Johnson&Johnson

Media contacts:
Jackie Zima Evans
+1 215 534-2973

Suzanne Frost
+1 416 317-0304

Investor contact:
Raychel Kruper
investor-relations@its.jnj.com

U.S. Medical Inquiries
+1 800 526-7736

For Immediate Release

RYBREVANT® (amivantamab-vmjw) in Combination With Chemotherapy Is the First FDA Approved Therapy for First-line Treatment of Patients With Non-Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations

Approval is based on results from the Phase 3 PAPILLON study, which demonstrated RYBREVANT® plus chemotherapy reduced the risk of disease progression or death by 61 percent versus chemotherapy alone in patients with previously untreated NSCLC with EGFR exon 20 insertion mutations

National Comprehensive Cancer Network® (NCCN®) updated its NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) to recommend amivantamab-vmjw (RYBREVANT®) plus chemotherapy as a preferred first-line regimen for patients with NSCLC with EGFR exon 20 insertion mutations

RARITAN, New Jersey (March 01, 2024) – Johnson & Johnson (NYSE: JNJ) announced today that following a priority review, the U.S. Food and Drug Administration (FDA) has approved RYBREVANT® (amivantamab-vmjw) in combination with chemotherapy (carboplatin-pemetrexed) for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations as detected by an FDA-approved test.[1] This FDA action converts the May 2021 accelerated approval of RYBREVANT® to a full approval based on the confirmatory Phase 3 PAPILLON study.

“When aiming for the best possible treatment outcomes, a targeted approach should be used in the first line for patients with EGFR exon 20 insertion mutations, as this is a commonly applied practice for patients with NSCLC harboring other molecular driver alterations,” said Joshua K. Sabari, M.D.*, an oncologist at NYU Langone’s Perlmutter Cancer Center and study investigator.* “The results observed in the PAPILLON study showed significant improvement in progression-free survival, supporting the use of this regimen as the potential standard-of-care in the first-line treatment of these patients.”

Worldwide, lung cancer is one of the most common cancers, with NSCLC making up 80 to 85 percent of all lung cancer cases.[2,3] Alterations in EGFR are the most common actionable driver mutations in NSCLC.[4] Clinical data show patients with EGFR exon 20 insertion mutations generally experience limited benefits with currently approved third-generation EGFR tyrosine kinase inhibitors and chemotherapy.[5,6] NSCLC driven by EGFR exon 20 insertion mutations carries a worse prognosis and shorter survival rates compared with lung cancer driven by other EGFR driver mutations.[7]

“For patients with lung cancer and their families, each breakthrough in treatment provides not only a new option, but a potential lifeline. The approval of RYBREVANT plus chemotherapy heralds a promising new first-line treatment option for patients newly diagnosed with non-small cell lung cancer where their driver mutation is an EGFR exon 20 insertion,” said Marcia Horn**, Executive Director of the Exon 20 Group and CEO of ICAN, International Cancer Advocacy Network. “This new regimen is a major advance over chemotherapy alone. We’ve seen first-hand the extended survival that Exon 20 Group patients experienced on RYBREVANT plus chemotherapy in the PAPILLON study, and we’re delighted that this historic treatment option, which specifically targets the EGFR exon 20 insertion mutation, has been approved.”

The FDA approval is based on positive results from the randomized, open-label Phase 3 PAPILLON study, which showed RYBREVANT® plus chemotherapy resulted in a 61 percent reduction in the risk of disease progression or death compared to chemotherapy alone.[1] Results also showed treatment with RYBREVANT® plus chemotherapy improved objective response rate (ORR) and progression-free survival (PFS).[1] Based on PAPILLON data, the National Comprehensive Cancer Network® (NCCN®) updated its’ NCCN Clinical Practice Guidelines (NCCN Guidelines®) to include a category 1 recommendation for

amivantamab-vmjw (RYBREVANT®) plus chemotherapy as a preferred first-line therapy for patients with NSCLC with EGFR exon 20 insertion mutations.[8 †‡]

“We are redefining care for patients with non-small cell lung cancer by advancing innovative regimens that can be used early, with the goal of extending survival,” said Kiran Patel, M.D., Vice President, Clinical Development, Solid Tumors, Johnson & Johnson Innovative Medicine. “RYBREVANT plus chemotherapy is the first targeted approach approved for the first-line treatment of patients with NSCLC with EGFR exon 20 insertion mutations. We look forward to building on this latest milestone as we continue to accelerate our transformative lung cancer portfolio.”

