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For Immediate Release

# Findings from landmark RESONATE-2 study confirm sustained survival benefit of IMBRUVICA® (ibrutinib) for first-line chronic lymphocytic leukaemia treatment with up to 10 years follow-up

*RESONATE-2 data presented at the 2024 European Hematology Association (EHA) Congress provide longest-term outcomes and safety data ever reported for a monotherapy BTK inhibitor, with a median progression-free survival of 8.9 years*[1]

*Additional findings from pooled analysis of three Phase 3 studies showed treatment with ibrutinib has the potential to achieve comparable overall survival to the general European population*[2]

**BEERSE, BELGIUM (14 June 2024)** – Janssen-Cilag International NV, a Johnson & Johnson company today announced findings from the final analysis of the Phase 3 RESONATE-2 study, demonstrating a significant and sustained progression-free and overall survival benefit in patients with previously untreated chronic lymphocytic leukaemia (CLL) receiving IMBRUVICA® (ibrutinib) monotherapy versus chlorambucil, at up to 10 years of follow-up.[1] The data were featured in a poster presentation at the 2024 European Hematology Association (EHA) Congress (Poster #P670), taking place in Madrid, Spain, from 13-16 June 2024.[1]

“When ibrutinib was first introduced more than ten years ago, it changed the course of chronic lymphocytic leukaemia (CLL) treatment, and today it remains a central part of the standard of care for patients living with B-cell malignancies,” said Alessandra Tedeschi, MD, Niguarda Hospital, Milan, Italy, clinical study investigator.† “The final analysis of the RESONATE-2 study confirms the favourable benefit-risk profile of ibrutinib is sustained over time, with the longest-follow up data of any targeted therapy in CLL, and demonstrates its potential to enable patients diagnosed with CLL today to look forward to the possibility of a normalised life expectancy.”

The Phase 3 RESONATE-2 study evaluated 269 previously untreated patients with CLL, aged 65 years or older, without del(17p), who were randomly assigned to receive either ibrutinib single-agent or chlorambucil for up to 12 cycles.[1] With up to ten years of follow-up, patients treated with ibrutinib demonstrated a significant and sustained progression-free survival (PFS) benefit versus patients treated with chlorambucil.[1] Median PFS was 8.9 years in the ibrutinib arm versus 1.3 years in the chlorambucil arm (hazard ratio [HR], 0.16; 95 percent CI, 0.11–0.22; p<0.0001).[1] The PFS benefit was significantly longer for patients treated with ibrutinib in all subgroups, including those with high-risk genomic features – TP53 mutation, unmutated IGHV or 11q deletion (HR, 0.09; 95 percent CI, 0.05–0.15; p<0.0001).[1] With up to 10 years of follow-up, the median OS had not been reached with ibrutinib, and at nine years the OS rate was 68 percent (95 percent CI, 58.6–75.7).[1] At 10 years, 27 percent of patients in the study remained on ibrutinib, with a median duration of treatment of 6.2 years (range, 0.06–10.2).[1]

Ibrutinib was well tolerated as a long-term treatment and no new safety signals emerged.[1] Rates of adverse events (AEs) of interest during years 8–9 and 9–10 were 28 percent (n=15) and 26 percent (n=11), respectively for hypertension, and eight percent (n=4) and nine percent (n=4), respectively for atrial fibrillation.[1] During the entire study period, 34 of 136 patients (25 percent) receiving ibrutinib had AEs of any Grade leading to dose reduction, of which 28 of 34 patients (82 percent) had all AEs resolved.[1] AEs of any Grade led to discontinuation of ibrutinib in 33 percent of patients (n=44) over the whole study duration, in 13 percent of patients (n=7) in year 8–9, and in 7 percent of patients (n=3) in year 9–10.[1] No patients discontinued ibrutinib due to progressive disease in years 9–10.[1]

