Sustained reduction of disability and cognitive decline with long-term siponimod treatment in patients with active SPMS: EXPAND data up to 5 years

Gavin Giovannoni[1], Ludwig Kappos[2], Robert J. Fox[3], Patrick Vermersch[4], Bruce A.C. Cree[5], Ralph H.B. Benedict[6], Amit Bar-Or[7], Nicolas Rouyrre[8], Daniela Piani-Meier[8], Thomas Hach[8], Shannon Ritter[9], Ajay Kilaru[8]; Frank Dahlke[8], Goeril Karlsson[8], Ralf Gold[10]

[1]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [2]Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland; [3]Mellen Center for Treatment and Research in Multiple Sclerosis, Neurological Institute, Cleveland, OH, USA; [4]University of Lille, Inserm U1172, CHU Lille, FHU Imminent, Lille, France; [5]UCSF Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco, San Francisco, CA, USA; [6]Department of Neurology, University at Buffalo, Buffalo, NY, USA; [7]Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [10]Department of Neurology, St Josef-Hospital/Ruhr-University Bochum, Bochum, Germany.

Background

In the EXPAND Core part, in the subgroup of patients with active secondary progressive multiple sclerosis (aSPMS: presence of relapses in the 2 years prior to screening and/or ≥1 T1 gadolinium-enhancing (Gd+) lesion at baseline), siponimod reduced the risk of 3-/6-month confirmed disability progression on Expanded Disability Status Scale (3m/6mCDP) by 31% and 37%, respectively, and the risk of decline in cognitive processing speed (CPS, 6-month confirmed cognition worsening of ≥4-point on Symbol Digit Modalities Test [6mCCW]) by 27% versus placebo.

Objectives

To assess the long-term efficacy and safety of siponimod in patients with aSPMS in the Core and Extension parts of the EXPAND study.

Methods

In patients with aSPMS who had received ≥1 dose of randomized treatment during Core part, and who entered the Extension (36 month extension data cut-off [6 April 2019]; total study duration ≤5 years), time to 3m/6mCDP, 6mCCW, and annualized relapse rate (ARR) were assessed for the Continuous (siponimod in the Core and Extension) and Switch (placebo in the Core and switched to open-label siponimod in the Core/Extension) groups.

Results

Of the 1651 patients randomized in the EXPAND Core part, 582 were with aSPMS (Continuous group: N=516; Switch group: N=263), of which 710 entered the Extension. The risk of 6mCDP was reduced by 29% (0.71 [0.57–0.90]; p=0.0044) for the Continuous versus Switch group, corresponding to an about 70% delay in time to 6mCDP across the 25th–40th percentile). Median time to 6mCDP was 48 months the Switch group and was not reached for the Continuous group. The risk of 6mCCW for the Continuous versus Switch group was reduced by 33% (0.67 [0.53–0.86]); p=0.0018), corresponding to an about 70% delay in time to 6mCCW across the 25th–30th percentile, median time to 6mCCW (55.5 months) was reached only for the Switch group. In patients without active disease, a nonsignificant trend for reduced risk of disability progression and cognitive worsening was observed for the Continuous vs Switch groups. A significant reduction in ARR for the Continuous versus Switch groups was observed in patients with (0.08 vs 0.12; p=0.0023) or without active disease (0.03 vs 0.08; p<0.0001).

Conclusion

In EXPAND, long-term data analyses in the Continuous versus Switch groups showed that siponimod treatment effects on disability, cognitive processing speed, and relapse outcomes in patients with active SPMS are sustained for up to 5 years, and highlight the value of early treatment initiation.

Funding statement: This study was funded by Novartis Pharma AG, Basel, Switzerland.

