

News Release

Your Contact

Alice McGrail: +1 781 738 8791

April 30, 2019

Merck KGaA, Darmstadt, Germany, to Present New Data on Mavenclad[®], Rebif[®] and the Investigational Therapy Evobrutinib at the AAN Annual Meeting 2019

- **20 abstracts will be presented during the AAN Annual Meeting 2019 to demonstrate Merck KGaA, Darmstadt, Germany's commitment and clinical development program in multiple sclerosis**

Darmstadt, Germany, April 30, 2019 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that data from across its multiple sclerosis (MS) portfolio will be presented at the American Academy of Neurology (AAN) 2019 Annual Meeting, 4–10 May 2019 in Philadelphia, United States. The company will present a total of 20 abstracts (18 posters and two platform presentations), including data on MAVENCLAD[®] (cladribine) tablets, the investigational therapy evobrutinib (an oral, selective Bruton's Tyrosine Kinase (BTK) inhibitor) and Rebif[®] (interferon beta-1a).

"The wealth of data to be presented at AAN 2019 highlights our continued progress across our portfolio of marketed products and investigational agents in multiple sclerosis," said Luciano Rossetti, Head of Global Research & Development for the Biopharma business of Merck KGaA, Darmstadt, Germany. "We are very proud of our commitment to further the understanding of multiple sclerosis and enhance our clinical development program to meet the needs of patients."

Key MAVENCLAD[®] data will include:

- Post-hoc analysis of the CLARITY Extension study to examine the durability of no evidence of disease activity-3 (NEDA-3) in relapsing MS (RMS) patients receiving cladribine tablets



News Release

- Integrated analysis of pooled long-term safety data of cladribine tablets in patients with MS collated from the CLARITY, CLARITY Extension, ORACLE-MS studies and the PREMIERE registry
- A new analysis of the speed of onset of the MRI effect is presented. At 3 months the effect on new inflammatory lesions was apparent in the ORACLE-MS study. In the same study consistency in clinical outcomes was observed across different patient subgroups defined by patient and disease characteristics at baseline
- Abstracts from the ORACLE-MS study describe the effect of cladribine tablets on early MS
- Results from studies investigating the biological effects of cladribine tablets, including the effect on lymphocyte proliferation, and endothelial responsiveness to tumour necrosis factor and its effect on hematopoietic precursors and immune cells, to offer further insights on the potential mode of action of cladribine tablets

Key evobrutinib data will include:

- Results of analysis of the efficacy and safety of evobrutinib in patients with RMS over 48 Weeks: a randomized, placebo-controlled, phase 2 study

Key Rebif® data will include:

- Investigation from the European Interferon Beta (IFN β) pregnancy registry and Nordic health study into the prevalence of pregnancy outcomes in IFN β -exposed women
- Results from the IMPROVE study on the dynamics of pseudo-atrophy in RMS patients treated with interferon beta-1a as assessed by monthly brain MRI

Merck KGaA, Darmstadt, Germany, will also be announcing the launch of a new, collaborative MS research network called 'MS-LINK' (**L**eadership and **I**nnovation **N**etwork), an initiative that brings together a community of multiple sclerosis stakeholders to form a scientific foundation for sustainable transformation of MS care, with the shared goal of improving patient outcomes.

Below is a selection of abstracts that have been accepted for presentation at AAN 2019:

News Release

MAVENCLAD (cladribine tablets) data			
Title	Lead Author	Poster	Presentation / Session
Durability of NEDA-3 status in patients with relapsing multiple sclerosis receiving cladribine tablets: CLARITY Extension	Giovannoni G	P3.2-100	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
Cladribine tablets were associated with rapid onset of improvements in MRI outcomes in the ORACLE-MS trial	Scarberry S	P3.2-061	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
The effect of cladribine tablets on delaying the time to conversion to CDMS or McDonald MS is consistent across subgroups in the ORACLE-MS study	Bowen J	P3.2-101	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
Untreated Patients with Multiple Sclerosis: Prevalence and Characteristics in Denmark and in the United States	Nørgaard M	P4.2-060	11:30 - 18:30 ET, Wednesday 8 May P4: MS Epidemiology, Co-Morbidities, and Modifiable Risk Factors
Updated safety analysis of cladribine tablets in the treatment of patients with multiple sclerosis	Cook S	P4.2-046	11:30 - 18:30 ET, Wednesday 8 May P4: MS Therapeutics: MOA and Safety
Gaps in treatment and treatment discontinuation	Nicholas J	P3.2-102	11:30 - 18:30 ET, Tuesday 7 May

