News Release

Your Contact
Erin-Marie Beals +1 781-681-2850

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New Efficacy and Safety Data on MS Portfolio to be Presented at ECTRIMS 2018

- **Late-breaking Phase II primary endpoint data for investigational therapy evobrutinib, the first oral BTK inhibitor to show clinical proof-of-concept in RMS**
- **Up to 10 years of patient experience provides further insight into the benefit-risk profile of investigational cladribine tablets**
- **Late-breaking data from multi-sponsored European IFNβPregnancy registry highlight Rebif safety outcomes during pregnancy**
- **A total of 23 abstracts for cladribine tablets, Rebif and evobrutinib will be presented at ECTRIMS 2018**

Darmstadt, Germany, October 8, 2018 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced that it will present data from approved and investigational multiple sclerosis (MS) treatments from its neurology and immunology portfolio at the 34th Congress of the European Committee for Treatment and Research In Multiple Sclerosis (ECTRIMS), taking place from 10–12 October 2018, in Berlin, Germany. Merck KGaA, Darmstadt, Germany will present 23 abstracts, including new safety and efficacy data on investigational cladribine tablets, Rebif® (interferon beta-1a) and investigational therapy evobrutinib, a highly-specific, oral Bruton's Tyrosine Kinase (BTK) inhibitor.

Key cladribine tablets data will include:

- An updated integrated safety analysis of patients from the CLARITY, CLARITY Extension and ORACLE-MS trials, including two additional years of data from the long-term PREMIERE Registry (up to 10-years of follow-up).
- An overview of the first six months of real-world evidence safety data on cladribine tablets.

Frankfurter Strasse 250
64293 Darmstadt · Germany
Hotline +49 6151 72-5000
www.emdgroup.com

Head Media Relations -62445
Spokesperson: -9591 / -7144 / -6328
Fax +49 6151 72 3138
media.relations@emdgroup.com

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- Results from a *post hoc* analysis of the CLARITY study will characterize relapse severity and frequency in relapsing-remitting MS (RRMS) patients in cladribine tablets versus placebo.
- New data from *post hoc* analyses to support the duration of effect of cladribine tablets across patient subgroups of different ages and with different disease activity status (in Years 3 and 4 post-treatment) will be presented.

Key late-breaking data presentations include:

- Results of primary 24-week MRI endpoint analysis, along with a description of interim key secondary and safety analysis from a Phase II study of investigational BTK-inhibitor evobrutinib in patients with relapsing MS. The late-breaking oral presentation will highlight the first evidence of clinical activity of a BTK-inhibitor in a non-oncology indication.
- Presentation highlighting pregnancy and infant outcomes with multiple IFNβ therapies, including Rebif®, from the European IFNβ pregnancy registry and Nordic health registers.

"We are proud to be presenting new data across our Neurology and Immunology franchise at Merck KGaA, Darmstadt, Germany during ECTRIMS 2018," said Luciano Rossetti, Head of Global R&D for the biopharma business of Merck KGaA, Darmstadt, Germany. "As we continue to enhance our understanding of the benefit-risk profile of cladribine tablets and the use of Rebif, we are also excited by the presentation of the first clinical data for a BTK inhibitor (evobrutinib) in an MS patient population."

Additional Merck KGaA, Darmstadt, Germany activities at ECTRIMS 2018:

- Results of the Merck KGaA, Darmstadt, Germany-sponsored 'MS in the 21st Century International Unmet Needs Survey' will show that MS patients have substantially different perceptions of the current unmet needs in MS compared with healthcare professionals (HCPs).
- Following on from the #MSInsideOut campaign launch on World MS Day earlier in the year, Merck KGaA, Darmstadt, Germany will be premiering the MS Inside Out Documentary film executively produced by Shift.ms during an event on October 11. At the event, Merck KGaA, Darmstadt, Germany will shine a light on the untold stories of MS, as well as revealing the findings

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and key results from a new global MS carers survey conducted in collaboration between leading international carer organizations IACO (International Alliance of Carer Organization) and Eurocarers. The data presented at ECTRIMS will further demonstrate the need for a deeper understanding of those affected by MS and their carer.

- Merck KGaA, Darmstadt, Germany will also be announcing the annual Grant for Multiple Sclerosis Innovation (GMSI) Award winners in Berlin. First launched at ECTRIMS 2012, the GMSI Award supports the advancement of science and medical research in the field of MS and provides a grant of up to €1,000,000 per year to one or more selected research projects.
- The company will be holding a press event on Wednesday, 10 October 2018, 15:00–16:25 (CET) at CityCube Conference Center (Room: London 1), Berlin, Germany.

