News Release

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Not intended for UK-based media

October 4, 2021

Merck KGaA, Darmstadt, Germany Completes Enrollment of Evobrutinib Phase III Clinical Trials Ahead of ECTRIMS 2021

- **Investigational evobrutinib is the first Bruton's tyrosine kinase (BTK) inhibitor to complete Phase III clinical trial enrollment in relapsing multiple sclerosis (RMS)**
- **Data from oral presentations at ECTRIMS show evobrutinib has a positive impact on important biomarkers of disease progression**
- **New independent data being presented found that patients treated with MAVENCLAD® (cladribine) tablets had increased antibody IgG titer levels similar to that of the general population after a complete course of an mRNA COVID-19 vaccine**

Darmstadt, Germany, October 4, 2021 – Merck KGaA, Darmstadt, Germany, a leading science and technology company, today announced enrollment has been completed in the Phase III EVOLUTION RMS clinical trial program, which is evaluating the efficacy and safety of investigational Bruton's tyrosine kinase (BTK) inhibitor evobrutinib in patients with relapsing multiple sclerosis (RMS). This milestone comes just ahead of the 37th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), taking place virtually from October 13-15, 2021, where 39 abstracts from the Company's multiple sclerosis (MS) portfolio will be presented. Data will include two oral presentations and a late-breaking ePoster on evobrutinib as well as late-breaking ePosters on MAVENCLAD® (cladribine) tablets including new interim data on patient-reported improvements in

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quality of life (QoL) and new independent data on MAVENCLAD patients who have received a complete course of an mRNA COVID-19 vaccine.

"The breadth of our data at ECTRIMS, paired with the rapid enrollment in our evobrutinib Phase III EVOLUTION RMS clinical trial program, further exemplifies a commitment to continue breaking boundaries in the science of MS," said Danny Bar-Zohar, Global Head of Development for the Healthcare business of Merck KGaA, Darmstadt, Germany. "By generating new data on MAVENCLAD to demonstrate the positive real-life impact it can have for people with RMS, and also on progressing evobrutinib with its dual mode of action targeting both B-cells and innate immune cells in the central nervous system and periphery, we are hoping to address the needs of people with RMS now and in the future."

Key MAVENCLAD® (cladribine) tablets data include:

- Updated post-approval safety data of MAVENCLAD demonstrating consistency of real-world experience with the profile reported in the Phase III and ongoing Phase IV trials, and providing evidence that patients receiving MAVENCLAD do not appear at increased risk of severe COVID-19 outcomes
- In an independent open label study, patients treated with MAVENCLAD were found to increase antibody immunoglobulin G (IgG) titer levels similar to healthy controls after a complete course of an mRNA COVID-19 vaccine. In the U.S., the MAVENCLAD label states that all immunizations should be administered according to immunization guidelines prior to starting MAVENCLAD
- A new interim analysis from the Phase IV CLARIFY-MS study demonstrating that patients living with RMS reported an improvement in physical and mental health at one year of MAVENCLAD treatment
- Real-world MAVENCLAD data from the MSBase Registry demonstrating adherence to MAVENCLAD and an annualized relapse rate similar to clinical trial data
- Late-breaking data including:
    - Long-term Efficacy for Patients Receiving Cladribine Tablets in CLARITY/CLARITY Extension: Primary Results from 9–15 Years of Follow-up in the CLASSIC-MS Study

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- Cladribine tablets after treatment with natalizumab (CLADRINA) trial - Interim analyses

Key evobrutinib data include:

- Data from a post-hoc analysis in the Phase II trial with evobrutinib demonstrated a reduction in volume of slowly expanding lesions (SELs), an in-vivo magnetic resonance imaging (MRI) correlate of chronic active inflammation and axonal loss within the central nervous system (CNS), which may be predictive of subsequent clinical disease progression in MS
- Results from the same trial showed that increased levels of blood neurofilament light chain (NfL), a marker of neuronal damage, at baseline were predictive of increased relapse and MRI lesion activity in the study and evobrutinib significantly reduced MRI and relapse outcomes
- Extensive safety profile characterization of evobrutinib in over 1000 patients from Phase II clinical trials in MS, rheumatoid arthritis and systemic lupus erythematosus demonstrating that overall evobrutinib treatment (all doses) was generally well tolerated across indications and elevations in liver enzymes were asymptomatic and reversible