Further data pooled from three Phase 3 randomised clinical studies on first-line ibrutinib treatment in patients with CLL were featured at EHA (Poster #P664).[2] The pooled analysis included RESONATE-2 (NCT01722487), ECOG1912 (NCT02048813), and iLLUMINATE (NCT02264574), which investigated ibrutinib as a single agent, or in combination with

rituximab, or obinutuzumab, respectively.[2,3,4,5] A combined total of 600 patients, aged 31-89, were treated with ibrutinib across the pooled studies.[2] At a median follow up of 49.7 months, OS was comparable between patients treated with ibrutinib and the age-matched general European population (HR, 1.232; 95 percent CI, 0.878–1.728; p=0.228) using survival probability by age group from the 2019 life tables published by the World Health Organization.[2] Estimated OS was also comparable for the subgroup of patients treated with ibrutinib aged 65 years and older (HR, 1.020; 95 percent CI, 0.702–1.483; p=0.916).[2] Estimated OS was similar to the age-matched European population when stratified by patients who received either single-agent ibrutinib (HR, 0.931; 95 percent CI, 0.583–1.489; p=0.766) or the combination of ibrutinib and rituximab or obinutuzumab (HR, 1.182; 95 percent CI, 0.718–1.943; p=0.511).[2] These data are consistent with a previous analysis of the US population, presented at the 2023 American Society of Hematology (ASH) Annual Meeting.[2,6]

“These findings suggest that treatment with ibrutinib, with or without the addition of a CD20 antibody, offers patients in Europe with chronic lymphocytic leukaemia the potential of a standard life expectancy, comparable to that of their peers,” said Edmond Chan**,** MBChB, M.D. (Res), EMEA Therapeutic Area Lead Haematology, Johnson & Johnson Innovative Medicine. **“**Our goal has been to change what a blood cancer diagnosis means, and with ibrutinib, we are proud to be at the forefront of leading where medicine is going.”

A poster presentation of real-world evidence (Poster #P1846) provided additional insights on the potential effect of ibrutinib dose reductions on duration of treatment (DOT) and time-to-next-treatment (TTNT) in patients treated with ibrutinib versus acalabrutinib in the first-line setting.[7] Findings suggest that ibrutinib dose-reductions may be an effective strategy to manage tolerability while maintaining clinical efficacy.[7]

Among 286 patients who initiated first-line single-agent ibrutinib at 420 mg/day, 15 percent (n=44) had a dose reduction; 171 patients initiated first-line single-agent acalabrutinib.[7] Mean time between first-line initiation and index date was 167 days in each cohort.[7] Mean follow-up time post-index was 425 and 221 days for ibrutinib dose-reduction and acalabrutinib cohorts, respectively.[7] Median duration of first-line therapy (including treatment-free interval) was 21.3 and 11.1 months for ibrutinib dose reduction and acalabrutinib cohorts, respectively.[7] A total of 37 percent (n=16) and 35 percent (n=60) patients discontinued treatment in the ibrutinib dose reduction and acalabrutinib cohorts, respectively; median DOT was not reached in the ibrutinib dose reduction cohort and was 9.5 months in the acalabrutinib cohort.[7] DOT was longer in the ibrutinib dose reduction cohort versus the acalabrutinib cohort (adjusted HR, 0.57, p=0.10).[7] A total of 16 percent (n=7) and 17 percent (n=29) patients in the ibrutinib dose reduction and acalabrutinib cohorts received the next treatment line during the follow-up period, respectively; median TTNT was not reached in either cohort.[7] TTNT was longer for the ibrutinib dose reduction cohort (adjusted HR, 0.61, p=0.36).[7] This real-world evidence is subject to potential confounding bias usually associated with observational research.

“These latest findings add to the robust data supporting ibrutinib, the most comprehensively studied Bruton’s tyrosine kinase inhibitor in the world, and the foundation of care in chronic lymphocytic leukaemia,” said Mark Wildgust, PhD, Vice President, Global Medical Affairs, Oncology, Johnson & Johnson Innovative Medicine. “As we reflect on a decade since its first approval, ibrutinib stands as a testament to progress that has redefined what it means to live with B-cell malignancies.”

### About RESONATE-2

RESONATE-2 (NCT01722487) is an international, multicentre, open-label, Phase 3 randomised study that compared first-line ibrutinib monotherapy with chlorambucil in treatment-naïve patients aged 65 years or older diagnosed with CLL/small lymphocytic leukaemia (n=269).[3] Patients were randomly assigned to receive either 420 mg of oral ibrutinib daily until disease progression or unacceptable toxicity occurred (n=136), or up to 12 cycles of intravenous chlorambucil (n=133, with initial doses ranging from 0.5 to 0.8 mg per kg on days 1–15 of each 28-day cycle).[1,3] The primary endpoint was PFS, as defined by the Independent Review Committee assessment of PFS, while OS, overall response rate (ORR), and safety served as secondary endpoints.[3]