News Release

among patients with multiple sclerosis newly-initiating once- or twice-daily oral disease-modifying drugs			P3: MS Clinical Trials and Therapeutic Research
Lymphopenia rates in CLARITY/CLARITY Extension are consistent in patients with or without high disease activity at baseline	Cook S	P3.2-062	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
Meta-analysis of real-world adherence and persistence of maintenance once- or twice-daily oral disease-modifying drugs (dimethyl fumarate, fingolimod, and teriflunomide) in multiple sclerosis	Nicholas J	P3.2-041	11:30 - 18:30 ET, Tuesday 7 May P3: MS Clinical Trials and Therapeutic Research
ADA genetic variants influence central inflammation and clinical characteristics in MS: implications for cladribine treatment	Stampanoni Bassi M	P4.2-044	11:30 - 18:30 ET, Wednesday 8 May P4: MS Therapeutics: MOA and Safety
Dissection of the distinct susceptibility of hematopoietic precursors and immune cells to cladribine	Carlini F	P4.2-045	11:30 - 18:30 ET, Wednesday 8 May P4: MS Therapeutics: MOA and Safety
Neuroblastoma cell line and lymphocytes talk for cladribine influenced	Ruggieri M	P2.2-095	11:30 - 18:30 ET, Monday 6 May

News Release

apoptosis and inflammation pathways in Multiple Sclerosis (MS): an "in vitro" study			P2: MS Immunology and Basic Science
Gene expression profiles of proteins involved in cladribine metabolism and their possible correlation with Epstein-Barr virus variants	Mechelli R	P2.2-096	11:30 - 18:30 ET, Monday 6 May P2: MS Immunology and Basic Science
Evobrutinib data			
Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Evobrutinib (M2951) in Patients with Relapsing Multiple Sclerosis over 48 Weeks: a Randomized, Placebo-Controlled, Phase 2 Study	Montalban X	Oral presentation	13:33 ET, Friday 10 May S56: MS Trials and Treatment
Inhibition of Bruton's Tyrosine Kinase Prevents Inflammatory Macrophage Differentiation: A Potential Role in Multiple Sclerosis	Alankus YB	P2.2-077	11:30 - 18:30 ET, Monday 6 May P2: MS Immunology and Basic Science
Inhibition of Bruton's Tyrosine Kinase Selectively Prevents Antigen-Activation of B cells and Ameliorates B-Cell-Mediated Experimental	Torke S	P2.2-063	11:30 - 18:30 ET, Monday 6 May P2: MS Immunology and Basic Science

News Release

Autoimmune Encephalomyelitis			
Rebif® (interferon beta-1a)			
Pregnancy and Infant Outcomes with Interferon Beta: Data from the European Interferon Beta Pregnancy Registry and MS Preg study conducted in Finland and Sweden	Hellwig K	450	13:44 ET, Thursday 9 May S49: MS Epidemiology and Risk Stratification
Dynamics of Pseudo- Atrophy in RRMS Patients Treated with Interferon beta-1a as Assessed by Monthly Brain MRI	De Stefano N	P5.2-047	11:30 - 18:30 ET, Thursday 9 May P5: MS Neuroimaging

All Merck KGaA, Darmstadt, Germany, press releases are distributed by e-mail at the same time they become available on the EMD Group Website. In case you are a resident of the USA or Canada please go to www.emdgroup.com/subscribe to register for your online subscription of this service as our geo-targeting requires new links in the email. You may later change your selection or discontinue this service.

About MAVENCLAD®

MAVENCLAD, approved by the U.S. Food and Drug Administration (FDA) on March 29, 2019, is the first and only short-course oral therapy for the treatment of adults with relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS). Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of multiple sclerosis (MS), and MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS). Patients should follow healthcare provider instructions including cancer screening, contraception and blood tests. The approved dose of MAVENCLAD is 3.5 mg per kg body weight over two years, administered as one treatment course of 1.75 mg per kg per year, each consisting of two treatment weeks. The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes. MAVENCLAD causes a dose-dependent reduction in lymphocyte counts followed by recovery.

Because cladribine is cytotoxic, special handling and disposal instructions should be followed.

MAVENCLAD has been approved in over 50 countries, including the European Union (EU), Canada, Australia and Switzerland, for various relapsing MS indications. Visit www.MAVENCLAD.com for more information.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks of**

News Release

the use of MAVENCLAD on an individual patient basis for patients with prior or increased risk of malignancy.

- **MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm.**

CONTRAINDICATIONS

- current malignancy.
- pregnancy, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 m after the last dose in each treatment course.
- human immunodeficiency virus (HIV).
- active chronic infections (e.g., hepatitis or tuberculosis).
- history of hypersensitivity to cladribine.
- breastfeeding while taking MAVENCLAD and for 10 days after the last dose.