Additional Company activities at ECTRIMS 2021:

- Satellite symposium: "Supporting patient needs in MS every step of the way" co-chaired by Prof. Gavin Giovannoni, Chair of Neurology, Barts and The London School of Medicine and Dentistry and Prof. Barbara Kornek, Department of Neurology at the University of Vienna (October 13, 2021, 9:00-10:00 EDT)
- Medical education symposium "MS innovation in practice: the continuing search for novel therapeutic targets" co-chaired by Prof. Patrick Vermersch, Vice President for research in biology and health at the University of Lille, and Dr. Xavier Montalban, Chairman & Director Neurology-Neuroimmunology Department & Neurorehabilitation Unit, Multiple Sclerosis Centre of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain (October 13, 2021, 11:45-12:45 EDT).

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To keep up-to-date with our activities at ECTRIMS, along with future data and information, follow us on Twitter @EMDSerono and LinkedIn: EMD Serono, Inc. #ECTRIMS2021 #MSInsideOut

Below is the full list of Merck KGaA, Darmstadt, Germany-related abstracts accepted for presentation at ECTRIMS 2021:

Oral Presentations:			
Abstract Name	**Authors**	**Presentation ID**	**Presentation Details**
Effects of evobrutinib, a Bruton's tyrosine kinase inhibitor, on slowly expanding lesions: an emerging imaging marker of chronic tissue loss in multiple sclerosis	D.L. Arnold, C. Elliott, X. Montalban, E. Martin, Y. Hyvert, D. Tomic	115	**Session:** Free Communications 2 - Treatment trials - Immunomodulation **Date:** October 14, 2021 **Time:** 10:57-11:04 EDT **Presenter:** Douglas L. Arnold
Evobrutinib significantly reduces relapses and magnetic resonance imaging outcomes in patients with multiple sclerosis: association with baseline neurofilament light chain levels	J. Kuhle, L. Kappos, X. Montalban, Y. Li, K. Thangavelu, Y. Hyvert, D. Tomic	116	**Session:** Free Communications 2 - Treatment trials - Immunomodulation **Date:** October 14, 2021 **Time:** 11:04-11:11 EDT **Presenter:** Jens Kuhle
Single cell analysis of cerebrospinal fluid leukocytes in treated multiple sclerosis patients	M. Heming, I. Lu, N. Schwab, D. Schafflick, C.C. Gross, H. Wiendl, G.M. zu Horste	134	**Session:** Free Communication 3: Pathology **Date:** October 15, 2021 **Time:** 6:33-6:40 EDT **Presenter:** Gerd Meyer zu Hörste
Activated Tfh1 cells infiltrate the cerebrospinal fluid in early multiple sclerosis	J.Morille, M. Mandon, S.Rodriguez, A.Garcia, S.Wiertlewski, L.Berthelot, K.Tarte, C.Delaloy, P.Amé,	025	**Session:** Scientific Session 2: Blood-Brain Barrier **Date:** October 15, 2021 **Time:** 8:04-8:11 EDT

