News Release

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Merck KGaA, Darmstadt, Germany Highlights New Data for Evobrutinib, First BTKi to Demonstrate Sustained Clinical Benefit for People with RMS through Three and a Half Years of Treatment

- **Phase II clinical trial data of evobrutinib demonstrated low disease activity and stable EDSS, with NfL levels, a marker of neuronal injury, remaining low in people with RMS after three and a half years of therapy**
- **Late-breaking data showed evobrutinib-treated patients mounted an antibody response to mRNA COVID vaccinations similar to that of healthy subjects**
- **Evobrutinib is an investigational highly-selective, oral, CNS-penetrant BTK inhibitor with the potential to become a best-in-class treatment option for people living with RMS**

Darmstadt, Germany, October 26, 2022 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced findings which demonstrated that annualized relapse rates (ARR) remained low and Expanded Disability Status Scale (EDSS) scores were stable in people with relapsing multiple sclerosis (RMS) treated with investigational evobrutinib through more than three and half years. Additionally, the number of T1 gadolinium-enhancing (Gd+) lesions and T2 lesion volume remained low for the duration of the open-label extension (OLE) of the Phase II clinical trial. These data, presented at the 38th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS),

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suggest the long-term positive benefits of evobrutinib for people with RMS as a potential best-in-class therapy.

Evobrutinib is an oral, highly selective, central nervous system (CNS) penetrant immunomodulator that has the potential to become a safe and highly efficacious treatment option for RMS by addressing both peripheral and central drivers of inflammation through inhibition of Bruton's tyrosine kinase (BTK) signaling in B cells as well as microglia. The dual-faceted approach of evobrutinib may offer better control of silent progression of the disease in between attacks on top of strong relapse control in people living with RMS.

"Disease progression is a top concern in the MS community. Learning more about silent disease progression without relapses will help us further our understanding of MS, along with potential treatments, as it has not just physical but also cognitive and mental deleterious impact," said Patrick Vermersch, MD, PhD, Vice President, Research in Biology and Health, University of Lille. "In this longest-running and most extensive analysis of any BTK inhibitor in development for RMS, evobrutinib maintained disease stability for up to three and half years. It also has the potential to directly address smoldering inflammation in RMS which contributes to the silent causes of disease progression. It has previously shown promising results in targeting central inflammation, including through its modulatory effects on microglia."

The OLE of the Phase II clinical trial evaluated the long-term treatment effect of evobrutinib on ARR, EDSS scores and several magnetic resonance imaging (MRI) outcomes, in people with RMS:

- Patients assigned to the initial 75mg twice-daily arm, maintained a low ARR of 0.13 throughout the course of the OLE. In addition, switching from 75mg once-daily to 75mg twice-daily in the OLE reduced ARR from 0.19 to 0.09
- Overall, mean EDSS scores, as well as MRI lesion activity remained low and stable throughout the entire study

These data points further strengthen the observations made previously that maximal BTK occupancy throughout the dosing interval achieved with twice-daily dosing is correlated to higher ARR reductions with evobrutinib.

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The Company also presented new long-term data from the Phase II clinical trial OLE which found reductions of blood neurofilament light chain (NfL) levels, a key biomarker which may predict future brain volume loss and disease progression. Patients experienced sustained and ongoing reductions in blood NfL levels compared to the double-blind period (DBP) and OLE baseline values. A dose of 75mg twice-daily significantly reduced NfL levels from week 12 (DBP), compared to placebo/evobrutinib 25mg once-daily showing an early dose-response. This reduction in NfL provides evidence evobrutinib may reduce neuronal damage in people with RMS.

"This is the first time that evidence of sustained efficacy out to three and a half years could be shown with a BTK inhibitor in RMS," said Jan Klatt, Senior Vice President, Head of Development Unit Neurology and Immunology, Merck KGaA, Darmstadt, Germany. "Combined with our previous data demonstrating reduced volume of slowly expanding lesions, indicative of an effect on microglia, and reduced neurofilament levels, a marker of neuronal injury, we are confident evobrutinib has the potential to offer best-in-class efficacy for people living with RMS."

Late-breaking data from a *post hoc* analysis of vaccinated patients (n=24) in the Phase II OLE were also presented, showing 96% of people with RMS treated with evobrutinib (75mg twice daily) were able to mount an antibody response following two doses of an mRNA COVID-19 vaccine, similar to untreated RMS patients and healthy subjects. The increase in antibody response in seronegative and seropositive patients demonstrated a preserved response to novel and recall antigens. This is the first time this could be shown with a BTK inhibitor in RMS and these findings are consistent with the modulation of B cell function, providing a potentially alternative treatment to B cell depletion approaches.

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.

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About the Open-Label Extension (OLE) Phase II Clinical Trial
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 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 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 2021, Merck KGaA, Darmstadt, Germany, generated sales of € 19.7 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 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.