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Two-Year Phase III Data Presented at AAN 61st Annual Meeting Show Positive Outcome of Cladribine Tablets in Patients with Multiple Sclerosis

- **Primary endpoint met with a significant reduction in relapse rate**
- **Secondary endpoints met including MRI measures, proportion of patients relapse-free and disability progression**
- **Submission for registration of Cladribine Tablets planned for mid-2009**

Seattle, WA, United States/ Geneva, Switzerland, April 29/30, 2009 – Merck Serono, a division of Merck KGaA, announced today detailed results of the two-year (96-week) placebo-controlled CLARITY¹ Phase III trial using Cladribine Tablets (Merck Serono's proprietary investigational oral formulation of cladribine) to treat patients with relapsing-remitting multiple sclerosis (MS). The results of the pivotal trial show that annual short-course treatment with Cladribine Tablets led to a significant reduction in the rate of clinical relapses, disability progression and brain lesions, as well as a significant increase in the proportion of patients who remained relapse-free. The data were presented today for the first time, as a late-breaking oral presentation at the 61st Annual Meeting of the American Academy of Neurology (AAN) in Seattle, WA.

“All primary and secondary endpoints of the CLARITY study were statistically significant and demonstrate that annual short-course treatment with Cladribine Tablets in this study was effective across multiple important clinical and MRI efficacy measures,” said Dr. Gavin Giovannoni, principal investigator of the study, Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, London, United Kingdom.

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“We are very pleased with the successful outcome of the CLARITY study,” said Elmar Schnee, President of Merck Serono. “This is an exciting development in multiple sclerosis clinical research, and represents an important step towards delivering an oral therapy to people living with this condition.”

The results from both Cladribine Tablets treatment groups in the study demonstrated a statistically significant reduction in the annualized rate of relapses compared to placebo (primary endpoint). Patients treated with the low-dose regimen of Cladribine Tablets experienced a 58% relative reduction in annualized relapse rates with respect to placebo (0.14 versus 0.33 for the placebo group; $p < 0.001$). Patients in the high-dose regimen group experienced a 55% relative reduction in annualized relapse rates with respect to placebo (0.15 versus 0.33; $p < 0.001$).

The proportion of patients who remained relapse-free (one secondary endpoint of the trial) was significantly higher in the Cladribine Tablets treatment groups than in the placebo group. Over the two-year period of the study, 80% of the patients treated with the low dose regimen of Cladribine Tablets and 79% of the patients treated with the high-dose regimen experienced no clinical relapse, compared with 61% of the patients from the placebo group ($p < 0.001$ for both dose regimens). Therefore, the relative risk to relapse in patients treated with Cladribine Tablets was approximately half of that seen in patients on placebo.

Treatment with Cladribine Tablets led to a more than 30% reduction in the risk of disability progression (another secondary endpoint) relative to placebo over the two-year period of the study (low-dose regimen: hazard ratio=0.67; $p=0.018$ – high-dose regimen: hazard ratio=0.69; $p=0.026$). Progression of disability was measured by a 1-point or greater increase in the Expanded Disability Status Scale (EDSS) sustained for at least three months (or at least a 1.5 point increase if baseline EDSS was 0; or 0.5 point increase if baseline EDSS was 5.0 and above).

Sustained and statistically significant reductions in different types of brain lesions as measured by each of the pre-specified key magnetic resonance imaging (MRI)

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secondary endpoints were shown and were consistent with clinical outcomes. Over the two year period of the study, both dose regimens of Cladribine Tablets demonstrated a statistically significant reduction of at least 70% in the mean number of active T1 gadolinium-enhanced lesions per subject per scan, the mean number of active T2 lesions per subject per scan, as well as the mean number of combined unique lesions per subject per scan, compared to placebo (reductions ranging from 73% to 88% depending on MRI measure and dose group; $p < 0.001$ for each of these MRI measures and for both dose regimens).

Overall, the frequencies of adverse events by MedDRA System Organ Class in both cladribine treatment groups were comparable to those observed in the placebo group. The most commonly reported adverse events were headaches, nasopharyngitis, upper respiratory tract infections and nausea. Lymphopenia, an expected event based on the presumed mechanism of action of cladribine, occurred more frequently in the Cladribine Tablets treatment groups (low-dose regimen: 22%; high-dose regimen: 31%; placebo: 2%).

The overall rate and incidence of infections in patients treated with Cladribine Tablets and placebo were similar. Herpes zoster infections were reported in 2.3% of patients treated with Cladribine Tablets. These herpes infections were localized to the skin and responded appropriately to treatment.