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	D-A.Laplaud, L.Michel		**Presenter:** Marion Mandon
MAVENCLAD® (cladribine) tablets ePoster Presentations:			
Long-term Efficacy for Patients Receiving Cladribine Tablets in CLARITY/CLARITY Extension: Primary Results from 9–15 Years of Follow-up in the CLASSIC-MS Study	G. Giovannoni, T. Leist, A. Aydemir, E. Verdun Di Cantogno, on behalf of the CLASSIC-MS Steering Committee	P975	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Gavin Giovannoni
Cladribine Tablets after treatment with natalizumab (CLADRINA) trial – Interim analyses	P. Sguigna, A. Okai, J. Kaplan, K. Blackburn, L. Tardo, B. Hayward, U. Boschert, L. Lebson, N. Manouchehri, R. Hussain, O. Stuve	P987	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Peter Sguigna
Improvements in QoL at 1 Year in Patients Treated With Cladribine Tablets for Highly Active Relapsing MS: An Interim Analysis of CLARIFY-MS	A. Solari, X. Montalban, J. Lechner-Scott, F. Piehl, B. Brochet, D. Langdon, R. Hupperts, K. Selmaj, E.K. Havrdova, F. Patti, Brieva L, Maida EM, N. Alexandri, P. Kamudoni, A. Nolting, B. Keller	P238	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Alessandra Solari
Post-Approval Safety of Cladribine Tablets With Particular Reference to COVID-19 Outcomes: An Update	G. Giovannoni, J. Berger, T. Leist, D. Jack, A. Galazka, A. Nolting, D. Damian	P766	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Gavin Giovannoni
High Adherence to Treatment With Cladribine Tablets for Multiple Sclerosis: Value-Added Benefit of a Nurse/Pharmacy-led Patient Support Programme During the COVID-19 Pandemic	J. Oh, M.S. Freedman, K. Vernon, M. Ayer, C. Lemieux, K. Morgan, T. Quinn, T. Vella, A. Allignol, M. Stein, E. Verdun di Cantogno, M. Sabidó	P741	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Jiwon Oh
Incidence of Infections and	J. Hillert, H. Butzkueven, M.	P767	**Date:** October 13, 2021

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Severe Lymphopenia in Patients Newly Initiating Cladribine Tablets or Fingolimod for Treatment of Multiple Sclerosis: CLARION Study	Soilu-Hänninen, T. Ziemssen, J. Kuhle, J.R. Berger, A. Aydemir, J. Sõnajalg, I. Bezemer, M. Sabidó		**Time:** 10:45-12:45 EDT **Presenter:** Jan Hillert
Disease-Modifying Treatment Patterns of Patients With Multiple Sclerosis and Newly Treated With Cladribine Tablets or Fingolimod: An Interim Analysis of the CLARION Study	H. Butzkueven, J. Hillert, J. Sõnajalg, M. Soilu-Hänninen, A. Aydemir, T. Ziemssen, J. Kuhle, M. Magyari, S. Wergeland, I. Bezemer, M. Sabidó	P742	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Helmut Butzkueven
Risk of Cancer with Disease-Modifying Drugs in Multiple Sclerosis: A New-User Cohort Design in the French Nationwide Claims Database	P. Bosco-Lévy, M. Sabidó, E. Guiard, P. Diez, C. Foch, C. Favary, J. Jové, E. Boutmy, P. Blin	P756	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Meritxell Sabidó
A Multi-Country Cohort Database Study to Assess Pregnancy and Infant Outcomes in Women Exposed to Cladribine Tablets: CLEAR Study	K. Hellwig, M. Magyari, T. McDonald, K. Gembert, S. Wergeland, M.k. Leinonen, A. Aydemir, M. Sabidó, A. Kawai, A. Arana	P185	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Kerstin Hellwig
MASTER-2 trial: Cladribine tablets in patients with relapsing-remitting multiple sclerosis and active secondary multiple sclerosis after suboptimal response to prior infusion/oral disease-modifying therapy (interim baseline results)	E.J. Fox, A.D. Bass, J. Aldridge, L.A. Lebson, D. Robertson	P851	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Edward Fox
Evaluation of therapy satisfaction with cladribine tablets in RMS	C. Grothe, L. Cepek, G. Reifschneider, T. Ziemssen, J. Richter, T. Wagner	P859	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT

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patients – Final results of the non-interventional study CLEVER			**Presenter:** Joachim Richter
Finnish cladribine tablets registry study 2 year data	S. Atula, E. Jarvinen, H. Kuusisto, I. Rauma, M. Ryytty, J. Sipilä, M. Soilu-Hänninen, M. Viitala	P691	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Ilkka Rauma
Outcomes after late Cladribine re-dosing in the Australian MSBase cohort	H. Butzkueven, T. Spelman, S. Hodgkinson, A. Van der Walt, K. Buzzard, O. Skibina, T. Kalincik, J. Lechner-Scott, R. Macdonell, E. Verdun di Cantogno	P865	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Helmut Butzkueven
Real-world experience with cladribine in the MSBase Registry	H. Butzkueven, T. Spelman, MSBase Investigators (TBC), E. Verdun di Cantogno	P825	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Helmut Butzkueven
Molecular biomarker signature associated with cladribine treatment	N. Fissolo, L. Calvo-Barreiro, H. Eixarch, U. Boschert, C. Espejo, X. Montalban, M. Comabella	P584	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Nicolás Fissolo
Effect of cladribine on differentiation of human neural precursor cells	H. Eixarch, L. Calvo-Barreiro, N. Fissolo, U. Boschert, M. Comabella, X. Montalban, C. Espejo	P899	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Herena Eixarch
Economic Analysis for Introduction of Cladribine Tablets as a Treatment for Relapsing-Remitting and High Disease Activity Multiple Sclerosis in Kuwait	R. Alroughani, M.A. Al-Melh, S. Farouk, A. Abokoura, E. Alsultan, A Boshra, R. Alcharif, R. Ojeil, S. Basu, A. Verma	P280	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Raed Alroughani
Effect of cladribine on COVID-19 serology responses	A. Vaknin-Dembinsky	P780	**Date:** October 13, 2021

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following 2 doses of the BNT162b2 mRNA vaccine in patients with multiple sclerosis			**Time:** 10:45-12:45 EDT **Presenter:** Ariel Rechtman
Effect of cladribine tablets in highly active MS monitored by global and regional brain atrophy status	A. Raji, G. Winkler	P709	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Alaleh Raji
Clinical Effectiveness and Safety of Cladribine Tablets for Patients Treated at least 12 Months in the Swedish post-market surveillance study "Immunomodulation and Multiple Sclerosis Epidemiology 10" (IMSE-10)	V. Rosengren, E. Ekström, L. Forsberg, S. Kågström, J. Hillert, P. Nilsson, C. Dahle, A. Svenningsson, J. Lycke, A-M. Landtblom, J. Burman, C. Martin, P. Sundström, M. Gunnarsson, F. Piehl, T. Olsson	P743	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Victoria Rosengren
Real-world patient profile of cladribine tablets in multiple sclerosis patients from Argentina	Rojas JI, Alonso R, Luetic G, Pappolla A, Miguez J, Patrucco L, Cohen L, Garcea O, Casas M, Silva B, Deri N, Liwacki S, Silva E, Piedrabuena R et al.	P853	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Juan Ignacio Rojas
Seroconversion following vaccination against SARS-CoV-2 in people with MS: impact of disease modifying therapy	N. Vickaryous, A.N. Asardag, J. Bestwick, S.N. Shah, K. George, K. Schmierer, G. Giovannoni, D. Baker, A. Kang, R. Dobson	P950	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Nikki Vickaryous
Rebif® (interferon beta-1a) subcutaneous injection ePoster Presentations:			
Development and Interrelation of Whole-Brain Atrophy and Lesion Volume During 5 Years' Treatment With Subcutaneous Interferon Beta-1a in Patients With a First Clinical	R.M. Mattiesing, G. Gentile, I. Brouwer, D. Jack, A. Seitzinger, F. Barkhof, N. De Stefano, B.M.J. Uitdehaag, J.W.R. Twisk, M. Battaglini, H. Vrenken	P430	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Rozemarijn Mattiesing