DOSING CONSIDERATIONS: After the completion of 2 treatment courses, do not administer additional MAVENCLAD during the next 2 years. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after completion of 2 treatment courses has not been studied.

ADDITIONAL WARNINGS AND PRECAUTIONS

- **Lymphopenia:** In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects. Monitor lymphocyte counts before and during treatment, periodically thereafter, and when clinically indicated.
- **Infections:** Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of patients treated with placebo in clinical studies. The most frequent serious infections included herpes zoster and pyelonephritis. Single fatal cases of tuberculosis and fulminant hepatitis B were reported in the clinical program. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD. Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Monitor for infections.
- **Hematologic Toxicity:** Mild to moderate decreases in neutrophil counts, hemoglobin levels, and platelet counts were observed. Severe decreases in neutrophil counts were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Obtain complete blood count (CBC) with differential including lymphocyte count before and during treatment, periodically thereafter, and when clinically indicated.
- **Risk of Graft-versus-Host Disease With Blood Transfusions:** Irradiation of cellular blood components is recommended.
- **Liver Injury:** Obtain liver function tests prior to treatment. Discontinue MAVENCLAD if significant injury is suspected.
- **Hypersensitivity:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Serious hypersensitivity reactions occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue treatment. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.

Adverse Reactions: The most common adverse reactions with an incidence of >20% for MAVENCLAD are upper respiratory tract infection, headache, and lymphopenia.

Drug Interactions/Concomitant Medication: Concomitant use of MAVENCLAD with immunosuppressive or myelosuppressive drugs and some immunomodulatory drugs (e.g., interferon beta) is not recommended and may increase the risk of adverse reactions. Avoid concomitant use of certain antiviral and antiretroviral drugs. Avoid concomitant use of BCRP or ENT/CNT inhibitors as they may alter bioavailability of MAVENCLAD.

Please see the full **Prescribing Information**, including **boxed WARNING** for additional information.

News Release

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 Rebif® (interferon beta-1a)

Rebif (interferon beta-1a) is used to treat relapsing forms of MS to decrease the frequency of relapses and delay the occurrence of some of the physical disability that is common in people with MS. The efficacy and safety of Rebif in controlled clinical trials beyond 2-years has not been established.

Important Safety Information:

Rebif is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

Rebif should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation, has been reported rarely in patients taking Rebif. The potential for liver injury should be considered when used in combination with other products associated with liver injury. Monitor liver function tests and patients for signs and symptoms of hepatic injury. Consider discontinuing Rebif if hepatic injury occurs.

Anaphylaxis and other allergic reactions (some severe) have been reported as a rare complication of Rebif. Discontinue Rebif if anaphylaxis occurs.

In controlled clinical trials, injection site reactions occurred more frequently in Rebif-treated patients than in placebo-treated and Avonex-treated patients. Injection site reactions including injection site pain, erythema, edema, cellulitis, abscess, and necrosis have been reported in the postmarketing setting. Do not administer Rebif into affected area until fully healed; if multiple lesions occur, discontinue Rebif until skin lesions are healed.

Decreased peripheral blood counts in all cell lines, including pancytopenia, have been reported in Rebif-treated patients. In controlled clinical trials, leukopenia occurred at a higher frequency in Rebif-treated patients than in placebo and Avonex-treated patients. Thrombocytopenia and anemia occurred more frequently in 44 mcg Rebif-treated patients than in placebo-treated patients. Patients should be monitored for symptoms or signs of decreased blood counts. Monitoring of complete blood and differential white blood cell counts is also recommended.

Cases of thrombotic microangiopathy (TMA), some fatal, have been reported with interferon beta products, including Rebif, up to several weeks or years after starting therapy. Discontinue Rebif if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

Caution should be exercised when administering Rebif to patients with pre-existing seizure disorders. Seizures have been temporally associated with the use of beta interferons, including Rebif, in clinical trials and in postmarketing reports.

The most common side effects with Rebif are injection-site disorders, headaches, influenza-like symptoms, abdominal pain, depression, elevated liver enzymes, and hematologic abnormalities.

There are no adequate and well-controlled studies in pregnant women. Rebif should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rebif full prescribing information is available at
http://www.emdserono.com/ms.country.us/en/images/Rebif_PI_tcm115_140051.pdf?Version=

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

News Release

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. The company's 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. Around 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 2018, Merck KGaA, Darmstadt, Germany, generated sales of € 14.8 billion in 66 countries.

Scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. This is how Merck KGaA, Darmstadt, Germany, has thrived since its founding in 1668. The founding family remains the majority owner of the publicly listed company. 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 business sectors of Merck operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials.