

News Release

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New Data Presented at ECTRIMS Show Evobrutinib is First BTK Inhibitor to Demonstrate a Significant Reduction in Slowly Expanding Lesions (SEL) in Patients with RMS

- **Phase II post-hoc data show evobrutinib reduced acute and chronic inflammation processes in the central nervous system that may be early indicators of MS disease progression**
- **Additional data indicate that evobrutinib treatment was associated with reduced MRI and relapse activity in a patient population with more severe prognosis, based on baseline neurofilament levels**
- **The first and only integrated safety analysis of a BTK inhibitor that includes MS patients demonstrated that evobrutinib is well-tolerated across three Phase II trials in more than 1000 patients suffering from autoimmune diseases, including RMS**

Darmstadt, Germany, 14 October 2021 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today shared data in an oral presentation from a Phase II post-hoc analysis, demonstrating that the oral, central nervous system (CNS)-penetrant, fully covalent Bruton's tyrosine kinase inhibitor (BTKi) evobrutinib impacted brain lesions associated with chronic inflammation in the CNS, making it the first BTKi to show significant reductions in slowly expanding lesions (SEL). SELs are chronic, active, demyelinated multiple sclerosis (MS) lesions, which are thought to be an early indicator of disease progression in MS. These data were presented at the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) days after the completion of enrollment



News Release

into the Phase III EVOLUTION RMS program, in which evobrutinib is being investigated, was announced.

“The presented analysis is the first to show a BTK inhibitor significantly reducing SEL volume in patients with relapsing MS, providing further evidence to support the mechanism of action of evobrutinib in the treatment of RMS and underscoring the molecule’s potential impact on neurodegeneration and disease progression,” said Dr. Xavier Montalban, Chairman & Director Neurology-Neuroimmunology Department & Neurorehabilitation Unit, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain.

The analysis from the Phase II study evaluated the effect of evobrutinib treatment on SEL volume from baseline to Week 48. Evobrutinib reduced SEL volume compared to placebo in a dose-dependent manner with the highest effect with 75 mg twice daily ($p=0.047$). In a subgroup analysis, the effect of evobrutinib on SEL volume was also especially apparent in patients with more advanced disease. SELs are a potential result of accumulating neuronal damage, especially axonal loss, and occur independently of acute inflammation associated with Gd+ lesions. These results, combined with the reduction in Gd+ lesions reported previously, suggest that evobrutinib reduces both acute and chronic neuroinflammation that together lead to worsening disability.

In addition to SEL volume measurement, assessing blood neurofilament light chain (NfL) levels is another emerging method to evaluate MS disease progression. Previously shared data showed that evobrutinib significantly lowers blood NfL levels as early as week 12, with levels remaining reduced at the last analyses time point at 24 weeks. New data from a secondECTRIMS oral presentation of a post-hoc analysis of the Phase II trial demonstrated that high levels of NfL at baseline were predictive of increased relapse and magnetic resonance imaging (MRI) lesion activity. Evobrutinib 75mg once daily or twice daily reduced MRI and relapse outcomes versus placebo or evobrutinib 25mg once daily over 24 weeks, even in more advanced MS subjects with high baseline NfL levels. These initial findings across NfL data combined with SEL data continue to show evobrutinib’s potential benefit in disease progression.

News Release

The most extensive integrated safety dataset of a BTK inhibitor in autoimmune diseases was also presented. The analysis, which utilized pooled data from three Phase II trials across systemic lupus erythematosus, rheumatoid arthritis and RMS from 1083 patients, included different doses of 25mg or 75mg once daily, or 50mg or 75mg twice daily. Evobrutinib was generally well tolerated with similar rates of adverse events between evobrutinib and placebo by indication and across trials. The most common adverse events reported were urinary tract infections (9.5% versus 8.5% placebo), nasopharyngitis (7.3% versus 5.5% placebo), diarrhea (6.2% versus 4.8% placebo) and alanine aminotransferase (ALT) increase (2.9% versus 1.5% placebo). Liver transaminase elevations were asymptomatic and reversible upon treatment discontinuation.

“New treatments are needed that target chronic neuroinflammation early in RMS to effectively prevent progression and accumulation of disability,” said Danny Bar-Zohar, MD, Global Head of Development, Healthcare business sector of Merck KGaA, Darmstadt, Germany. “Evobrutinib’s first of its kind BTKi data on both SEL and NfL, which are thought to predict disease progression, further substantiate our belief in evobrutinib’s potential as a best-in-class treatment for people living with relapsing MS.”

About Evobrutinib

Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS). It is an oral, highly selective inhibitor of Bruton’s tyrosine kinase (BTK) which is important in the development and functioning of various immune cells including B lymphocytes and macrophages. Evobrutinib is designed to inhibit primary B cell responses such as proliferation and antibody and cytokine release, without directly affecting T cells. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

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 the Merck KGaA, Darmstadt, Germany’s commitment to MS, the company also have a pipeline focusing on discovering new therapies that have the potential in other neuroinflammatory and immune-mediated diseases, including systemic lupus erythematosus (SLE).

News Release

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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 electronics. 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.