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Demyelinating Event in the REFLEX/ION Study			
Development and Interrelation of Spatiotemporal Patterns of Brain Atrophy and Lesions During 5 Years' Treatment With Subcutaneous Interferon Beta-1a in Patients With a First Clinical Demyelinating Event in the REFLEX/ION Study	G. Gentile, R.M. Mattiesing, I. Brouwer, D. Jack, A. Seitzinger, F. Barkhof, N. De Stefano, B.M.J. Uitdehaag, H. Vrenken, M. Battaglini	P458	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Giordano Gentile
Exploratory Analysis of Serum GDF-15 Levels in Patients Receiving Subcutaneous Interferon Beta-1a in the REFLEX Trial	M. Coray, A. Seitzinger, S. Roy, M.S. Freedman, F. Barkhof, G. Comi, N. De Stefano, L. Kappos, J. Kuhle, M. Mehling	P674	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Mali Coray
INFORM – Interferon-Beta Exposure in the 2nd and 3rd Trimester of Pregnancy – a Register-Based Drug Utilisation Study in Finland and Sweden	M. Sabidó, K. Suzart-Woischnik, N. Grimes, L.M. Prach, L. Zhao, K.M. Hakkarainen	P794	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Meritxell Sabido
Evobrutinib ePoster Presentations:			
Safety profile characterization of evobrutinib in over 1000 patients from phase II clinical trials in multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus	X. Montalban, D. Wallace, M.C. Genovese, D. Tomic, D. Parsons-Rich, C. Le Bolay, A. Kao, H. Guehring	P727	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Xavier Montalban
The role of human and mouse BTK in myeloid cells	C. Bassani, M. Molinari, V. Martinelli, R. Grenningloh, U. Boschert, G. Comi,	P656	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Cinthia Farina

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	G. Martino, L. Muzio, C. Farina		
Targeting BTK in chronic CNS autoimmunity inhibits activation of microglia	A. Geldaris, S. Torke, R. Grenningloh, U. Boschert, W. Brück, M.S. Weber	P971	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Anastasia Geladaris
Non-Product Specific ePoster Presentations:			
DISCOntinuation of disease-modifying therapies in MS (DISCOMS) Extension – Study Design and Baseline Demographics	E. Engebretson, G. Cutter, R. Fox, I. Kister, A. Miller, C. Morgan, R. Seale, J.R. Corboy	P751	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** John Corboy
Genome-wide mapping of patient's autoantibody targets to understand and predict Multiple Sclerosis pathogenesis and patient responses to Interferon β-1a therapy	E.B. DiCillo, E. Kountikov, M. Zhu, W. Zhang, B. Hayward, D.E. Harlow, S. Lanker, J.L. Bennet, T.F. Tedder	P361	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Europe B DiCillo
Towards a new resource for the MS brain: a cross-brain bank proteomic atlas of non-lesional neocortex	P. Bouman, D. Pitt, D. Reich, J. Schneider, D. Bennett, R. Nagra, R. Reynolds, J. Geurts, J. Corboy, P. De Jager	P317	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Philip De Jager
Multiplexed imaging of the multiple sclerosis meninges using mass cytometry	V. Ramaglia, M. Zuo, N. Fransen, S. Zandee, A. Prat, I. Huitinga, A. Bar-Or, J.L. Gommerman	P319	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Valeria Ramaglia
Interprofessional collaboration and patient-provider communication challenges in MS care: A mixed-methods needs assessment	S. Péloquin, K. Schmierer, J. Oh, T. Leist, S. Murray, P. Lazur	P903	**Date:** October 13, 2021 **Time:** 10:45-12:45 EDT **Presenter:** Sophie Peloquin
Neuropsychological measures associated with disease severity	N. Gur, E. Ganelin Cohen, T. Pilowsky Peleg	P990	**Date:** October 13, 2021

in pediatric onset multiple sclerosis			**Time:** 10:45-12:45 EDT **Presenter:** Noa Gur

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 80 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

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY

- **Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD**
- **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. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant**

CONTRAINDICATIONS

- Patients with current malignancy.
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during and for 6 months after the last dose in each treatment course. May cause fetal harm.
- Patients with human immunodeficiency virus (HIV).
- Patients with active chronic infections (e.g., hepatitis or tuberculosis).
- Patients with a history of hypersensitivity to cladribine.
- Women intending to breastfeed while taking MAVENCLAD tablets and for 10 days after the last dose.