Warnings and Precautions include Infusion Related Reactions (IRR), Interstitial Lung Disease (ILD)/Pneumonitis, Dermatologic Adverse Reactions, Ocular Toxicity and Embryo-fetal Toxicity. The most common adverse reactions (≥20 percent) were rash, nail toxicity, stomatitis, IRR, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea and vomiting. The most common Grade 3 or 4 laboratory abnormalities (≥2 percent) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.[1]

About the PAPILLON Study

PAPILLON (NCT04538664) is a randomized, open-label Phase 3 study evaluating the efficacy and safety of RYBREVANT® in combination with chemotherapy, compared with chemotherapy alone, in newly diagnosed patients with advanced or metastatic NSCLC characterized by EGFR exon 20 insertion mutations. The primary endpoint of the study is PFS (using RECIST v1.1 guidelines[§]) as assessed by blinded independent central review (BICR). Secondary endpoints include ORR, PFS after first subsequent therapy, time to symptomatic progression and overall survival (OS). Patients who received chemotherapy alone were allowed to receive RYBREVANT® monotherapy in the second-line setting after confirmation of disease progression.[10]

About RYBREVANT®

RYBREVANT® (amivantamab-vmjw), a fully-human bispecific antibody targeting EGFR and MET with immune cell-directing activity is approved in the U.S., Europe and in other markets around the world as monotherapy 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.[1] This indication is approved under accelerated approval based on ORR and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. RYBREVANT® is also approved in the U.S. in combination with chemotherapy (carboplatin and pemetrexed) for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test. In October 2023, a type II extension of indication application was submitted to the European Medicines Agency (EMA) seeking approval of RYBREVANT® for this indication. In December 2023, Johnson & Johnson submitted an sBLA together with a New Drug Application (NDA) to the U.S. FDA for RYBREVANT® in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or L858R substitution mutations, as detected by an FDA-approved test. This submission is based on the Phase 3 MARIPOSA study and was granted Priority Review in February 2024. A marketing authorization application (MAA) and type II extension of indication application were also submitted to the EMA seeking approval of lazertinib in combination with RYBREVANT® based on the MARIPOSA study. In November 2023, Johnson & Johnson submitted an sBLA to the U.S. FDA for RYBREVANT® in combination with chemotherapy for the treatment of patients with EGFR-mutated NSCLC who progressed on or after osimertinib based on the MARIPOSA-2 study. A type II extension of indication application was also submitted to the EMA seeking the approval of RYBREVANT® for this indication.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for NSCLC[‖] prefer next-generation sequencing-based strategies over polymerase chain reaction-based approaches for the detection of EGFR exon 20 insertion variants. The NCCN Guidelines® include:

- Amivantamab-vmjw (RYBREVANT®) plus carboplatin and pemetrexed as a preferred (Category 1 recommendation) first-line therapy in treatment-naive patients with newly diagnosed advanced or metastatic EGFR exon 20 insertion mutation-positive advanced NSCLC, or as a subsequent therapy option (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.[8 †‡]
- Amivantamab-vmjw (RYBREVANT®) plus chemotherapy as a preferred (Category 1 recommendation) subsequent therapy for patients with locally advanced or metastatic NCSLC with EGFR exon 19 deletions or exon 21 L858R mutations who experienced disease progression after treatment with osimertinib.[8 †‡]
- Amivantamab-vmjw (RYBREVANT®) as a subsequent therapy option (Category 2A recommendation) for patients that have progressed on or after platinum-based chemotherapy with or without an immunotherapy and have EGFR exon 20 insertion mutation-positive NSCLC.[8 †‡]

In addition to the Phase 3 PAPILLON study, RYBREVANT® is being studied in multiple clinical trials in NSCLC, including:

- The Phase 3 MARIPOSA-2 (NCT04988295) study evaluating the efficacy and safety of RYBREVANT® and chemotherapy in patients with locally advanced or metastatic EGFR ex19del or L858R substitution NSCLC who had disease progression on or after treatment with osimertinib. Data for this randomized Phase 3 study presented at the ESMO 2023 Congress demonstrated statistically significant and clinically meaningful improvement in PFS in patients receiving RYBREVANT® plus chemotherapy with and without lazertinib versus chemotherapy.[11,12]
- The Phase 3 MARIPOSA (NCT04487080) study assessing RYBREVANT® in combination with lazertinib, a novel third-generation EGFR TKI, versus osimertinib and versus lazertinib alone in the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions (ex19del) or L858R substitution mutations. Data for this randomized Phase 3 study presented at the ESMO 2023 Congress showed statistically significant and clinically meaningful improvement in progression-free survival in patients with EGFR-mutated advanced NSCLC treated with RYBREVANT® plus lazertinib versus osimertinib.[13,14]
- The Phase 1 CHRYSALIS (NCT02609776) study evaluating RYBREVANT® in participants with advanced NSCLC.[15]

- The Phase 1/1b CHRYSALIS-2 (NCT04077463) study evaluating RYBREVANT® in combination with lazertinib and lazertinib as a monotherapy in patients with advanced NSCLC with EGFR mutations.[16]
- The Phase 1 PALOMA (NCT04606381) study assessing the feasibility of subcutaneous (SC) administration of amivantamab based on safety and pharmacokinetics and to determine a dose, dose regimen and formulation for amivantamab SC delivery.[17]
- The Phase 2 PALOMA-2 (NCT05498428) study assessing subcutaneous amivantamab in participants with advanced or metastatic solid tumors including EGFR-mutated NSCLC.[18]
- The Phase 3 PALOMA-3 (NCT05388669) study assessing lazertinib with subcutaneous amivantamab compared to intravenous amivantamab in participants with EGFR-mutated advanced or metastatic NSCLC.[19]
- The Phase 1/2 METalmark (NCT05488314) study assessing RYBREVANT® and capmatinib combination therapy in locally advanced or metastatic NSCLC.[20]
- The Phase 1/2 PolyDamas (NCT05908734) study assessing RYBREVANT® and cetrelimab combination therapy in locally advanced or metastatic NSCLC.[21]
- The Phase 2 SKIPPirr study (NCT05663866) exploring how to decrease the incidence and/or severity of first-dose infusion-related reactions with RYBREVANT® in combination with lazertinib in relapsed or refractory EGFR-mutated advanced or metastatic NSCLC.[22]
- The Phase 2 COCOON study (NCT06120140) will evaluate enhanced dermatological care to reduce rash and paronychia in patients with EGFR-mutated NSCLC treated first-line with amivantamab plus lazertinib.[23]

For more information, visit: https://www.RYBREVANT.com.

About Non-Small Cell Lung Cancer

Worldwide, lung cancer is one of the most common cancers, with NSCLC making up 80 to 85 percent of all lung cancer cases.[2,3] The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[24] Among the most common driver mutations in NSCLC are alterations in EGFR, which is a receptor tyrosine kinase controlling cell growth and division.[4] EGFR mutations are present in 10 to 15 percent of Western patients with NSCLC with adenocarcinoma histology and occur in 40 to 50 percent of Asian patients.[4,24,25,26,27,28] EGFR ex19del or EGFR L858R mutations are the most common EGFR mutations.[29] The five-year survival rate for all people with advanced NSCLC and EGFR mutations treated with EGFR TKIs is less than 20 percent.[30,31] Patients with EGFR ex19del or L858R mutations have a real-world five-year OS of 19 percent.[32]

RYBREVANT® IMPORTANT SAFETY INFORMATION[1]

WARNINGS AND PRECAUTIONS
The safety population of RYBREVANT® with carboplatin and pemetrexed described in Warnings and Precautions was based on 151 patients in the PAPILLON study.

The safety population of RYBREVANT® as a single agent described in Warnings and Precautions was based on 129 patients in the CHRYSALIS study.

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

RYBREVANT® with Carboplatin and Pemetrexed

RYBREVANT® in combination with carboplatin and pemetrexed can cause infusion-related reactions. Based on the safety population, infusion-related reactions occurred in 42% of patients treated with RYBREVANT® in combination with carboplatin and pemetrexed, including Grade 3 (1.3%) adverse reactions. The incidence of infusion modifications due to IRR was 40%, and 0.7% of patients permanently discontinued RYBREVANT®.

RYBREVANT® as a Single Agent

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
RYBREVANT® can cause interstitial lung disease (ILD)/pneumonitis.

