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Merck KGaA, Darmstadt, Germany Highlights New Four-Year Efficacy and Safety Data for Investigational BTK Inhibitor, Evobrutinib, in RMS

- **Data from the ongoing Phase II extension showed treatment benefits of evobrutinib were maintained over four years and remained consistent with the efficacy and safety profile seen in earlier data**
- **Evobrutinib is an investigational highly-selective, oral, CNS-penetrant BTK inhibitor with the potential to become a safe and highly efficacious treatment option for people living with RMS**

Darmstadt, Germany, February 23, 2023 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced updated long-term efficacy and safety data for investigational evobrutinib that continue to show a favorable safety and tolerability profile, consistent with what was seen earlier in the double-blind period (DBP) of the clinical trials. These data also continue to demonstrate its treatment benefit in reducing annualized relapse rates (ARR) over four years in people with relapsing multiple sclerosis (RMS). Data will be presented at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2023, taking place February 23-25.

Data from the ongoing Phase II open-label extension (OLE) trial of evobrutinib showed that treatment benefits were maintained over four years, with no new safety signals. Pooled ARR at week 228 of the OLE for all patients across the original DBP dosing groups was 0.13, with a further reduction seen in the period after switching

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News Release

from evobrutinib 75mg once-daily to 75mg twice-daily, from 0.19 to 0.10. For those receiving 75mg twice-daily dosing in the DBP, ARR was 0.11 at the end of DBP and 0.12 at week 228 of OLE. These data further support the twice-daily dosing currently being examined in Phase III clinical trials.

Overall, treatment emergent adverse events (TEAEs) were mild/moderate in the OLE, with 3.3% (n=7) of patients with RMS experiencing a serious TEAE. No new safety signals were seen in the OLE and evobrutinib continued to show consistent tolerability after up to four years of treatment. There was no dose dependent increase in TEAEs observed in patients who switched to twice-daily evobrutinib 75mg in the OLE.

"The MS community needs treatment options for both relapses and progression independent of relapse. This new long-term data complements previously presented data demonstrating evobrutinib's impact on novel markers indicative of progression independent of relapse, such as slowly expanding lesions. Together, these data highlight evobrutinib's potential to deliver a safe and highly efficacious option for people living with RMS," said Jan Klatt, Senior Vice President, Head of Development Unit Neurology & Immunology, Merck KGaA, Darmstadt, Germany. "We look forward to presenting detailed results from our fully enrolled Phase III clinical trials in the near future."

Additionally, at ACTRIMS, data will be presented that includes analyses of the CLARIFY-MS study, showing the potential of MAVENCLAD® (cladribine) tablets to improve outcomes in an impactful way for people living with RMS.

- Participants maintained their employment status over the two years of the study, which included the COVID-19 pandemic, with 43.4% (n=209) of patients employed full-time at month 24, compared to 47.5% (n=229) at baseline.
- Cognitive function remained stable over two years of treatment as measured at baseline, 12 and 24 months through the Brief International Cognitive Assessment for MS (BICAMS) battery, which is comprised of tests of mental processing speed and memory.

News Release

To keep up to date with our activities at ACTRIMS along with future data and information, please visit merckneurology.com/newsroom or follow us on Twitter @MerckHealthcare and LinkedIn: Healthcare Business of Merck

About Evobrutinib
Evobrutinib is an oral, CNS-penetrating, highly selective inhibitor of Bruton's tyrosine kinase (BTK) in clinical development as a potential treatment for relapsing multiple sclerosis (RMS). It is the first BTK inhibitor to demonstrate clinical efficacy in the largest Phase II study with follow-up beyond three years as well as demonstrate an impact on early biomarkers of ongoing central inflammation that correlate with disease progression, including slowly expanding lesions (SEL) volume and levels of blood neurofilament light chain protein (NfL). Evobrutinib is designed to modulate B cell responses such as proliferation and antibody and cytokine release, as well as modulate macrophage/microglia activation. During Phase II, the BTKi dose finding study demonstrated that BID dosing achieved maximal efficacy with >95% BTK occupancy maintained in 98% of patients before the next dose. Evobrutinib is currently under clinical investigation and is not approved for any use anywhere in the world.

About the Open-Label Extension (OLE) Phase II Clinical Trial with Evobrutinib
In the 48 week double-blind period (DBP), patients with RMS were assigned to one of five treatment groups: placebo (switching to 25mg once-daily evobrutinib after 24 weeks), 25mg or 75mg once-daily evobrutinib, 75mg twice-daily evobrutinib, or open-label dimethyl fumarate (120mg twice daily for the first week and 240mg twice daily thereafter). At week 48, patients could enter the OLE and received evobrutinib 75mg once daily for a mean time of 49.8 weeks before switching to 75mg twice daily for the remainder of the OLE.

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.

News Release

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.

News Release

- **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), generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD).

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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 60,000 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 2021, Merck KGaA, Darmstadt, Germany, generated sales of € 19.7 billion in 66 countries.

News Release

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.