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Up to 10-Years of Follow-up Data Reaffirm Safety Profile of Investigational Cladribine Tablets

- **Real-world evidence and longer clinical trial follow-up show no increased incidence of serious adverse events**
- **Additional post-hoc data analyses support sustained efficacy of cladribine tablets in patients with relapsing MS with high disease activity**

Darmstadt, Germany, October 10, 2018 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced the presentation of new data for cladribine tablets at the 34th Congress of the European Committee for Treatment and Research In Multiple Sclerosis (ECTRIMS) in Berlin, Germany. The data presented at ECTRIMS 2018 build on the existing real-world and clinical evidence around the safety and efficacy of cladribine tablets and reaffirm the benefit-risk profile of the oral treatment which is taken for a maximum of 20 days over two years.

Based on an integrated analysis of patients from the CLARITY, CLARITY EXT, and ORACLE-MS trials, including two additional years of data from the long-term PREMIERE Registry, the treatment emergent adverse event (TEAE) profile associated with cladribine tablets in patients with relapsing MS (RMS) was confirmed, with no new safety findings. The integrated analysis is based on patients followed for up to 10 years[1] (923 patients received cladribine tablets 3.5 mg/kg; 641 patients received placebo). As part of this analysis, an overview of the post-approval safety data from EU approval on August 2017 to July 2018 also showed no new safety or tolerability signals for cladribine tablets.

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Adjusted adverse events incidences per 100 patient-years (Adj-AE per 100PY) for those experiencing ≥1 serious TEAE were 3.88 for cladribine tablets and 3.24 for placebo in the two-year update, versus 4.00 for cladribine tablets and 3.57 for placebo reported previously. In addition to serious TEAE, Adj-AE per 100PY were also analyzed for serious lymphopenia, serious infection and infestations, serious herpes zoster, serious neoplasm, benign, malignant and unspecified. Results showed no new adverse events for cladribine tablets have been seen since the first approval in Europe last year. A total of 47 adverse drug reactions were reported from post-approval sources, none of which were new safety findings.

"In my opinion, we are entering an era of immune reconstitution therapy (IRT) in MS, where therapy is intermittently administered but which has an effect on the disease that lasts much longer than the period of dosing," said Prof. Gavin Giovannoni, a lead investigator in the CLARITY studies and Chair of Neurology, Barts and The London School of Medicine and Dentistry. "The new data presented suggest cladribine tablets delivers sustained efficacy well beyond the dosing regimen with no new safety signals found in the long-term."

P*ost hoc* analyses of CLARITY EXT show that following 20 days of treatment with cladribine tablets 3.5 mg/kg in Years 1 and 2 annual NEDA-3 status was sustained in patients treated with cladribine tablets 3.5 mg/kg or placebo up to the end of Year 4[2].There is also an analysis of EDSS, and clinical and MRI outcomes in patients with high disease activity.

A further *post hoc* analysis of CLARITY data indicated that the relapse and MRI efficacy of cladribine tablets does not appear to be impacted by age, consistent with previous similar analyses[3]. Data from this study showed that qualifying relapses were reduced in RMS patients aged below and above 45. With regards to MRI measures, the data showed that the number of cumulative new T1 Gd+ and active T2 lesions at Week 96 was reduced with cladribine tablets compared to placebo in both age groups[3].

"The data presented at ECTRIMS 2018 highlight our commitment to continuing to understand the extended benefit-risk profile of cladribine tablets," said Luciano Rossetti, Head of Global R&D for the biopharma business of Merck KGaA, Darmstadt,

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Germany. "With more and more patients able to access cladribine tablets globally, it becomes increasingly important for us to invest in scientific research that helps to clarify how patients may benefit from our therapies."

About Cladribine Tablets
Cladribine tablets is an investigational short-course oral therapy that is thought to selectively target lymphocytes which may be integral to the pathological process of relapsing MS (RMS). Cladribine tablets is currently under clinical investigation and not approved for the treatment for any use in the United States. MAVENCLAD® has received approvals for patients with highly active RMS as defined by clinical or imaging features in the European Union (EU), Israel, Argentina, United Arab Emirates, Chile and Lebanon. MAVENCLAD® is also approved in Canada and Australia.

The clinical development program for cladribine tablets includes:

- The CLARITY (Cladribine Tablets Treating MS Orally) study: a two-year Phase III placebo-controlled study designed to evaluate the efficacy and safety of cladribine tablets as a monotherapy in patients with RRMS.
- The CLARITY extension study: a Phase III placebo-controlled study following on from the CLARITY study, which evaluated the safety and efficacy of cladribine tablets over two additional years beyond the two-year CLARITY study, according to the treatment assignment scheme for years 3 and 4.
- The ORACLE MS (Oral Cladribine in Early MS) study: a two-year Phase III placebo-controlled study designed to evaluate the efficacy and safety of cladribine tablets as a monotherapy in patients at risk of developing MS (patients who have experienced a first clinical event suggestive of MS).
- The ONWARD (Oral Cladribine Added ON to Interferon beta-1a in Patients With Active Relapsing Disease) study: a Phase II placebo-controlled study designed primarily to evaluate the safety and tolerability of adding cladribine tablets treatment to patients with relapsing forms of MS, who have experienced breakthrough disease while on established interferon-beta therapy.
- PREMIERE (Prospective Observational Long-term Safety Registry of Multiple Sclerosis) study: a long-term follow-up safety registry of multiple sclerosis patients who participated in cladribine tablets clinical studies.

The clinical development program of cladribine tablets in MS comprises close to 12,000 patient years of data with over 2,700 patients included in the clinical trial program, and up to 10 years of follow-up in some patients.

In the two-year CLARITY study, the most commonly reported adverse event (AE) in patients treated with cladribine tablets was lymphopenia. The incidence of infections was 48.3% with cladribine tablets and 42.5% with placebo, with 99.1% and 99.0% respectively rated mild-to-moderate by investigators.

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 and Multiple Sclerosis
For more than 20 years, Merck KGaA, Darmstadt, Germany has been relentlessly focused on understanding the journey people living with MS face in order to create a meaningful, positive experience for them and the broader MS community. However, there is still much that is unknown about this complex and unpredictable disease. Merck KGaA, Darmstadt, Germany is digging deeper to advance the science and reconstruct a new understanding of MS, inside and out. We are committed to delivering solutions that improve the lives of all those affected by MS.

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

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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.

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[1] Cook S et al. Updated safety analysis of Cladribine Tablets in the treatment of patients with multiple sclerosis. Presentation at ECTRIMS 2018
[2] Vermersch P et al. Sustained efficacy in relapsing remitting multiple sclerosis following switch to placebo treatment from Cladribine Tablets in patients with high disease activity at baseline. Presentation at ECTRIMS 2018
[3] Giovannoni G et al. An exploratory analysis of the efficacy of Cladribine Tablets 3.5mg/kg in patients with relapsing multiple sclerosis stratified according to age above and below 45 years in the CLARITY study. Presentation at ECTRIMS 2018