

May 2, 2018

## **Investigational Cladribine Tablets Data in *Multiple Sclerosis Journal* Show a Strong Treatment Effect in Patients with Highly Active Multiple Sclerosis**

- **Post-hoc analysis from the 2-year CLARITY study demonstrated that Cladribine Tablets reduced the risk of 6-month EDSS progression by 47% vs placebo**
- **Patients with highly active multiple sclerosis had a strong treatment effect, reducing the risk by 82% vs placebo**

Darmstadt, Germany, May 2, 2018 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced the *Multiple Sclerosis Journal* publication of data outlining the effects of investigational Cladribine Tablets treatment on two subgroups of patients with highly active relapsing multiple sclerosis (MS)<sup>1</sup>. These results reaffirm the clinical and radiological efficacy previously demonstrated with Cladribine Tablets treatment in patients with relapsing MS.

“This analysis provides valuable insights on the effect of Cladribine Tablets on patients with ongoing disease activity despite treatment with platform therapy, as well as naïve patients with more relapses at baseline, who tend to do worse over time,” 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 efficacy data presented in this publication show an even greater risk reduction on expanded disability status scale (EDSS) progression with Cladribine Tablets in patients with highly active MS.”



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In this post-hoc analysis, two clinically relevant definitions of high disease activity were selected to effectively identify patients more likely to experience disease progression. Patients from the CLARITY study with high disease activity were categorized by fulfilling one of two overlapping criteria, which reflect those included in the EU SmPC for Cladribine Tablets:

- High Relapse Activity (HRA): Patients with  $\geq 2$  relapses during the year prior to study entry, whether on disease-modifying drug (DMD) treatment or not
- High Relapse Activity plus Disease Activity on Treatment (HRA + DAT): patients with  $\geq 1$  relapse and  $\geq 1$  T1 Gadolinium-enhancing (Gd) + or  $\geq 9$  T2 lesions during the year prior to study entry while on therapy with other DMDs, plus patients with  $\geq 2$  relapses during the year prior to study entry, whether on DMD treatment or not

“Merck KGaA, Darmstadt, Germany is committed to deepening our understanding of the benefit-risk profile of this innovative MS treatment in patient populations with a high need for an effective disease-modifying therapy,” said Luciano Rossetti, Head of Global R&D for the biopharma business of Merck KGaA, Darmstadt, Germany.

HRA and HRA + DAT patients showed clinical and MRI responses to Cladribine Tablets that were generally better than, or at least comparable with, the outcomes previously seen in the overall CLARITY study population. In both high disease subgroups, Cladribine Tablets was shown to reduce the risk of 6-month EDSS progression by 82% vs placebo, compared to a 47% reduction in the overall CLARITY study population. The newly published analysis also evaluated disease-free status, showing that in the HRA + DAT subgroup, treatment with Cladribine Tablets was significantly more likely to result in NEDA\* (odds ratio<sup>†</sup> 7.82 (95% CI 4.03–15.19;  $p < 0.0001$ ) when compared with the non-HRA + DAT subgroup 4.46 (95% CI 3.13–6.26)). The HRA subgroup was also more likely to achieve NEDA, but a statistically significant difference was not observed when compared to the non-HRA group.

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\* No evidence of disease activity (NEDA) was defined as patients having no relapses, no 3-month confirmed EDSS worsening, no T1 Gd+ lesions and no active T2 lesions

<sup>†</sup> Odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure

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The relative risk of cumulative new T1 Gd+ lesions for patients in both high-disease subgroups treated with Cladribine Tablets was low, with strong effects observed in each treatment subgroup. Overall, the subgroup-specific safety analysis for patients with HRA and HRA+DAT did not reveal evidence for new safety findings compared with those previously described for the overall CLARITY population.

### **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. In August 2017, the European Commission granted marketing authorization for Cladribine Tablets, marketed as MAVENCLAD®, for the treatment of highly active relapsing forms of multiple sclerosis as defined by clinical or imaging features, in the 28 countries of the EU in addition to Norway, Liechtenstein and Iceland. In December 2017, Health Canada approved MAVENCLAD for the treatment of relapsing forms of MS.

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 two-year Phase III placebo-controlled study following on from the CLARITY study, designed to evaluate the safety and efficacy of Cladribine Tablets over an extended administration for four years.
- 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 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 Tablets. This includes more than 10,000 patient years of data with over 2,700 patients included in the clinical trial program, and more than 10 years of observation 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.

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**About Merck KGaA, Darmstadt, Germany**

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Merck KGaA, Darmstadt, Germany, is a leading science and technology company in healthcare, life science and performance materials. More than 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 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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<sup>1</sup> Giovannoni G, Soelberg Sorensen P, Cook S et al. Efficacy of cladribine tablets in high disease activity subgroups of patients with relapsing multiple sclerosis: A post-hoc analysis of the CLARITY study. Multiple Sclerosis Journal May 2018