssen Pharmaceutical Companies, and Pharmacyclics LLC, an AbbVie company. Janssen affiliates market IMBRUVICA in EMEA (Europe, Middle East and Africa) as well as the rest of the world, except for the United States, where Janssen Biotech, Inc. and Pharmacyclics LLC co-market it.

These data will be presented in full by RESONATE-2 study investigator Alessandra Tedeschi, M.D., Medical Director, Azienda Ospedaliera Niguarda Ca Granda, Milan, Italy, during the "CLL: Therapy, Excluding Transplantation: Upfront CLL Therapy Excluding Transplantation" session on Monday, December 7, at 7:30am Eastern Time (ET) / 1.30pm Central European Time (CET).

"The RESONATE-2 trial is ground-breaking as the first randomised Phase 3 trial of B-cell receptor antagonist, ibrutinib, in previously untreated CLL," said Professor Peter Hillmen, Haematology, St. James's University Hospital, Leeds, who is an investigator in the RESONATE-2 clinical trial. "The results of RESONATE-2 are impressive. The improvement in progression free survival for ibrutinib in front-line treatment compared to chlorambucil is statistically significant. The improvement in overall survival for ibrutinib compared to chlorambucil even with a pre-planned cross-over to ibrutinib is unexpected. This indicates that the best outcomes will be achieved with ibrutinib when it is used as the initial therapy in patients with CLL."

The Independent Review Committee (IRC) found ibrutinib significantly prolonged PFS compared with chlorambucil. The hazard ratio (HR) was 0.16 (95 percent CI, 0.09-0.28; P<0.001), which represents a reduction in the risk of progression or death by 84 percent versus chlorambucil (median not reached vs. 18.9 months); the PFS rate at 18 months was 90 percent for ibrutinib versus 52 percent for chlorambucil. Ibrutinib also significantly prolonged OS (HR=0.16: 95 percent CI, 0.05, 0.56; P=0.001) with a 24-month survival rate of 98 percent, compared to 85 percent for patients in the chlorambucil arm. Additionally, ibrutinib was associated with a significantly higher ORR (86 percent vs. 35 percent; P<0.001) as assessed by the IRC and significantly increased the rate of sustained improvements in both haemoglobin and platelets.[1]

"RESONATE-2 is the first Phase 3 head-to-head trial to evaluate the efficacy and safety of ibrutinib monotherapy versus traditional chemotherapy in patients with treatment-naïve CLL. The strength of these data may very well represent a turning point in the treatment of CLL/SLL and change when it may be appropriate to treat these patients with ibrutinib," said Jane Griffiths, Company Group Chairman, Janssen Europe, Middle East and Africa. "We continue to see positive results with ibrutinib, and it is particularly exciting to see the extent of new data at ASH, demonstrating our commitment to exploring ibrutinib use for those who could most benefit from it, and our growing haematology offering."

The safety of ibrutinib in this patient population was consistent with previously reported studies. It is worth noting that exposure to treatment and adverse event (AE) follow-up was nearly 2.5 times longer for ibrutinib compared with chlorambucil and 87 percent of patients randomised to ibrutinib were still on therapy at the time of analysis. Overall, AEs leading to treatment discontinuation were less frequent with ibrutinib than with chlorambucil (nine percent vs. 23 percent, respectively). The most common AEs ($\geq$20 percent) of any Grade in the RESONATE-2 trial for ibrutinib were diarrhoea (42 percent), fatigue (30 percent), cough (22 percent) and nausea (22 percent); AEs for chlorambucil included nausea (39 percent), fatigue (38 percent), neutropenia (23 percent) and vomiting (20 percent). Hypertension occurred at a higher rate in the ibrutinib arm (14 percent; Grade 3 in four percent, no Grade 4 or 5). All six patients with

Grade 3 hypertension were managed with hypertensive medication and did not require ibrutinib dose reduction or discontinuation. Four ibrutinib patients experienced Grade 3 haemorrhage and one experienced Grade 4 haemorrhage.[1] Atrial fibrillation occurred in eight patients (six percent) in the ibrutinib arm and was primarily Grade 2 in six patients and Grade 3 in two patients. It was managed with discontinuation in two patients and without a dose modification in remaining patients.

