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# RYBREVANT® (amivantamab-vmjw) Provides Higher Activity and Longer Duration of Response When Used in Combination with Lazertinib in Patients with Advanced EGFR-Mutant Non-Small Cell Lung Cancer Who Have Failed Osimertinib

*New analysis from CHRYSALIS study presented at the ESMO Annual Congress 2021 supports simultaneously targeting the extracellular and catalytic domains of EGFR*

**September 19, 2021 (RARITAN, N.J.)** – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced a new analysis from the CHRYSALIS (NCT02609776) study evaluating RYBREVANT® (amivantamab-vmjw) monotherapy and a combination regimen with lazertinib in advanced non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations who progressed after osimertinib.[1] The analysis showed higher activity and longer duration of response (DOR) in patients treated with the combination therapy, demonstrating the potential benefit of targeting the extracellular (outer) and catalytic (internal) domains of EGFR, even in patients with documented resistance to third-generation EGFR tyrosine kinase inhibitors (TKIs).[1] The results were presented in a mini-oral presentation at the European Society for Medical Oncology (ESMO) Annual Congress 2021 virtual meeting on Sunday, September 19 (Abstract #1192MO).

"Despite advances in targeted therapies, non-small cell lung cancer with EGFR mutations remains a disease with considerable unmet need, especially when prior standard treatments have failed," said Natasha B. Leighl, M.D., MMSc, FRCPC, FASCO, Lung Medical Oncology Lead, Princess Margaret Cancer Centre in Toronto, Canada, and presenting study investigator.† "This analysis shows that targeting two domains of EGFR using amivantamab and lazertinib combination therapy demonstrated higher and more durable response than targeting only one domain. These findings provide insight into a potential new treatment approach for patients whose lung cancer has progressed on standard treatment."

In this descriptive cross-cohort analysis, patients who had progressed on osimertinib received RYBREVANT® as a monotherapy (n=121), with a majority (85 percent) preselected for C797S/other EGFR resistance mutations or mesenchymal-epithelial transition (MET) amplification.[1] The RYBREVANT® and lazertinib combination group included patients who had progressed on osimertinib but who were chemotherapy-naïve (n=45 [38 percent with EGFR/MET-based resistance]).[1] Disease response using overall response rate (ORR), per Response Evaluation Criteria in Solid Tumors Version 1.1* (RECIST v1.1) was the primary endpoint.[1,2]

Antitumor activity was observed in the group treated with RYBREVANT® in combination with lazertinib, with an ORR of 36 percent (95 percent confidence interval [CI]; 22 – 51), with one patient (2 percent) with complete response and 15 patients (33 percent) with partial responses (PR).[1] The median DOR was 9.6 months (95 percent CI; 5.3 – not reached).[1] In contrast, the RYBREVANT® monotherapy group had an ORR of 19 percent (95 percent CI; 12 – 27) and median DOR of 5.9 months (95 percent CI; 4.2 – 12.6).[1] The clinical benefit rate (CBR), which consisted of complete response, partial response or stable disease at 11 weeks or longer, was 64 percent in the combination group (95 percent CI; 49 – 78) and 48 percent in the monotherapy group (95 percent CI; 39 – 57).[1] The combination group experienced central nervous system (CNS) progression in 7 percent of patients, with 4 percent being new CNS lesions, while the monotherapy group documented 17 percent of patients with CNS progression, with 13 percent being new CNS lesions.[1]

The safety profiles for both combination and monotherapy therapy were consistent with previously reported data, and no new safety signals were identified.[1] Treatment-emergent adverse events (AEs) greater than or equal to 20 percent for RYBREVANT® and lazertinib as a combination therapy include infusion-related reaction (78 percent), acneiform dermatitis

(51 percent), paronychia (49 percent), nausea (44 percent), hypoalbuminemia (38 percent), peripheral edema (38 percent), pruritus (31 percent), dry skin (29 percent), rash (27 percent), constipation (27 percent), stomatitis (27 percent), fatigue (27 percent), dyspnea (24 percent), increased aspartate aminotransferase (22 percent), diarrhea (22 percent), dizziness (22 percent), hypocalcemia (20 percent), vomiting (20 percent) and headache (20 percent).[1] Treatment-emergent AEs greater than or equal to 20 percent for RYBREVANT® as a monotherapy include infusion-related reaction (69 percent), paronychia (37 percent), acneiform dermatitis (28 percent), hypoalbuminemia (26 percent), rash (26 percent), constipation (26 percent), nausea (24 percent), dyspnea (23 percent) and pruritus (22 percent).[1]

In May, the U.S. Food and Drug Administration (FDA) approved RYBREVANT®, a fully human bispecific antibody, as the first targeted treatment for patients with NSCLC with EGFR exon 20 insertion mutations.[3] Additional analyses of RYBREVANT® are ongoing. Lazertinib was approved earlier this year in South Korea for patients with NSCLC with EFGR mutations and T90M mutations.

"The approval of RYBREVANT as a monotherapy was a pivotal moment in the treatment of patients with difficult-to-treat non-small cell lung cancer with EGFR exon 20 insertion mutations. This new analysis builds on the established safety and efficacy profile of RYBREVANT, showing its value for a broader group of patients with EGFR mutations when combined with lazertinib," said Sylvie Laquerre, Ph.D., Vice President, Disease Area Leader, Solid Tumor Targeted Therapies, Janssen Research & Development, LLC. "Janssen is committed to evaluating the potential of these treatments as we work toward transforming the treatment landscape for people with lung cancer."