### About the Phase 3 RESONATE-2 (NCT01722487), ECOG1912 (NCT02048813) and iLLUMINATE (NCT02264574) pooled analysis

OS for ibrutinib-treated patients was compared with expected survival of the respective age-matched European population using survival probability by age group from 2019 life tables published by the World Health Organisation.[2] Age at randomisation of trial was used for age matching of patients.[2] Available probabilities for 5-year age intervals were converted to a daily scale to avoid immortal time bias.[2] OS was analysed using Kaplan-Meier methodology; HRs were derived from a Cox proportional hazard model using trial and simulated data.[2]

### About the real-world clinical outcomes analysis on first-line ibrutinib dose reduction versus acalabrutinib among patients with CLL

Previously untreated adults with CLL who initiated single-agent ibrutinib at 420 mg/day or single-agent acalabrutinib were identified using a large US claims database (21 November 2018–30 June 2023).[7] Patients treated with ibrutinib were included if they had a dose reduction during first-line treatment.[7] Outcomes were measured from date of ibrutinib dose reduction (index date) or from an imputed acalabrutinib index date that replicated the distribution of

time between first-line initiation and dose-reduction observed in the ibrutinib dose-reduction cohort.[7] Baseline characteristics were balanced between cohorts using inverse probability of treatment weighting (IPTW).[7] DOT was defined as the time from index date to the last day of supply before a >90-day gap in consecutive days of supply or initiation of a next line of therapy.[7] TTNT was defined as time from index date to the initiation of a next line of therapy.[7] DOT and TTNT were compared using IPTW-weighted Kaplan-Meier curves and Cox proportional hazards models.[7]

## About Ibrutinib

Ibrutinib is a once-daily oral medication that is jointly developed and commercialised by Janssen Biotech, Inc. and Pharmacyclics LLC, an AbbVie company.[8] Ibrutinib blocks the BTK protein, which is needed by normal and abnormal B-cells, including specific cancer cells, to multiply and spread.[9] By blocking BTK, ibrutinib may help move abnormal B-cells out of their nourishing environments and inhibits their proliferation.[10]
Ibrutinib is approved in more than 100 countries and has been used to treat almost 300,000 patients worldwide.[11] There are more than 50 company-sponsored clinical trials, including 18 Phase 3 studies, over 11 years evaluating the efficacy and safety of ibrutinib.[8,12] In October 2021, ibrutinib was added to the World Health Organization's Model Lists of Essential Medicines (EML), which refers to medicines that address global health priorities and which should be available and affordable for all.[13]

Ibrutinib was first approved by the European Commission (EC) in 2014, and approved indications to date include:[8]

- As a single agent or in combination with rituximab or obinutuzumab or venetoclax for the treatment of adult patients with previously untreated CLL
- 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
- As a single agent for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)
- As a single agent for the treatment of 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. In combination with rituximab for the treatment of adult patients with WM

For a full list of adverse events and information on dosage and administration, contraindications and other precautions when using ibrutinib please refer to the Summary of Product Characteristics.

## About Chronic Lymphocytic Leukaemia

CLL is typically a slow-growing blood cancer of the white blood cells.[14] The overall incidence of CLL in Europe is approximately 4.92 cases per 100,000 persons per year and it is about 1.5 times more common in men than in women.[15] CLL is predominantly a disease of the elderly, with a median age of 72 years at diagnosis.[16] While patient outcomes have dramatically improved in the last few decades, the disease is still characterised by consecutive episodes of disease progression and the need for therapy.[17] Patients are often prescribed multiple lines of therapy as they relapse or become resistant to treatments.[18]

## About Johnson & Johnson

At Johnson & Johnson, we believe health is everything. Our strength in healthcare innovation empowers us to build a world where complex diseases are prevented, treated, and cured, where treatments are smarter and less invasive, and solutions are personal. Through our expertise in Innovative Medicine and MedTech, we are uniquely positioned to innovate across the full spectrum of healthcare solutions today to deliver the breakthroughs of tomorrow, and profoundly impact health for humanity.

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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 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 Pharmaceutica NV, Janssen-Cilag Limited, Janssen Research & Development, LLC, Janssen Biotech, Inc., Janssen Global Services, LLC 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 31, 2023, 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 Janssen Pharmaceutica NV, Janssen-Cilag Limited, Janssen Research & Development LLC, Janssen Biotech, Inc., Janssen Global Services, LLC nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.*

†Dr. Tedeschi has provided consulting, advisory, and speaking services to Johnson & Johnson; she has not been paid for any media work.

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