Full title: Rates of Lymphopenia in Years 1–4 in Patients with Relapsing Multiple Sclerosis Treated Annually with Cladribine Tablets.

Authors: Stuart Cook[1], Giancarlo Comi[2], Gavin Giovannoni[3], Peter Rieckmann[4], Per Soelberg-Sorensen[5], Patrick Vermersch[6], Fernando Dangond[7], Christine Hicking[8]

[1]Rutgers, The State University of New Jersey, New Jersey Medical School, Newark, NJ, USA; [2]Department of Neurology and Institute of Experimental Neurology, Università Vita-Salute San Raffaele, Ospedale San Raffaele, Milan, Italy; [3]Queen Mary University of London, Blizard Institute, Barts and The London School of Medicine and Dentistry, London, UK; [4]Neurologische Klinik, Akademisches Krankenhaus Sozialstiftung Bamberg, Germany; [5]Danish MS Center, Department of Neurology, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark; [6]Université de Lille, CHU Lille, LIRIC-INSERM U995, FHU Imminent, Lille, France; [7]EMD Serono, Inc., Billerica, MA, US; [8]Merck KGaA, Darmstadt, Germany.

Background: The CLARITY and CLARITY Extension studies demonstrated the efficacy of cladribine tablets in patients with relapsing multiple sclerosis. The most common adverse event was lymphopenia, consistent with the mechanism of action of cladribine tablets.

Objective: Evaluate whether lymphopenia persists following annual treatment with cladribine tablets.

Methods: Lymphopenia by grade (NCI CTCAE v3.0) for patients randomised to cladribine tablets 3.5mg/kg in CLARITY and re-randomised to cladribine tablets 3.5mg/kg in CLARITY Extension (7 mg/kg cumulative dose over 4 years; N=186) are reported. Patients with Grade 0 lymphopenia ($\geq 1.0\times10^9$ cells/L) before the first course of cladribine tablets and Grade 0/1 ($\geq 0.8\times10^9$ cells/L) prior to administration in Years 2, 3 and 4 were included in the analysis.

Results: 176 patients were Grade 0 at CLARITY baseline and 167 were Grade 0/1 at CLARITY Extension baseline. Grade 3 lymphopenia was observed in 1% of patients at Week 13 in Year 1, and in 7%, 11% and 12% at Week 12 in Years 2, 3 and 4, respectively. By Week 24 in Years 1, 2, 3 and 4, Grade 3 lymphopenia was observed in 1%, 4%, 4% and 4% of patients, respectively. By Week 36 in Years 1, 2, 3 and 4, Grade 3 lymphopenia was observed in 1%, 2%, 2% and 2% of patients, respectively. Grade 3 lymphopenia was only observed in Week 48 of Year 2 (1% of patients). Grade 3 lymphopenia was reported in <18% of patients at any time point. No patients had Grade 4 lymphopenia at the end of any years.

Conclusions: No patients included in this analysis experienced Grade 4 lymphopenia at the end of any treatment year. Grade 3 lymphopenia was uncommon. This study demonstrates the effectiveness

of lymphocyte-based treatment criteria in minimising the incidence of severe, sustained lymphopenia during treatment with cladribine tablets.

Disclosures: This study was sponsored by EMD Serono Inc, a business of Merck KGaA, Darmstadt, Germany (in the USA), and Merck Serono SA, Geneva, an affiliate of Merck KGaA Darmstadt, Germany (ROW).

Author disclosures:

S. Cook has received honoraria for lectures/consultations from Merck Serono, Bayer HealthCare, Sanofi-Aventis, Neurology Reviews, Biogen Idec, Teva Pharmaceuticals, and Actinobac Biomed Inc.; has served on advisory boards for Bayer HealthCare, Merck, Actinobac Biomed, Teva Pharmaceuticals, and Biogen Idec; and received grant support from Bayer HealthCare.

G. Comi has received consulting fees from Novartis, Teva Pharmaceutical Industries Ltd., Sanofi-Aventis, Merck, Receptors, Biogen Idec, Genentech-Roche, and Bayer Schering; lecture fees from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Merck Serono, Biogen Dompè, Bayer Schering, and Serono Symposia International Foundation; and trial grant support from Novartis, Teva Pharmaceutical Ind. Ltd., Sanofi-Aventis, Receptors, Biogen Idec, Genentech-Roche, Merck, Biogen Dompè, and Bayer Schering.

G. Giovannoni has received speaker honoraria and consulting fees from Abbvie, Atara Bio, Bayer Schering Pharma, Biogen Idec FivePrime, GlaxoSmithKline, GW Pharma, Merck, , Pfizer Inc, Protein Discovery Laboratories, Teva Pharmaceutical Industries Ltd, Sanofi-Genzyme, UCB, Vertex Pharmaceuticals, Ironwood, and Novartis; and has received research support unrelated to this study from Biogen Idec, Merck, Novartis, and Ironwood.

P. Rieckmann has received honoraria for lectures/steering committee meetings from Merck, Biogen Idec, Bayer Schering Pharma, Boehringer-Ingelheim, Sanofi-Aventis, Genzyme, Novartis, Teva Pharmaceutical Industries, and Serono Symposia International Foundation.

Per Soelberg-Sorensen has served on advisory boards for Biogen, Merck, Novartis, Teva, MedDay Pharmaceuticals, and GSK; on steering committees or independent data monitoring boards in trials sponsored by Merck, Teva, GSK, and Novartis; has received speaker honoraria from Biogen Idec, Merck Serono, Teva, Sanofi-Aventis, Genzyme, and Novartis. His department has received research support from Biogen, Merck, Teva, Novartis, Roche, and Genzyme.

P. Vermersch has received honoraria or consulting fees from Biogen, Sanofi-Genzyme, Bayer, Novartis, Merck, GSK, Roche and Almirall; and research support from Biogen, Sanofi-Genzyme, Bayer, and Merck.

F. Dangond is an employee of EMD Serono, Inc., Billerica, USA, a business of Merck KGaA, Darmstadt, Germany.

C. Hicking is an employee of Merck KGaA, Darmstadt, Germany.