News Release

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Merck KGaA, Darmstadt, Germany Announces New Data Strengthening Evidence for Continued Safe and Effective MAVENCLAD® Use During the COVID-19 Pandemic

- **New analysis indicates a specific immune repopulation pattern in people treated with MAVENCLAD, which may contribute to their ability to fight infections and develop protective antibodies from vaccines**
- **Independent study from Israel showed MAVENCLAD-treated patients receiving COVID-19 vaccine were able to mount antibody response similar to that of healthy subjects**
- **Updated safety data show MAVENCLAD-treated patients with confirmed or suspected COVID-19 continue to have a disease course similar to the general population**

Darmstadt, Germany, April 23, 2021 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced a new analysis from the MAGNIFY-MS sub-study showing a specific immune repopulation pattern in patients with relapsing multiple sclerosis (RMS) treated with MAVENCLAD® (cladribine) tablets, which may contribute to their ability to fight infections and develop protective antibodies from vaccines. The data were presented at the 2021 American Academy of Neurology (AAN) Annual Meeting that was held virtually April 17-22, 2021.

In the MAGNIFY-MS study, reduction of memory B cells occurred as early as one month after MAVENCLAD initiation with lowest levels sustained for up to 12 months, while naïve B cells, which are typically required for the generation of antibody responses following vaccination, began recovering immediately. Previously shared data from MAGNIFY-MS indicated that patients receiving MAVENCLAD are able to

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mount responses to influenza and varicella zoster vaccines, irrespective of lymphocyte count.

In the U.S., the MAVENCLAD label states that all immunizations should be administered according to immunization guidelines prior to starting MAVENCLAD.

"The findings presented at AAN further our understanding of how MAVENCLAD impacts the immune system, and how it may exert a therapeutic effect in patients with multiple sclerosis while repopulating cells which support immune responses," said Heinz Wiendl, MD, Department of Neurology with Institute of Translational Neurology, University of Muenster, Germany. "These important data indicate that in addition to addressing MS relapses and progression, patients treated with MAVENCLAD may be able to simultaneously mount a proper vaccine response – a particularly important finding at this time."

In addition, a recent independent study conducted by Anat Achiron, MD, PhD, FAAN and colleagues, The Multiple Sclerosis Center at Sheba Medical Centre and Sackler School of Medicine Tel Aviv University, Israel, and recently published in *Therapeutic Advances in Neurological Disorders*, shows that patients who have taken MAVENCLAD were able to generate COVID-19 antibodies following the mRNA vaccine from Pfizer/BioNTech administered 4.4 months after last MAVENCLAD dosing. The observational analysis showed that all 23 relapsing-remitting MS patients treated with MAVENCLAD who received the Pfizer/BioNTech mRNA vaccine developed a protective SARS-COV-2 IgG antibody response [antibody titer >1.1 is considered positive; median=7.0], which was similar to the comparison group of MS patients not receiving any immunomodulatory treatments and healthy subjects. Humoral response to the COVID-19 vaccine was independent of lymphocyte count. No unexpected safety findings post first and second dose of Pfizer/BioNTech COVID-19 vaccination were identified in MS patients, according to another recent publication in the *Multiple Sclerosis Journal*.

"Bringing MAVENCLAD-treated patients into a state where they can live their lives as normally as possible during a global pandemic is of utmost importance to us," said Danny Bar-Zohar, MD, Global Head of Development for the Healthcare business sector of Merck KGaA, Darmstadt, Germany. "Beyond the convenient oral

dosing schedule, proven efficacy, and well-characterized safety profile of MAVENCLAD, newly generated data now show encouraging initial evidence for these patients' ability to generate adequate antibody response to COVID-19 vaccination, which is so important for patients."

The ability to mount an adequate immune response is critical as the COVID-19 pandemic impacts patients living with chronic disease around the world. As presented at AAN, and also published in MSaRD, an updated post-approval safety analysis provided a look at outcomes from cases of COVID-19 in MAVENCLAD-treated patients. The safety database analysis included cases of confirmed (n=160) or suspected (n=101) COVID-19 in MAVENCLAD-treated patients. Based on the analysis, the majority of patients had mild to moderate respiratory symptoms and none required mechanical ventilation. MAVENCLAD-treated patients had a similar disease course with COVID-19 compared with the general population who acquired COVID-19.

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.

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 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 while taking MAVENCLAD tablets 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. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.
- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of 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.
- **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 if clinically significant injury is suspected.
- **Hypersensitivity:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. 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.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD 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.

Avoid concomitant use of certain 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, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

Please see the 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 2.8 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).

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and performance materials. Around 58,000 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 advancing gene editing technologies and discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2020, Merck KGaA, Darmstadt, Germany, generated sales of € 17.5 billion in 66 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 EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials. Since its founding 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.