Short title (max. 45 characters): Interferon β-1a and Neurofilament Light Chain

Title: Effect of Interferon β-1a Treatment on Serum Neurofilament Light Chain Levels in Patients with a First Clinical Demyelinating Event in the REFLEX trial

Authors: J. Kuhle (main author)[1], D. Leppert[1], G. Comi[2], N. De Stefano[3], L. Kappos[4], M. S. Freedman[5], S. Roy[6], D. Issard[7]

[1]Department of Medicine, Biomedicine & Clinical Research, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland;

[2]Department of Neurology and Institute of Experimental Neurology, Università Vita-Salute San Raffaele, Ospedale San Raffaele, Milan, Italy;

[3]Department of Neurological and Behavioural Sciences, University of Siena, Siena, Italy;

[4]Neurologic Clinic and Policlinic, Departments of Clinical Research and Biomedical Engineering, University Hospital Basel, and University of Basel, Switzerland;

[5]University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada;

[6]Merck, Aubonne, Switzerland, a division of Merck KGaA, Darmstadt, Germany;

[7]Cytel Inc, Geneva, Switzerland.

Introduction: In REFLEX, patients (pts) with a first clinical demyelinating event (FCDE) treated with subcutaneous interferon β-1a (scIFNβ-1a) 44μg once (qw) or three times weekly (tiw) had significantly delayed conversion to multiple sclerosis (MS; McDonald [McD]-2005 criteria).

Objectives: Assess the effects of scIFNβ-1a 44μg qw or tiw vs placebo (PBO) on serum Neurofilament light chain (sNfL), a promising marker of neuronal injury in pts with FCDE in REFLEX. Explore the predictive value of NfL for conversion to McD-MS.

Methods: Pts were randomised to scIFNβ-1a tiw (n=171), qw (n=175) or PBO (n=171) over 2 yrs; pts converting to clinically definite MS (CDMS) switched to open-label scIFNβ-1a tiw (only data collected to CDMS conversion are included). Serum NfL levels analysed at baseline (Month [M]0), M6, M12, M24. Pts with sNfL data at M0 and ≥1 other time point were included. Treatment effect on sNfL levels was compared using ANCOVA on log-transformed sNfL data, M0 log-sNfL concentration as covariate, data presented for M6, M12. Least Square Mean (LSM; 95% confidence interval [CI]) sNfL concentrations are reported, unless stated otherwise. Percentages of pts converting to McD-MS 2005 by M24 were calculated by Kaplan Meier curve.

Results: At M0, median sNfL concentration of 26.1 pg/ml defined low/high NfL subgroups;mean (standard deviation) sNfL levels:scIFNβ-1a tiw, 45.7(62.4) pg/ml;scIFNβ-1a qw 54.6(106.2) pg/ml;PBO, 59.3(90.8) pg/ml. At M6, LSM (95%CI) sNfL concentration was significantly reduced vs PBO (19.3[17.7-21.2]pg/ml;n=147) with scIFNβ-1a tiw (15.7[14.4-17.2]pg/ml;p=0.002;n=142), scIFNβ-1a qw (15.7[14.4-17.2]pg/ml;p=0.001;n=154). At M12, LSM (95%CI) sNfL concentration was only significantly reduced with scIFNβ-1a tiw (14.0[12.7-15.5];p=0.015;n=131) vs PBO (16.9[15.2-18.8];n=117). Proportionally fewer pts with low sNfL converted to McD-MS by M24 (tiw:49.1%[37.9%-60.3%];qw:69.4%[59.0%-79.8%];PBO:80.2%[71.5%-88.8%]) than high sNfL (tiw:75.2%[65.6%-84.8%];qw:80.6% [72.2%-89.0%];PBO:91.2%[84.7%-97.6%]).

Conclusion: Treatment with scIFNβ-1a tiw or qw reduced sNfL levels in pts with FCDE as early as 6-months post-baseline. High baseline sNfL levels were associated with earlier conversion to McD-MS.

Disclosures: Funded by Merck KGaA, Darmstadt, Germany

ENCORE, previously presented at ECTRIMS 2019; 11–13 September; Stockholm, Sweden

Author Disclosures

JK: institution (University Hospital Basel) has received and exclusively used for research support: consulting fees from Biogen, Novartis, Protagen AG, Roche, and Teva; speaker fees from the Swiss MS Society, Biogen, Genzyme, Merck, Novartis, Roche; travel expenses from Merck Serono, Novartis, and Roche; and grants from the ECTRIMS Research Fellowship Programme, University of Basel, Swiss MS Society, Swiss National Research Foundation (320030_160221), Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, and Roche.

DL: is a former employee of Novartis.

GC: has received consulting and speaking fees from Novartis, Teva Pharmaceutical Industries Ltd., Teva Italia Srl, Sanofi Genzyme, Genzyme corporation, Genzyme Europe, Merck KGaA, Merck Serono S.p.A, Celgene Group, Biogen Idec, Biogen Italia Srl, F. Hoffman-La Roche, Roche SpA, Almirall SpA, Forward Pharma, Medday, Excemed.

NDS: is a consultant for Schering, Biogen-Idec, Teva, Novartis, Sanofi-Genzyme, Roche, and Merck-Serono; has grants or grants pending from FISM and Novartis, is on the speakers bureaus of Biogen-Idec, Teva, Novartis, Sanofi-Genzyme, Roche, and Merck-Serono; has received travel funds from Teva, Novartis, Sanofi-Genzyme, Roche, and Merck-Serono.

LK: institution (University Hospital Basel) has received in the last 3 years and used exclusively for research support: steering committee, advisory board, and consultancy fees (Actelion, Addex, Bayer HealthCare, Biogen Idec, Biotica, Genzyme, Lilly, Merck KGaA, Mitsubishi, Novartis, Ono Pharma, Pfizer, Receptos, Sanofi, Santhera, Siemens, Teva, UCB, and Xenoport); speaker fees (Bayer HealthCare, Biogen Idec, Merck KGaA, Novartis, Sanofi, and Teva); support of educational activities (Bayer HealthCare, Biogen, CSL Behring, Genzyme, Merck KGaA, Novartis, Sanofi, and Teva); license fees for Neurostatus products;

and grants (Bayer HealthCare, Biogen Idec, European Union, Innoswiss, Merck KGaA, Novartis, Roche Research Foundation, Swiss MS Society, and Swiss National Research Foundation).

MSF: has received honoraria or consultation fees from Actelion, Bayer HealthCare, Biogen Idec, Chugai, EMD Canada, Genzyme, Hoffman La Roche, Novartis, Sanofi, Teva.

SR: SR is an employee of Merck, Aubonne, Switzerland, a division of Merck Healthcare KGaA, Darmstadt, Germany.

DI: DI is an employee of Cytel Inc., Geneva, Switzerland and has received fees for consultancy services from Merck Healthcare KGaA, Darmstadt, Germany.