WARNINGS AND PRECAUTIONS

- **Malignancies:** Treatment with MAVENCLAD may increase the risk of malignancy. After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.
- **Risk of Teratogenicity:** MAVENCLAD may cause fetal harm when administered to pregnant women. In females of reproductive potential, exclude pregnancy before initiation of each

treatment course of MAVENCLAD and prevent by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment.

- **Lymphopenia:** MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. 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:** MAVENCLAD can reduce the body's immune defense and may increase the likelihood of 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. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. In patients treated with parenteral cladribine for oncologic indications, cases of progressive multifocal leukoencephalopathy (PML) have been reported. No case of PML has been reported in clinical studies of cladribine in patients with MS.
- **Hematologic Toxicity:** In addition to lymphopenia, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. In general, 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:** Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.
- **Liver Injury:** In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) compared to 0 placebo patients. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment. Discontinue if clinically significant injury is suspected.
- **Hypersensitivity:** In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD, occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine.
- **Cardiac Failure:** In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

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. Acute short-term therapy with corticosteroids can be administered.

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.

Use in Specific Populations: Studies have not been performed in pediatric or elderly patients, pregnant or breastfeeding women. Use in patients with moderate to severe renal or hepatic impairment is not recommended.

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

About Rebif® (interferon beta-1a)

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Rebif (interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It is used to decrease the frequency of relapses and delay the occurrence of some of the physical disability that is common in people with MS.

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.

Epidemiological data do not suggest a clear relationship between interferon beta use and major congenital malformations, but interferon beta may cause fetal harm based on animal studies. Data from a large human population-based cohort study, as well as other published studies over several decades, have not identified a drug-associated risk of major birth defects with interferon beta products during early pregnancy. Findings regarding a potential risk for low birth weight or miscarriage with the use of interferon beta products in pregnancy have been inconsistent.

Please see the full Prescribing Information for additional information: https://www.emdserono.com/us-en/pi/rebif-pi.pdf

About Evobrutinib
Evobrutinib (M2951) is in clinical development to investigate its potential as a treatment for multiple sclerosis (MS). 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. Evobrutinib is currently under clinical investigation and not approved for any use anywhere in the world.

About Multiple Sclerosis

News Release

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 2.8 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 in Neurology and Immunology
Merck KGaA, Darmstadt, Germany has a long-standing legacy in neurology and immunology, with significant R&D and commercial experience in multiple sclerosis (MS). The company's current MS portfolio includes two products for the treatment of relapsing MS – Rebif® (interferon beta-1a) and MAVENCLAD® (cladribine) tablets. Merck KGaA, Darmstadt, Germany aims to improve the lives of patients by addressing areas of unmet medical needs. In addition to Merck KGaA, Darmstadt, Germany's commitment to MS, the company also has a pipeline focusing on discovering new therapies that have potential in other neuroinflammatory and immune-mediated diseases, including systemic lupus erythematosus (SLE).

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About Merck KGaA, Darmstadt, Germany
Merck KGaA, Darmstadt, Germany, a leading science and technology company, operates across healthcare, life science and electronics. Around 58,000 employees work to make a positive difference to millions of people's lives every day by creating more joyful and sustainable ways to live. From advancing gene editing technologies and discovering unique ways to treat the most challenging diseases to enabling the intelligence of devices – the company is everywhere. In 2020, Merck KGaA, Darmstadt, Germany, generated sales of € 17.5 billion in 66 countries.

The company holds the global rights to the name and trademark "Merck" internationally. The only exceptions are the United States and Canada, where the business sectors of Merck KGaA, Darmstadt, Germany operate as EMD Serono in healthcare, MilliporeSigma in life science, and EMD Performance Materials. Since its founding 1668, scientific exploration and responsible entrepreneurship have been key to the company's technological and scientific advances. To this day, the founding family remains the majority owner of the publicly listed company.