Below are a selection of abstracts that have been accepted for presentation at ECTRIMS 2018:

Cladribine Tablets Presentations			
Title	**Authors**	**Abstract No.**	**Presentation Date/Time/Session**
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	Giovannoni G, Rammohan K, Cook S, Soelberg-Sorensen P, Vermersch P, Keller B, Verdun di Cantogno E	A-0950-0028-00859	Session Title: Poster Session 3 Session Date: 12.10.2018 Presenting Time: 12:15-14:15 h
Sustained efficacy in relapsing remitting multiple sclerosis following switch to placebo treatment from Cladribine Tablets in patients with high disease activity at baseline	Vermersch P, Giovannoni G, Soelberg-Sorensen P, Keller B, Jack D	A-0950-0028-00886	Session Title: Poster Session 1 Session Date: 10.10.2018 Presenting Time: 17:00-19:00 h.
CLARITY: An analysis of severity and frequency of relapses in patients with relapsing-remitting multiple sclerosis	Schippling S, Sormani M P, De Stefano N, Giovannoni G, Galazka	A-0950-0028-01315	Session Title: Poster Session 1 Session Date: 10.10.2018

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treated with Cladribine Tablets or placebo	A, Keller B, Alexandri N		Presenting Time: 17:00-19:00 h.
Lymphopenia rates in CLARITY/CLARITY Extension are unrelated to disease activity at baseline	Cook S, Giovannoni G, Vermersch P, Soelberg-Sorensen P, Keller B, Jack D	A-0950-0028-00836	Session Title: Poster Session 2 Session Date: 11.10.2018 Presenting Time: 17:15-19:15 h.
Updated safety analysis of Cladribine Tablets in the treatment of patients with multiple sclerosis	Cook S, Giovannoni G, Leist T, Syed S, Nolting A, Schick R	A-0950-0028-00889	Session Title: Poster Session 2 Session Date: 11.10.2018 Presenting Time: 17:15-19:15 h
Durability of NEDA-3 status in patients with relapsing multiple sclerosis receiving Cladribine Tablets: CLARITY Extension	Giovannoni G, Keller B, Jack D	A-0950-0028-01763	Session Title: Poster Session 2 Session Date: 11.10.2018 Presenting Time: 17:15-19:15 h
ADA genetic variants influence central inflammation and clinical characteristics in MS: implications for cladribine treatment	Stampanoni Bassi M, Buttari F, Simonelli I, Sica F, Furlan R, Marfia G A, Salvetti M, Uccelli A, Matarese G, Visconti A, Centonze D	A-0950-0028-01895	Poster Session 1 10 October 2018 Presenting Time: 17:00-19:00 h
Neuroblastoma cell line and lymphocytes talk for cladribine influenced apoptosis and inflammation pathways in Multiple Sclerosis (MS): an "in vitro" study	Ruggieri M, Mastrapasqua M, Gargano C D, Palazzo C, Frigeri A, Paolicelli D, Visconti A, Trojano M on behalf of MSRUN group.	A-0950-0028-01704	ePoster
Dissection of the distinct susceptibility of hematopoietic precursors and immune cells to cladribine	Carlini F, Ivaldi F, Kerlero de Rosbo N, Boschert U , Visconti A, Uccelli A	A-0950-0028-01855	ePoster
Gene expression profiles of proteins involved in Cladribine metabolism and their possible correlation with Epstein-Barr virus variants	Mechelli R, Manfrè G, Pellicciari G, Reniè R, Romano C, Ristori G, Visconti A, Salvetti M	A-0950-0032-01730	Poster Session 3 12 October 2018 Presenting Time: 12:15-14:15 h

