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Merck KGaA, Darmstadt, Germany Initiates Pivotal Phase III Program for Investigational Evobrutinib in Relapsing Multiple Sclerosis

- **EVOLUTION RMS 1 and 2 pivotal Phase III trials will investigate the efficacy and safety of evobrutinib in relapsing multiple sclerosis (RMS)**
- **Evobrutinib is the first oral, highly selective Bruton's Tyrosine Kinase (BTK) inhibitor to show clinical proof of concept in RMS**
- **Decision to initiate Phase III program based on effect seen with evobrutinib on MRI endpoints at 24 weeks and annualized relapse rate over 48 weeks in Phase II**
- **Unique collaboration with Accelerated Cure Project for Multiple Sclerosis provided guidance on patient-reported outcomes (PROs) measures and clinical study design**

Darmstadt, Germany, September 10, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced the initiation of two global pivotal Phase III trials (EVOLUTION RMS 1 and 2) studying the efficacy and safety of evobrutinib, an oral, highly selective Bruton's Tyrosine Kinase (BTK) inhibitor in adult patients with relapsing multiple sclerosis (RMS).

"Evobrutinib is a potential innovation for people living with MS, as it may offer a novel dual mechanism of action that is thought to impact myeloid cells in addition to B-cells and thus could address MS pathobiology in a fundamentally new way," said Luciano Rossetti, Head of Global R&D for the Biopharma business of Merck KGaA, Darmstadt, Germany. "Evobrutinib, which was developed in our own laboratories, is an oral, highly selective BTK inhibitor that has shown clinical proof of concept in RMS. Progressing this molecule into Phase III is an important step for

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us and the MS community, with an opportunity to further advance on benefit-risk considerations for RMS patients."

Evobrutinib is entering Phase III trials following the results of the Phase II clinical trial, which met its primary endpoint over 24 weeks of treatment, where the total cumulative number of T1 gadolinium-enhancing lesions was reduced with evobrutinib compared with placebo. The reduction of T1 gadolinium-enhancing lesions was observed at 12 weeks, the first time point at which MRI data was available, and maintained through 48 weeks with evobrutinib 75 mg QD and 75 mg BID. Further data show that the effect on relapse reduction observed at Week 24 was maintained through 48 weeks.

In the Phase II trial, the most commonly observed adverse events of any grade associated with evobrutinib included nasopharyngitis and increases in levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lipase. All events had an onset within 24 weeks of treatment initiation and were reversible on treatment discontinuation with no clinical consequences within the 52-week safety period. During the course of the study, 85 percent of patients (227 out of 267) completed 52 weeks of treatment.

EVOLUTION RMS 1 and 2 are multicenter, randomized, parallel group, double-blind, active-controlled studies comparing evobrutinib twice-daily with interferon beta-1a given intramuscularly once a week. The primary endpoint of both studies is annualized relapse rate (ARR) at Week 96. Secondary endpoints include time to first occurrence of 12- and 24-week confirmed Expanded Disability Status Scale (EDSS) Progression and total number of gadolinium-enhancing (Gd+) T1 lesions and new or enlarging T2 lesions assessed by magnetic resonance imaging.

As part of the company's commitment to patient-focused drug development, Merck KGaA, Darmstadt, Germany collaborated with the Accelerated Cure Project (ACP) for Multiple Sclerosis and its iConquerMS people-powered research network to capture and integrate the perspectives of people affected by MS into the design and implementation of the clinical trials. Through this innovative collaboration, a council of individuals living with MS provided feedback and insights on the choice of patient-reported outcomes (PROs) endpoints in the trials, specifically in relation to relevance

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of PRO measures to the real-world patient experience and insights on patient-facing materials. This engagement largely focused on the two PROs included as secondary endpoints: change from baseline in Patient Reported Outcomes Measurement Information System (PROMIS) MS Physical Function (PF) and the PROMIS MS Fatigue Scores at 96 Weeks.

"Even with the most effective therapies for RMS, more than 50% of patients experience clinical or subclinical disease activity, therefore a need still exists for novel oral therapies that address MS pathobiology differently," noted Dr. Xavier Montalban, Professor of Medicine and Department Division Director, Neurology, at the University of Toronto, Director of the MS Centre at St. Michael's Hospital, Canada, Chairman & Director Neurology-Neuroimmunology Department & Neurorehabilitation Unit, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain and principal investigator for the EVOLUTION RMS 2 trial. "We look forward to seeing the outcomes of this clinical program following the promising Phase II results."

Trial recruitment is currently underway with the goal of 1,900 patients enrolled. The target completion is in June 2023.

About Evobrutinib
Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). 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. BTK inhibition is thought to suppress autoantibody-producing cells, which preclinical research suggests may be therapeutically useful in certain autoimmune diseases. The global Phase III clinical development program evaluating evobrutinib in MS includes two pivotal studies, EVOLUTION RMS 1 and 2. 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 2.3 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, with a robust pipeline focusing on discovering new therapies that have the potential to modulate key pathogenic mechanisms in MS. Merck KGaA, Darmstadt, Germany aims to improve the lives of those living with MS, by addressing areas of unmet medical needs.

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The company`s robust immunology pipeline focuses on discovering new therapies that have the potential to modulate key pathogenic mechanisms in chronic diseases such as MS, systemic lupus erythematosus (SLE) and forms of arthritis, including rheumatoid arthritis (RA) and osteoarthritis (OA).

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany is a leading science and technology company in healthcare, life science and performance materials. Around 52,000 employees work to further develop technologies that improve and enhance life – from biopharmaceutical therapies to treat cancer or multiple sclerosis, cutting-edge systems for scientific research and production, to liquid crystals for smartphones and LCD televisions. In 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 billion in 66 countries.

Scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. This is how Merck KGaA, Darmstadt, Germany has thrived since its founding in 1668. The founding family remains the majority owner of the publicly listed company. Merck KGaA, Darmstadt, Germany holds the global rights to the Merck name and brand. 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.