Merck KGaA
Darmstadt, Germany

News Release

Your Contact
alice.mcgrail@emdgroup.com
Phone: +1 781 738 8791

May 10, 2019

Positive Phase II Data Further Highlights Clinical Proof of Concept for Evobrutinib, First Oral Bruton´s Tyrosine Kinase (BTK) Inhibitor to Report Positive Phase II Clinical Results in MS

- **48-week results provide additional evidence of relapse reduction for investigational evobrutinib**
- **Evobrutinib demonstrated rapid lesion reductions on MRI at week 12 that were maintained through week 48, with no new safety signals identified over 52 weeks**
- **Data presented at the American Academy of Neurology 2019 Annual Meeting and simultaneously published in the NEJM**

Darmstadt, Germany, May 10, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced new 48-week results of the double-blind, randomised, placebo-controlled, Phase II study of evobrutinib in patients with relapsing multiple sclerosis (RMS). The results have been presented at the American Academy of Neurology (AAN) 2019 Annual Meeting in Philadelphia, United States with simultaneous publication in the *New England Journal of Medicine (NEJM)*. Evobrutinib is the first oral, highly selective Bruton's tyrosine kinase (BTK) inhibitor to show clinical proof of concept in RMS.

Previously reported data showed that the study had 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. With evobrutinib 75 mg QD (once a day) and 75 mg BID (twice a day), rapid reductions in number of T1 Gd+ lesions were observed by week 12 of treatment. New data showed that the effect on T1 gadolinium-enhancing lesions reduction seen at week 12 was maintained through 48 weeks with evobrutinib 75 mg QD and 75 mg BID.

Frankfurter Strasse 250
64293 Darmstadt · Germany
Hotline +49 6151 72-5000
www.emdgroup.com

Head of Media Relations -6328
Spokesperson: -9591 / -7144 / -8908 / -55707

News Release

"These positive Phase II evobrutinib data are a great example of the strength of our pipeline and commitment to developing new, innovative treatments in multiple sclerosis," said Luciano Rossetti, Head of Global Research & Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. "As a leader in autoimmune diseases and MS we are proud of this in-house discovery at Merck KGaA, Darmstadt, Germany. We look forward to continuing to investigate the potential of evobrutinib as we continue to address unmet patient needs in MS care."

With evobrutinib 75 mg BID, annualized relapse rate (ARR) (confidence interval) was 0.11 (0.04-0.25) with 79 percent of patients remaining relapse free over 48 weeks of treatment. For reference, at 24 weeks, ARR for evobrutinib 75 mg BID was 0.08 (0.01-0.30) and 0.37 (0.17-0.70) for placebo.

No treatment associated infections, infestations, or lymphopenia were observed and no new safety signals were identified over 52 weeks. The most common treatment-related TEAEs (>10%) included nasopharyngitis and increased ALT. The percentage of shifts from baseline to Grade 2 or greater in ALT were 5.7%, 3.8%, and 13% in the evobrutinib 25mg QD, 75mg QD and 75mg BID groups, respectively. The corresponding shifts in ALT in the placebo group over 24 weeks was 7.5%. 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 study period. During the course of the study, 85 percent of patients (227 out of 267) completed 52 weeks of treatment.

"Building on our initial analysis at 24 weeks, these new data further demonstrate the potential role of evobrutinib in relapsing multiple sclerosis, subject to further clinical investigation" said Dr. Xavier Montalban, Professor of Medicine and Department Division Director, Neurology, at the University of Toronto and Director of the MS Centre at St. Michael's Hospital, Canada, and Chairman & Director Neurology-Neuroimmunology Department & Neurorehabilitation Unit, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain. "Evobrutinib is the first Bruton's tyrosine kinase inhibitor to demonstrate clinical proof of concept in multiple sclerosis. We are pleased that these 48-week data further support our continued clinical development of evobrutinib and investigation into its efficacy for patients with MS."

News Release

These 48-week results are a new analysis following the initial 24-week presentation of the data at the 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Berlin, Germany, on October 12, 2018.

Merck KGaA, Darmstadt, Germany presented a total of 20 abstracts (18 posters and two platform presentations) during AAN 2019. For further information on the evobrutinib 48-week abstract please see here:

- Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib in Patients with Relapsing Multiple Sclerosis over 48 Weeks: a Randomized, Placebo-Controlled, Phase 2 Study – presented at 13:33 ET on Friday 10 May during the S56: MS Trials and Treatment session.

The presentation of these data read-outs showcases the breadth of Merck KGaA, Darmstadt, Germany`s multiple sclerosis (MS) portfolio and further underscores its commitment to the advancement of MS treatment.

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. Selectivity has been *assessed in vitro*. 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. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About the Evobrutinib Multiple Sclerosis Phase II Study
This double-blind, placebo-controlled, 48-week, Phase II study evaluates the safety and efficacy of evobrutinib in patients aged 18–65 years with relapsing multiple sclerosis (RMS). Patients were randomised to evobrutinib 25mg QD, 75mg QD, 75mg BID, PBO or open-label dimethyl fumarate (240mg BID; reference arm). The primary endpoint was the sum of T1 gadolinium-enhancing lesions at weeks 12, 16, 20, and 24. Key secondary endpoints included annualised relapse rate (ARR) at week 48 and safety. For more information about the study, visit ClinicalTrials.gov.

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 Immunology
Merck KGaA, Darmstadt, Germany, has a long-standing legacy in immunology, with significant R&D and commercial experience in multiple sclerosis. The company`s robust immunology pipeline focuses on discovering new therapies that have the potential to modulate key pathogenic mechanisms in chronic

News Release

diseases such as MS, systemic lupus erythematosus (SLE) and forms of arthritis, including rheumatoid arthritis (RA) and osteoarthritis (OA).

About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, is a leading science and technology company in healthcare, life science and performance materials. More than 53,000 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 2017, Merck KGaA, Darmstadt, Germany, generated sales of € 15.3 billion in 66 countries.

Founded in 1668, Merck KGaA, Darmstadt, Germany, is the world's oldest pharmaceutical and chemical company. The founding family remains the majority owner of the publicly listed corporate group. 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 company operates as EMD Serono, MilliporeSigma and EMD Performance Materials.