News Release

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Merck KGaA, Darmstadt, Germany Unveils New MAVENCLAD® Four-Year Data Highlighting Benefits of Early Treatment and Sustained Efficacy Across Multiple Measures of Disease Activity

- **Phase IV studies demonstrate the consistent safety and high efficacy of MAVENCLAD on NEDA-3, MRI and cognition outcomes over four years**
- **New data on blood and CSF biomarkers show the impact of MAVENCLAD to promote immune cell reconstitution, while clinical data confirmed 93.7% of patients free from PIRA**
- **MAVENCLAD has now treated more than 100,000 patients globally, underscoring its trusted efficacy and safety profile**

Darmstadt, Germany, September 12, 2024 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced presentations showcasing the long-term safety profile, sustained efficacy data, and durable effect of MAVENCLAD® (cladribine) tablets in individuals with relapsing multiple sclerosis (RMS). Among 34 total MAVENCLAD presentations are data from several MAGNIFY-MS sub-studies demonstrating the impact of MAVENCLAD on disability progression, central inflammation, and an oral presentation on immune reconstitution effects. These data, along with six other company abstracts, will be presented at the 40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) taking place September 18-20 in Copenhagen.

"The efficacy of MAVENCLAD has long been established through traditional endpoints from our original pivotal trials and beyond. Now, with additional measures

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of the impact on neuroinflammation and progression, we can reaffirm and further solidify its long-term efficacy position within the MS treatment landscape," said Alexander Kulla, Senior Vice President & Medical Unit Head Neurology & Immunology at Merck KGaA, Darmstadt, Germany. "MAVENCLAD continues to demonstrate its consistent safety profile with sustained benefits, impacting the lives of more than 100,000 people living with MS."

Results from the MAGNIFY-MS extension, a Phase IV study evaluating patients (n=219) on MAVENCLAD with highly active RMS, confirmed 79.2% of patients achieved no evidence of disease activity (NEDA-3) during Year 4 of the treatment. The annualized relapse rate (ARR) remained low overall (0.09) and was further reduced (0.06) in treatment-naïve patients over four years. Similarly, the CLARIFY-MS extension showed the sustained benefits in MAVENCLAD-treated patients (n=280) on cognition, in addition to MRI outcomes and relapses, four years after the initial treatment dose. Specific to cognition, 77.5% of patients had improved or stable scores at four years, based on the 8-point cut-off of the Symbol Digit Modalities Test (SDMT). In both studies, safety data aligned with the established profile from clinical trials.

Two-year data from a MAGNIFY-MS sub-study found patients with highly active RMS treated with MAVENCLAD had low overall disability accrual, including low rates of progression independent of relapse activity (PIRA). At two years, rates for all disability measures were low overall with 93.7% of patients free from PIRA. The reduction of PIRA is especially notable in treatment-naïve patients (3.4% vs 8.5% in treatment-experienced patients), emphasizing the benefits of early treatment initiation with MAVENCLAD. Overall, these data suggest that MAVENCLAD is likely to preserve the physical abilities and prevent relapses in individuals with RMS, supporting the sustained efficacy and durable effect of MAVENCLAD.

Building on prior data, which showed MAVENCLAD reduces or eliminates oligoclonal bands in the cerebrospinal fluid (CSF), new two-year data demonstrate reductions in gene expression and protein levels of markers associated with inflammation, including pro-inflammatory cytokines, providing insights into the potential multifaceted effect of MAVENCLAD in the peripheral blood and CSF. This data suggests that immune reconstitution following treatment with cladribine tablets may

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shift the immune system to a less pathogenic state. Analyses of CSF proteomics and T and B cell transcriptomics further substantiate the clinical findings, suggesting the potential of MAVENCLAD to reduce disease activity and progression in RMS patients.

To view our 40 accepted abstracts and posters to be presented from across our MS portfolio at ECTRIMS, including innovative analyses of MAVENCLAD using artificial intelligence, please visit the Programme.

About MAVENCLAD®
MAVENCLAD, approved by the U.S. Food and Drug Administration (FDA) on March 29, 2019, is the first and only short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of multiple sclerosis (MS), and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). Patients should follow healthcare provider instructions including cancer screening, contraception, and blood tests. The approved dose of MAVENCLAD is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year, each consisting of two treatment weeks. The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. MAVENCLAD causes a dose-dependent reduction in lymphocyte counts followed by recovery.

Because cladribine is cytotoxic, special handling and disposal instructions should be followed.

