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Cladribine Tablets Significantly Reduced Brain Atrophy in Patients with Multiple Sclerosis

- **Post hoc analysis of Phase III CLARITY study data recently published in *Multiple Sclerosis Journal* showed statistically significant reduction in brain atrophy in patients on a short course of investigational Cladribine Tablets over two years compared with patients receiving placebo**
- **These findings correlated with effects on clinical progression as measured by the EDSS scale, a method of quantifying disability in multiple sclerosis**

Darmstadt, Germany, February 9, 2017 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced the publication of the results of a post hoc analysis of the Phase III CLARITY study in *Multiple Sclerosis Journal*. The post hoc analysis showed that Cladribine Tablets reduced the annualised rate of brain volume loss – also known as brain atrophy – compared with placebo in patients with relapsing remitting multiple sclerosis (RRMS).

In addition, the analysis found that patients with lower rates of brain atrophy showed the highest probability of remaining free from disability progression at two years. This supports existing findings that increased brain volume loss over time is associated with worse clinical outcomes such as increased disability progression and cognitive changes, in patients with multiple sclerosis.

“Evidence shows that brain atrophy in general accumulates throughout the course of multiple sclerosis and is associated with disability progression. This analysis is



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important because it confirms the link between reduced brain atrophy and reduced disability progression found in the CLARITY study,” said Nicola De Stefano, lead author of the publication and Associate Professor of Neurology, Department of Medicine, Surgery and Neuroscience, University of Siena.

The CLARITY study was a two-year (96-week), randomised, double-blind, placebo-controlled Phase III study of Cladribine Tablets in 1,326 people with RRMS. The CLARITY study primary (rate of relapse at 96 weeks) and key secondary endpoints (proportion of patients who were relapse free and the time to sustained progression of disability) were met. These outcomes and safety results were published in *The New England Journal of Medicine*.

The brain atrophy analysis evaluated the effect of Cladribine tablets on brain volume loss (BVL) over 2 years in RMS and the association of BVL with confirmed disability progression in 1,025 (77.3%) of the patients in CLARITY. The mean percentage brain volume loss per year was significantly reduced in patients treated with Cladribine Tablets 3.5 mg/kg ($-0.56\% \pm 0.68$, $p=0.010$, $n=336$) and 5.25 mg/kg ($-0.57\% \pm 0.72$, $p=0.019$, $n=351$) compared with patients treated with placebo ($-0.70\% \pm 0.79$, $n=338$). The risk of disability progression was also significantly lower in patients treated with Cladribine Tablets 3.5 mg/kg (HR 0.63, 95% CI 0.438, 0.894; $p=0.010$) and 5.25 mg/kg (HR 0.58, 95% CI 0.406, 0.833; $p=0.003$) than in those treated with placebo. After adjusting for treatment group, percentage brain volume loss per year showed a significant correlation with the cumulative probability of disability progression in the overall study population (HR 0.67, 95% CI 0.571, 0.787; $p<0.0001$).

“These findings reinforce and expand on the consistent and positive effect of Cladribine Tablets in improving clinically relevant outcomes, such as reducing relapse rate and disability, and further our resolve to make this investigational therapy available for patients living with RRMS,” said Steven Hildemann, MD, PhD, Global Chief Medical Officer and Head of Global Medical Affairs and Safety, Merck KGaA, Darmstadt, Germany.

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CLARITY study design

The CLARITY study was a two-year (96-week), randomised, double-blind, placebo-controlled, international study. It randomised 1,326 patients with relapsing remitting MS according to the revised McDonald criteria. Study participants were randomised to one of three different treatment groups consisting of two different dose regimens of Cladribine Tablets or matching placebo tablets (1:1:1 ratio).

The primary endpoint of the CLARITY study was the relapse rate over 96 weeks. Secondary endpoints included MRI endpoints, proportion of subjects relapse-free and disability progression at 96 weeks.

Lymphopenia was the most commonly reported adverse event (AE) in patients treated with Cladribine Tablets. The incidence of infections was 48.3% with Cladribine Tablets and 42.5% with placebo, with 99.1% and 99.0% rated mild-to-moderate by investigators.

About Cladribine Tablets

Cladribine Tablets is an investigational short-course oral therapy that selectively and periodically targets lymphocytes thought to be integral to the pathological process of MS. Cladribine Tablets is currently under clinical investigation and not yet approved for the treatment for any use in the United States, Canada and Europe. In July 2016, the European Medicines Agency (EMA) accepted for review the Marketing Authorisation Application (MAA) of Cladribine Tablets for the treatment of relapsing remitting multiple sclerosis.

The clinical development program for Cladribine Tablets includes:

- The CLARITY (CLAdRIbine Tablets Treating MS Orally) study and its extension: 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 and its two-year extension designed to provide data on the long-term safety and efficacy of extended administration of Cladribine Tablets for up to four years.
- The ORACLE MS (ORAI 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 Patients Who Have Participated in Cladribine Clinical Studies) study: interim long-term follow-up data from the prospective registry, PREMIERE, to evaluate the safety and efficacy of Cladribine

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Tablets. The follow-up will consist of over 10,000 patient years of exposure in total, with follow-up in some patients exceeding eight years at completion.

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. Although many treatments exist there is a need for an effective therapy without the risks associated with continuous immunosuppression and which reduces the need for frequent switches.

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Merck KGaA, Darmstadt, Germany, is a leading science and technology company in healthcare, life science and performance materials. Around 50,000 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 2015, Merck KGaA, Darmstadt, Germany, generated sales of € 12.85 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. We hold the global rights to the „Merck“ name and brand except in the United States and Canada, where the company operates as EMD Serono, MilliporeSigma and EMD Performance Materials.

Merck KGaA, Darmstadt, Germany, is one of the world's leading suppliers of effect pigments for the coatings, plastics, printing, cosmetic, food and pharmaceutical industries. Effect pigments underscore the emotional impact of color and are an important design element when creating surfaces with a special appearance or quality. Application possibilities range from cars to packaging and high-tech products up to building façades. In addition to decorative effect pigments, Merck KGaA, Darmstadt, Germany, offers pigments that also have functional applications such as heat-reflecting or anti-counterfeiting pigments.