News Release

Your Contact
Erin-Marie Beals +1 781-681-2850

October 12, 2018

# Positive Late-Breaking Phase II Data Evaluating Investigational Oral Therapy, Evobrutinib in RMS

- **First Bruton's Tyrosine Kinase inhibitor (BTKi) demonstrating clinical proof-of-concept in relapsing multiple sclerosis (RMS)**
- **Study met primary endpoint demonstrating significant reduction in Gd+ enhancing T1 lesions on MRI with evobrutinib versus placebo**
- **Clinically meaningful decrease in annual relapse rates observed**

Darmstadt, Germany, October 12, 2018 – Merck KGaA, Darmstadt, Germany, the vibrant science and technology company, today announced the 24-week results of the double-blind, randomised, placebo-controlled, 48-week, Phase II study of evobrutinib in patients with relapsing multiple sclerosis (RMS) at the 34th Congress of the European Committee for Treatment and Research In Multiple Sclerosis (ECTRIMS) in Berlin, Germany. In this study, dimethyl fumarate (240mg BID) represented an open-label reference arm, and there were no formal statistical comparisons between dimethyl fumarate and evobrutinib or placebo. The study met its primary endpoint, with evobrutinib 75mg QD (once-daily) and 75mg BID (twice-daily) significantly reducing the number of gadolinium enhancing T1 (T1 Gd+) lesions measured at weeks 12, 16, 20 and 24 in comparison to patients receiving placebo. Evobrutinib is a highly-specific, oral Bruton's Tyrosine Kinase (BTK) inhibitor and the first BTK inhibitor to show clinical proof-of-concept in relapsing MS.

"We are among the first to evaluate a BTK inhibitor for chronic autoimmune diseases, and we continue to be highly encouraged by the results we've seen in patients with relapsing MS thus far," said Luciano Rossetti, Global Head of Research & Development at the Biopharma business of Merck KGaA, Darmstadt, Germany. "Evobrutinib was discovered in-house at Merck KGaA, Darmstadt, Germany and is



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

Head Media Relations -62445
Spokesperson: -9591 / -7144 / -6328
Fax +49 6151 72 3138
media.relations@emdgroup.com

# News Release

an example of the innovation coming from our own labs. We have a long history of delivering innovative solutions with the aim of advancing MS care, and look forward to further exploring the potential of evobrutinib in future clinical trials."

Ninety-one percent of randomised patients (244 of 267) completed 24 weeks of treatment. Mean (SD) total T1 Gd+ lesions (weeks 12-24) was 3.85 (5.44), 4.06 (8.02), 1.69 (4.69) and 1.15 (3.70) in the placebo, evobrutinib 25mg QD, 75mg QD and 75mg BID groups, respectively. Compared to placebo, T1 Gd+ lesions per scan were significantly reduced with evobrutinib 75mg QD (lesion rate ratio [RR]=0.30; p=0.0015) and 75mg BID (RR=0.44; p=0.0313), but not 25mg QD (RR=1.45; p=0.295), with evidence of a dose-response relationship (trend test p=0.0011).

"The results of this study highlight the potential of BTK inhibitors as an oral disease-modifying treatment for relapsing MS," 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. "These findings suggest that the dual mechanism of action of evobrutinib, which impacts pathogenic adaptive and innate immune cells in multiple sclerosis, could translate into clinical efficacy."

Evobrutinib also led to clinically relevant decreases in annualized relapse rate (ARR). A reduction in ARR was seen with evobrutinib 75mg QD (0.13; p=0.09) and 75mg BID (0.08; p=0.06) versus placebo (0.37), with evidence of a dose-response relationship (trend test p=0.01).

An additional secondary endpoint examined the total number of T2 lesions as assessed by MRI. Mean (SD) new or enlarging T2 lesions (weeks 12-24) was 5.96 (6.99), 6.52 (11.57), 3.41 (10.75) and 2.19 (4.72) in the placebo, evobrutinib 25mg QD, 75mg QD and 75mg BID groups, respectively. Compared to placebo, new or enlarging T2 lesions per scan were significantly reduced with evobrutinib 75mg BID (RR=0.42; p=0.019).

Treatment with evobrutinib was well tolerated and no treatment associated infections, infestations, or lymphopenia were observed. The most common treatment-related TEAEs (>5%) included increased ALT, AST and lipase in the 75 mg BID group; these events were reversible and asymptomatic. The percentage of

# News Release

shifts from Grade 0 to Grade 3 or greater in ALT were 1.9%, 5.7%, 2.1% and 6.1% in the the placebo, evobrutinib 25mg QD, 75mg QD and 75mg BID groups, respectively.

The results, which include the dimethyl fumarate (240mg BID) reference arm, are being presented in a late-breaking oral presentation, "Primary Analysis of a Randomised, Placebo-Controlled, Phase II Study of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib (M2951) in Patients with Relapsing Multiple Sclerosis" at ECTRIMS 2018 in Berlin, Germany, on October 12, 2018 at 2:15pm CET. A recording of the session will be available after the congress on onlinelibrary.ectrims-congress.eu.

Merck KGaA, Darmstadt, Germany presented three additional posters on evobrutinib and a total of 23 abstracts from the Company's MS portfolio at ECTRIMS, underscoring the company's rich legacy in advancing MS treatment and ongoing commitment to future therapies.

For more information about the data presented at ECTRIMS, please visit https://www.ectrims-congress.eu/2018.html.



**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 specific 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. 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-remitting multiple sclerosis (RRMS) or secondary progressive multiple sclerosis (SPMS) with superimposed relapses. 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 Gd+ lesions at weeks 12, 16, 20, and 24. Key secondary endpoints included annualised relapse rate (ARR) at week 24 and safety. Primary analysis (evobrutinib groups versus PBO) was planned when all patients reached 24 weeks of treatment or prematurely discontinued. 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

# News Release

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. Our 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).

**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.