RYBREVANT® with Carboplatin and Pemetrexed

Based on the safety population, Grade 3 ILD/pneumonitis occurred in 2.6% of patients treated with RYBREVANT® in combination with carboplatin and pemetrexed. All patients required permanent discontinuation.

RYBREVANT® as a Single Agent

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
RYBREVANT® can cause rash (including dermatitis acneiform), pruritus and dry skin.

RYBREVANT® with Carboplatin and Pemetrexed

RYBREVANT® in combination with carboplatin and pemetrexed can cause dermatologic adverse reactions. Based on the safety population, rash occurred in 89% of patients treated with RYBREVANT® in combination with carboplatin and pemetrexed, including Grade 3 (19%) adverse reactions. Rash leading to dose reductions occurred in 19% of patients; 2% permanently discontinued RYBREVANT®, and 1.3% discontinued pemetrexed.

RYBREVANT® as a Single Agent

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® as a single agent.

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
RYBREVANT® can cause ocular toxicity including keratitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, and uveitis.

RYBREVANT® with Carboplatin and Pemetrexed

Based on the safety population, RYBREVANT® in combination with carboplatin and pemetrexed can cause ocular toxicity including blepharitis, dry eye, conjunctival redness, blurred vision, and eye pruritus. All events were Grade 1-2.

RYBREVANT® as a Single Agent

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
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 last dose of RYBREVANT®.

Adverse Reactions
RYBREVANT® with Carboplatin and Pemetrexed

For the 151 patients in the PAPILLON clinical trial who received RYBREVANT® in combination with carboplatin and pemetrexed, the most common adverse reactions (≥20%) were rash (90%), nail toxicity (62%), stomatitis (43%), infusion-related reaction (42%), fatigue (42%), edema (40%), constipation (40%), decreased appetite (36%), nausea (36%), COVID-19 (24%), diarrhea (21%), and vomiting (21%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased albumin (7%), increased alanine aminotransferase (4%), increased gamma-glutamyl transferase (4%), decreased sodium (7%), decreased potassium (11%), decreased magnesium (2%), and decreases in white blood cells (17%), hemoglobin (11%), neutrophils (36%), platelets (10%), and lymphocytes (11%).

Serious adverse reactions occurred in 37% of patients who received RYBREVANT® in combination with carboplatin and pemetrexed. Serious adverse reactions in ≥2% of patients included rash, pneumonia, ILD, pulmonary embolism, vomiting, and COVID-19. Fatal adverse reactions occurred in 7 patients (4.6%) due to pneumonia, cerebrovascular accident, cardio-respiratory arrest, COVID-19, sepsis, and death not otherwise specified.

RYBREVANT® as a Single Agent

For the 129 patients in the CHRYSALIS clinical trial who received RYBREVANT® as a single agent, the most common adverse reactions (≥20%) were rash (84%), IRR (64%), paronychia (50%), musculoskeletal pain (47%), dyspnea (37%), nausea (36%), fatigue (33%), edema (27%), stomatitis (26%), cough (25%), constipation (23%), and vomiting (22%). The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased lymphocytes (8%), decreased albumin (8%), decreased phosphate (8%), decreased potassium (6%), increased alkaline phosphatase (4.8%), increased glucose (4%), increased gamma-glutamyl transferase (4%), and decreased sodium (4%).

Serious adverse reactions occurred in 30% of patients who received RYBREVANT®. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Please read the full Prescribing Information for RYBREVANT®.

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. Learn more at https://www.jnj.com/ or at www.janssen.com/johnson-johnson-innovative-medicine. Follow us at @JanssenUS and @JNJInnovMed. Janssen Research & Development, LLC, and Janssen Biotech, Inc., are both Johnson & Johnson companies.

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 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 of Janssen Research & Development, LLC, Janssen Biotech, Inc., and 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; competition, including technological advances, new products and patents attained by competitors; challenges to patents; 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 1, 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 Research & Development, LLC, Janssen Biotech, Inc., and Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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*Dr. Sabari has served as a consultant to Johnson & Johnson; he has not been paid for any media work.

**Ms. Horn has not been paid for any media work.

†See the NCCN Guidelines for detailed recommendations, including other treatment options.

‡The NCCN Guidelines for NSCLC provide recommendations for certain individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays or commercial laboratories.

§RECIST (v1.1) 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, stay the same or get bigger.

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