*RECIST (version 1.1) refers to Response Evaluation Criteria in Solid Tumors, which is a standard way to measure how well solid tumors respond to treatment and is based on whether tumors shrink, remain the same or increase in size.[2]

**About RYBREVANT®**

RYBREVANT® (amivantamab-vmjw) received accelerated approval by the U.S. FDA in May 2021 for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.[4] Shortly after FDA approval, the

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer included amivantamab-vmjw (RYBREVANT®) as a subsequent therapy option with a Category 2A recommendation for patients that have progressed on or after platinum-based chemotherapy with or without immunotherapy and have EGFR exon 20 insertion mutation-positive advanced NSCLC.[5] Janssen has filed regulatory submissions for RYBREVANT® with health authorities in Europe and other markets.

RYBREVANT® is being studied in multiple clinical trials, including the Phase 1/1b CHRYSALIS-2 (NCT04077463) study assessing the combination of RYBREVANT® and lazertinib in patients who have progressed after treatment with osimertinib and chemotherapy; as first-line therapy in untreated advanced EGFR-mutated NSCLC in the Phase 3 MARIPOSA (NCT04487080) study assessing amivantamab in combination with lazertinib; the planned Phase 3 MARIPOSA-2 (NCT04988295) study assessing the efficacy of lazertinib, RYBREVANT® and carboplatin-pemetrexed versus carboplatin-pemetrexed in patients with locally advanced or metastatic EGFR exon 19 deletion or exon 21 L858R substitution NSCLC after osimertinib failure; the Phase 3 PAPILLON (NCT04538664) study assessing RYBREVANT® in combination with carboplatin-pemetrexed versus chemotherapy alone in patients with advanced or metastatic EGFR-mutated NSCLC and exon 20 insertion mutations; and the Phase 1 PALOMA (NCT04606381) study assessing the feasibility of subcutaneous (SC) administration of RYBREVANT® based on safety and pharmacokinetics and to determine a dose, dose regimen and formulation for RYBREVANT® SC delivery.[6,7,8,9,10,11]

*Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V.5.2021. ©National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed June 15, 2021. To view the most recent and complete version of the guidelines, visit NCCN.org.

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**About Lazertinib**

Lazertinib is an oral, third-generation, brain-penetrant, EGFR TKI that targets both the T790M mutation and activating EGFR mutations while sparing wild type-EGFR.[12] Interim safety and efficacy results from the lazertinib Phase 1/2 study were published in *The Lancet Oncology* in 2019. In 2018, Janssen Biotech, Inc. entered into a license and collaboration agreement with Yuhan Corporation for the development of lazertinib.

**About the CHRYSALIS Study**

CHRYSALIS (NCT02609776) is an open-label, multicenter, first-in-human Phase 1 study to evaluate the safety, pharmacokinetics and preliminary efficacy of RYBREVANT® as a monotherapy and in combinations, including with lazertinib, in patients with advanced NSCLC with various EGFR mutations.[6] The study is enrolling 460 patients with advanced NSCLC.[6] The study consists of two parts: The first consists of amivantamab monotherapy and combination dose escalations, and the second consists of amivantamab monotherapy and combination dose expansions.[6]

**About Non-Small Cell Lung Cancer (NSCLC)**

Worldwide, lung cancer is one of the most common cancers, and NSCLC makes up 80 to 85 percent of all lung cancers.[13,14] The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[14] Among the most common driver mutations in NSCLC are alterations in EGFR, which is a receptor tyrosine kinase supporting cell growth and division.[15] Epidermal growth factor receptor mutations are present in 10 to 15 percent[15,16,17,18,19] of people with NSCLC adenocarcinoma and occur in 40 to 50 percent of Asians.[20,21] The five-year survival rate for all people with metastatic NSCLC and EGFR mutations treated with EGFR TKIs is less than 20 percent.[22,23]

**RYBREVANT® IMPORTANT SAFETY INFORMATION**[4]

**WARNINGS AND PRECAUTIONS**

**Infusion Related Reactions**[4]

RYBREVANT® can cause infusion related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

Based on the safety population, IRR occurred in 66% of patients treated with RYBREVANT®. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued RYBREVANT® due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT® as recommended. Administer RYBREVANT® via a peripheral line on Week 1 and Week 2. Monitor patients for any signs and symptoms of infusion reactions during RYBREVANT® infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT® based on severity.

**Interstitial Lung Disease/Pneumonitis**[4]

RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis. Based on the safety population, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT®, with 0.7% of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT® due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT® in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed.

**Dermatologic Adverse Reactions**[4]

RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin. Based on the safety population, rash occurred in 74% of patients treated with RYBREVANT®, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT® was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis occurred in one patient (0.3%) treated with RYBREVANT®.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT®. Advise patients to wear protective clothing and use broad spectrum UVA/UVB sunscreen. Alcohol free emollient cream is recommended for dry skin.

If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

**Ocular Toxicity**[4]

RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis. Based on the safety population, keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT®. All events were Grade 1-2. Promptly refer patients presenting with eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT® based on severity.

**Embryo Fetal Toxicity**[4]

Based on its mechanism of action and findings from animal models, RYBREVANT® can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT®.

**Adverse Reactions**[4]

The most common adverse reactions (≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyl transferase, and decreased sodium.

Please read full Prescribing Information for RYBREVANT®.

**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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†Dr. Leighl has been a paid consultant to Janssen; she has not been paid for any media work.

*Cautions Concerning Forward-Looking Statements*

*This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding RYBREVANT® (amivantamab-vmjw) and lazertinib. 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 Janssen Research & Development, LLC, Janssen Biotech, Inc., 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 January 3, 2021, 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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