There were three deaths in the ibrutinib arm and 17 deaths on the chlorambucil arm over the median follow-up of 18.4 months. None of the patients who progressed on the ibrutinib arm died during the subsequent follow-up period.[1]

RESONATE-2 is a Pharmacyclics-sponsored trial and is the second Phase 3 study demonstrating a significant benefit of ibrutinib vs. a comparator.[2,3] The trial enrolled 269 patients with CLL/SLL aged 65 years or older without prior treatment in the U.S., EU and other regions. CLL patients with deletion of the short arm of chromosome 17 (del 17p CLL) were excluded from the trial as single-agent chlorambucil is not recognised as an appropriate therapy in this patient population. Patients were randomised to receive either ibrutinib 420 mg orally, once daily until progression or toxicity or chlorambucil 0.5 to 0.8 mg/kg on days one and 15 of each 28-day cycle for up to 12 cycles. The primary endpoint of the study was PFS as assessed by an IRC according to the International Workshop on Chronic Lymphocytic Leukaemia (iWCLL) 2008 criteria, with modification for treatment-related lymphocytosis. Key secondary endpoints included ORR, OS, rate of haematologic improvement and safety.[1]

The RESONATE-2 results are the basis for a Type II variation application to the European Medicines Agency (EMA), seeking to broaden the existing marketing authorisation for IMBRUVICA to include previously untreated patients with CLL, which was which was announced on November 3, 2015. More information about the study can be found on www.clinicaltrials.gov.

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About IMBRUVICA® (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.[4] By blocking this BTK protein, ibrutinib helps kill and reduce the number of cancer cells. It also slows down the worsening of the cancer.[5]

Ibrutinib is approved in Europe for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), or adult patients with chronic lymphocytic leukaemia (CLL) who

have received at least one prior therapy, or in first line patients with CLL in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy;[6] it is also approved for adult patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy;[6] regulatory approval for additional uses has not yet been granted. Investigational uses for ibrutinib, alone and in combination with other treatments, are under way in several blood cancers including CLL, MCL, WM, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), multiple myeloma (MM) and marginal zone lymphoma (MZL).

Ibrutinib is co-developed by Cilag GmbH International, a member of the Janssen Pharmaceutical Companies, and Pharmacyclics LLC, an AbbVie company. 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 Janssen Biotech, Inc. and Pharmacyclics LLC co-market it. Janssen and Pharmacyclics are continuing an extensive clinical development programme for ibrutinib, including Phase 3 study commitments in multiple patient populations – please see the IMBRUVICA summary of product characteristics for further information.

About CLL

In most patients, CLL is generally a slow-growing blood cancer of the white blood cells called B-lymphocytes.[7] The median age at diagnosis is 72 years,[8] and incidence rates among men and women in Europe are approximately 5.87 and 4.01 cases per 100,000 persons per year, respectively.[9] CLL is a chronic disease; median overall survival ranges between 18 months and more than 10 years according to the stage of disease.[10] 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.

CLL cells are found in both the lymphatic system and the blood.[11] When the cancer cells are located mostly in the lymph nodes, the disease is called small lymphocytic lymphoma (SLL). Both CLL and SLL are considered different manifestations of the same entity, as classified in the fourth edition of the *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*.[12]

Janssen 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 haematologic 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, individualised use of our therapies; as well as safe and effective identification and treatment of early changes in the tumour microenvironment.

About Janssen

Janssen Pharmaceutical Companies of Johnson & Johnson are dedicated to addressing and solving the most important unmet medical needs of our time, including oncology (e.g., multiple myeloma and prostate cancer), immunology (e.g., psoriasis), neuroscience (e.g., schizophrenia, dementia and pain), infectious disease (e.g., HIV/AIDS, hepatitis C and tuberculosis), and cardiovascular and metabolic diseases (e.g., diabetes). Driven by our commitment to patients, we develop sustainable, integrated healthcare solutions by working side-by-side with healthcare stakeholders, based on partnerships of trust and transparency. More information can be found on www.janssen-emea.com. Follow us on www.twitter.com/janssenEMEA for our latest news.

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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. 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 any of the Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in new product development, including obtaining regulatory approvals; uncertainty of commercial success; 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 behaviour and spending patterns or financial distress of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; manufacturing difficulties and delays; 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 undertake to update any forward-looking statement as a result of new information or future events or developments.

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