More than 100,000 patients have been treated with MAVENCLAD since its launch in 2019. MAVENCLAD has been approved in over 80 countries, including the European Union (EU), Canada, Australia and Switzerland, for various relapsing MS indications. Visit www.MAVENCLAD.com for more information.

IMPORTANT SAFETY INFORMATION

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.**
- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant.**

CONTRAINDICATIONS

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients infected with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.

- Women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose.

WARNINGS AND PRECAUTIONS

- **Malignancies:** Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.

- **Risk of Teratogenicity:** MAVENCLAD may cause fetal harm when administered to pregnant women. In females of reproductive potential, exclude pregnancy before initiation of each treatment course of MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment.

- **Lymphopenia:** MAVENCLAD causes a dose-dependent reduction in lymphocyte count. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before, during, and after treatment.

- **Infections:** Serious, including life-threatening or fatal, infections have occurred. MAVENCLAD reduces the body's immune defense, and an increased risk of infections has been observed in patients receiving MAVENCLAD. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies; serious or severe infections occurred in 2.4% of MAVENCLAD- treated patients and 2.0% of placebo-treated patients. The most frequent serious infections included herpes zoster and pyelonephritis. Fungal infections were observed, including cases of coccidioidomycosis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program.
    - Screen patients for active and latent infections (tuberculosis, hepatitis B or C). Delay treatment until infection is fully resolved or controlled.
    - Vaccinate patients who are seronegative for varicella zoster virus (VZV) prior to treatment. Vaccinate patients who are seropositive to VZV with recombinant, adjuvanted zoster vaccine either prior to or during treatment, including when their lymphocyte counts are less than or equal to 500 cells per microliter.
    - Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections.
    - Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with parenteral cladribine for oncologic indications. No case of PML has been reported in clinical studies of cladribine in patients with MS. Obtain a baseline magnetic resonance imaging (MRI) within 3 months before initiating the first treatment course of MAVENCLAD. At the first sign of PML, withhold MAVENCLAD and perform an evaluation.
    - Administer all immunizations (except as noted for VZV) according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD due to risk of infection.

- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.

- **Graft-versus-Host Disease with Blood Transfusions:** Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications. In patients who require blood transfusion, irradiation of cellular blood components is recommended.

- **Liver Injury:** In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0 placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue MAVENCLAD if clinically significant liver injury is suspected.

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- **Hypersensitivity:** If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.
- **Cardiac Failure:** In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis. Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling).

Adverse Reactions: The most common adverse reactions (incidence of >20%) are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions: Concomitant use of with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Acute short-term therapy with corticosteroids can be administered. Monitor for additive effects on the hematological provide with use of hemotoxic drugs. Avoid concomitant use of antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Use in Specific Populations: Studies have not been performed in pediatric, or elderly patients >65 years, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.
To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono, Inc. at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see FULL PRESCRIBING INFORMATION, including **BOXED WARNING,** for additional information.

About Multiple Sclerosis
Multiple sclerosis (MS) is a chronic, inflammatory condition of the central nervous system and is the most common non-traumatic, disabling neurological disease in young adults. It is estimated that approximately 2.9 million people have MS worldwide. While symptoms can vary, the most common symptoms of MS include blurred vision, numbness or tingling in the limbs and problems with strength and coordination. The relapsing forms of MS are the most common.

Merck KGaA, Darmstadt, Germany in Neurology and Immunology
Merck KGaA, Darmstadt, Germany has a long-standing legacy in neurology and immunology, with significant R&D and commercial experience in multiple sclerosis (MS). The company's current MS portfolio includes two products for the treatment of relapsing MS – Rebif® (interferon beta-1a) and MAVENCLAD® (cladribine) tablets. Merck KGaA, Darmstadt, Germany aims to improve the lives of patients by addressing areas of unmet medical needs. In addition to Merck KGaA, Darmstadt, Germany's commitment to MS, the company also has a pipeline focusing on discovering new therapies that have potential in other neuroinflammatory and immune-mediated diseases, including systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE) and generalized myasthenia gravis (gMG).

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across life science, healthcare and electronics. Around 63,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From providing products and services that accelerate drug development and manufacturing as well as discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2023, Merck KGaA, Darmstadt, Germany, generated sales of €21 billion in 65 countries.

The company holds the global rights to the name and trademark "Merck" internationally. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany, operate as MilliporeSigma in life science, EMD Serono in healthcare and EMD Electronics in electronics. Since its founding in 1668, scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.

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