In patients treated with Cladribine Tablets, four malignancies were reported during the study (cervical stage 0, melanoma, ovarian and pancreatic), and a case of choriocarcinoma was reported at week 14 of gestation in a cladribine-treated patient who became pregnant 6 months after completion of the study. Observed malignancies were isolated cases across different organ systems. The current ongoing clinical studies with Cladribine Tablets will provide data on a larger patient population and a longer duration of treatment to collect more conclusive information on this safety aspect.

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Merck Serono plans to submit Cladribine Tablets for registration to the European Medicines Agency (EMA) and to the US Food and Drug Administration (FDA) in mid-2009.

¹ CLARITY: CLAdRibine Tablets Treating MS Orally

About the CLARITY study

The CLARITY study was a two-year (96-week), randomized, double-blind, placebo-controlled, international trial. It randomized 1,326 patients with relapsing-remitting MS according to the revised McDonald criteria². Study participants were randomized to one of three different treatment groups consisting of two different dose regimens of Cladribine Tablets or matching placebo tablets (1:1:1 ratio). Cladribine Tablets were given in two or four treatment courses in the first year, with each course consisting of once daily administration for four to five consecutive days, which means study patients took Cladribine Tablets for 8 to 20 days during the year. In the second year, two treatment courses were administered to all patient groups. The primary endpoint of the CLARITY study was the qualifying relapse rate at 96 weeks. Secondary endpoints included MRI endpoints, proportion of subjects qualifying relapse-free and disability progression at 96 weeks. Out of the 1,326 randomized patients, 90% of patients treated with Cladribine Tablets completed the study (92% in the lower total dose group and 89% in the higher total dose group) compared to 87% in the placebo group.

About Cladribine Tablets

Merck Serono's proprietary oral formulation of cladribine (Cladribine Tablets) is currently being evaluated in Phase III as a treatment for patients with relapsing forms of multiple sclerosis (MS). Cladribine is a small molecule that may interfere with the behavior and the proliferation of certain white blood cells, particularly lymphocytes, which are thought to be involved in the pathological process of MS.

The clinical development program for cladribine tablets includes:

- The CLARITY (CLAdRibine Tablets Treating MS Orally) extension study: a two-year placebo-controlled extension of the CLARITY study, 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 trial 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). This trial was announced in September 2008.
- The ONWARD (Oral Cladribine Added ON To Rebif New Formulation in Patients With Active Relapsing Disease) study: a Phase II placebo-controlled trial 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. This trial was announced in January 2007.

Cladribine Tablets have been granted a fast track designation by the US Food and Drug Administration based on the need for an oral therapy in a subset of patients with relapsing forms of multiple sclerosis.

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About Merck Serono and multiple sclerosis

Merck Serono is a leader in multiple sclerosis (MS) with Rebif® (interferon beta-1a), a disease-modifying drug used to treat relapsing forms of MS, which is registered in more than 80 countries worldwide. Full prescribing information for this product can be obtained by contacting the Company or visiting its website. Additional therapeutic options are currently under development at Merck Serono, including 'Cladribine Tablets', currently in Phase III and potentially the first oral therapy for MS, as well as several products in early stage development. Merck Serono also is taking a leading role in developing an understanding of the role of genetics in MS.

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 more than two 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.

About Merck Serono

Merck Serono is the division for innovative prescription pharmaceuticals of Merck, a global pharmaceutical and chemical group. Headquartered in Geneva, Switzerland, Merck Serono discovers, develops, manufactures and markets innovative small molecules and biopharmaceuticals to help patients with unmet medical needs. Its North American business operates in the United States and Canada as EMD Serono.

Merck Serono has leading brands serving patients with cancer (Erbix®), multiple sclerosis (Rebif®, interferon beta-1a), infertility (Gonal-f®, follitropin alfa), endocrine and cardiometabolic disorders (Glucophage®, metformin); (Concor®, bisoprolol); (Euthyrox®, levothyroxine); (Saizen® and Serostim®, somatropin). Not all products are available in all markets.

With an annual R&D expenditure of around € 1bn, Merck Serono is committed to growing its business in specialist-focused therapeutic areas including neurodegenerative diseases, oncology, fertility and endocrinology, as well as new areas potentially arising out of research and development in autoimmune and inflammatory diseases.

About Merck

Merck is a global pharmaceutical and chemical company with total revenues of € 7.6 billion in 2008, a history that began in 1668, and a future shaped by 32,700 employees in 60 countries. Its success is characterized by innovations from entrepreneurial employees. Merck's operating activities come under the umbrella of Merck KGaA, in which the Merck family holds an approximately 70% interest and free shareholders own the remaining approximately 30%. In 1917 the U.S. subsidiary Merck & Co. was expropriated and has been an independent company ever since.

For more information, please visit www.merckserono.com or www.merck.de