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	on behalf of MSRUN group		
A Systematic Review of Real-world Adherence and Persistence of Daily Oral Disease-Modifying Drugs (Dimethyl Fumarate, Fingolimod, and Teriflunomide) in Multiple Sclerosis	Edwards NC, Edwards RA, Dellarole A, Grosso M, Phillips A	TBC	Poster Session 3 12 October 2018 Presenting Time: 12:15-14:15 h
Rebif® (interferon beta-1a) Presentations			
Subcutaneous Interferon beta-1a, 10-Year Results from the United Kingdom Multiple Sclerosis Risk Sharing Scheme	Harty G, Wong S L, Gillett A, Davies A	A-0950-0030-00894	Session Title: Poster Session 2 Session Date: 11.10.2018 Presenting Time: 17:15-19:15 h.
Rapid reduction of lesion accumulation in specific white matter tracts as assessed by lesion mapping in RR-MS patients treated with IFN beta-1a	De Stefano N, Giorgio A, Gentile G, Stromillo M L, Visconti A, Battaglini M	A-0950-0023-02002	ePoster
Dynamics of pseudo-atrophy in RRMS patients treated with Interferon beta-1a as assessed by monthly brain MRI	De Stefano N, Giorgio A, Gentile G, Stromillo M L, Visconti A, Sormani M P, Battaglini M	A-0950-0023-02027	Session Title: Poster Session 2 Session Date: 11.10.2018 Presenting Time: 17:15-19:15 h.
A Real-World Comparison of Infections and Lymphocyte Counts among Relapsing-Remitting Multiple Sclerosis Patients 50 years or older treated with Subcutaneous Interferon-Beta 1a or Dimethyl Fumarate	Hayward B, Cardoso S, Grosso M, Ansari S, Napoli S	A-0950-0031-02072	Session Title: Poster Session 1 Session Date: 10.10.2018 Presenting Time: 17:00-19:00 h.

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Value of the MoCA test to detect cognitive impairment in MS patients without subjective cognitive complaints	K. Charest, A. Tremblay, R. Langlois, É. Roger, P. Duquette, I. Rouleau	A-0950-0009-01537	ePoster
Rebif® (interferon beta-1a) Late-breaker Presentation			
Pregnancy and Infant Outcomes with Interferon Beta: Data from the European Interferon Beta Pregnancy Registry and Population Based Registries in Finland and Sweden	Hellwig K, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Klinger J, Huppke P, Ornoy A, Korhonen P, Myhr K-M, Montgomery S , Burkill S on behalf of the European Interferon Beta Pregnancy Study Group	A-0950-0000-02658	Session Title: Poster Session 3 Session Date: Friday, 12 October 2018 Presenting Time: 12.15 – 14.15 h
Evobrutinib (Bruton's Tyrosine Kinase Inhibitor) Presentations			
Safety, Tolerability, Pharmacokinetics and Concentration-QT Analysis of the Novel BTK Inhibitor Evobrutinib (M2951) in Healthy Volunteers	Becker A, Martin E, Ona V, Mitchell DY, Willmer J, Johne A	A-0950-0028-01166	Session Title: Poster Session 1 Session Date: 10.10.2018 Presenting Time: 17:00-19:00 h
BTK Inhibition Prevents Inflammatory Macrophage Differentiation: A Potential Role in MS	Alankus YB, Grenningloh R, Haselmeyer P, Bender, A, Bruttger J	A-0950-0028-01194	Session Title: Poster Session 1 Session Date: 10.10.2018 Presenting Time: 17:00-19:00 h.
Inhibition of Bruton's Tyrosine Kinase Selectively Prevents Antigen-Activation of B Cells and Ameliorates B Cell-Mediated Experimental Autoimmune Encephalomyelitis	Torke S, Grenningloh R, Boschert U, Weber MS	A-0950-0028-01220	Session Title: Poster Session 1 Session Date: 10.10.2018 Presenting Time: 17:00-19:00 h.
Evobrutinib (Bruton's Tyrosine Kinase Inhibitor) Late-breaker Presentation			

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Primary analysis of a randomised, placebo-controlled, phase 2 study of the Bruton's tyrosine kinase inhibitor evobrutinib (M2951) in patients with relapsing multiple sclerosis	Montalban X, Arnold DL, Weber MS, Staikov I, Piasecka-Stryczynska K, Willmer J, Martin E, Dangond F, Wolinsky JS	A-0950-0000-02722	Scientific Session 17: Late Breaking News Scientific Session, Hall A Session Date: 12.10.2018 Presenting Time: 14:39-14:51 h
Additional Merck KGaA, Darmstadt, Germany-sponsored Presentations			
Comparing patient and healthcare professional perceptions on multiple sclerosis management and care – where do their priorities differ? Results from a qualitative survey.	Rieckmann P, Langdon D on behalf of MS in the 21st Century Steering Group, and Contango E V	A-0950-0034-01926	Session Title: Poster Session 3 Session Date: 12.10.2018 Presenting Time: 12:15-14:15 h.
MS in the 21st Century mapping study identifying the global educational offerings for multiple sclerosis patients	Rieckmann P, Langdon D on behalf of MS in the 21st Century Steering Group, and Contango E V	A-0950-0034-01860	ePoster

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. In December 2017, Health Canada and the Therapeutic Goods Administration (TGA) in Australia approved MAVENCLAD® for the treatment of relapsing-remitting MS (RRMS).

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 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 selective 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.

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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 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 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.