Disclosure of conflict of interest

Gavin Giovannoni is a steering committee member on the daclizumab trials for AbbVie, the BG12 and daclizumab trials for Biogen, the fingolimod and siponimod trials for Novartis, the laquinimod trials for Teva and the ocrelizumab trials for Roche. He has also received consultancy fees for advisory board meetings for oral cladribine trials for Merck KGaA, Sanofi Genzyme, and in relation to DSMB activities for Synthon BV, as well as honoraria for speaking at the Physicians' summit and several medical education meetings. He is also the Co-Chief Editor of Multiple Sclerosis and Related Disorders (Elsevier).

Ludwig Kappos' institution (University Hospital Basel) received in the last 3 years and used exclusively for research support at the Department: steering committee, advisory board, consultancy fees and support of educational activies from: Actelion, Allergan, Almirall, Baxalta, Bayer, Biogen, Celgene/Receptos, CSL-Behring, Desitin, Excemed, Eisai, Genzyme, Japan Tobacco, Merck, Minoryx, Novartis, Pfizer, F. Hoffmann-La Roche Ltd, Sanofi Aventis, Santhera, Teva, and license fees for Neurostatus-UHB products; the research of the MS center in Basel has been supported by grants from Bayer, Biogen, Novartis, the Swiss MS Society, the Swiss National Research Foundation, Inno-Suisse, the European Union, and Roche Research Foundations.

Robert J. Fox has received personal consulting fees from Actelion, Biogen, Celgene, EMD Serono, Genentech, Immunic, Novartis, Sanofi, Teva, and TG Therapeutics. I have served on advisory committees for Actelion, Biogen, Immunic, and Novartis, and received clinical trial contract and research grant funding from Biogen and Novartis.

Patrick Vermersch has received honoraria and consulting fees from Biogen, Sanofi, Teva, Novartis, Merck, Celgene and Roche, and research support from Biogen, Sanofi, Roche and Merck.

Bruce A.C. Cree has received personal compensation for consulting from Abbvie, Akili, Alexion, Biogen, EMD Serono, Novartis, Sanofi Genzyme and TG Therapeutics.

Ralph H.B. Benedict has received fees from Acorda Therapeutics, Biogen, EMD Serono, Genentech-Roche, Mallinckrodt, National Multiple Sclerosis Society, Novartis Pharmaceuticals Corporation and Sanofi Genzyme.

Amit Bar-Or has participated as a speaker in meetings sponsored by and received consulting fees and/or grant support from: Janssen/Actelion; Atara Biotherapeutics, Biogen Idec, Celgene/Receptos, Roche/Genentech, Medimmune, Merck/EMD Serono, Novartis, Sanofi-Genzyme.

Ralf Gold has received compensation for serving as a consultant or speaker from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He, or the institution he works for, has received research support from Bayer HealthCare, Biogen Idec, Merck Serono, Novartis and Teva Neuroscience. He has also received honoraria as a Journal Editor from SAGE and Thieme Verlag.

Nicolas Rouyrre, **Daniela Piani Meier, Thomas Hach, Shannon Ritter, Ajay Kilaru, Frank Dahlke** and **Goeril Karlsson** are employees of Novartis.

Abstract topic

- Biomarkers and Bioinformatics
- Biosensors

- Biostatistical Methods
- Clinical Outcome Measures
- Clinical Trials
- Comorbidities
- Diagnostic Criteria and Differential Diagnosis
- Disease Modifying Therapies – Mechanism of Action
- Disease Modifying Therapies – Risk Management
- Epidemiology
- Experimental Models
- Gender Differences, Hormones and Sex Chromosomes
- Genetics and Epigenetics
- Imaging
- Internet and Social Media
- Machine Learning/Network Science
- Microbiome
- Metabolomics
- Neuromyelitis Optica and Anti-MOG Disease
- Neuro-Ophthalmology
- Neuroprotection, Regeneration and/or Remyelination
- Neuropsychology and Cognition
- Observational Studies
- Pathogenesis – Immunology
- Pathogenesis – Neurodegeneration
- Pathogenesis – Role of Glia
- Pathogenesis – the Blood-Brain Barrier
- Pediatric MS
- Prognostic Factors
- Patient-Reported Outcomes and Quality of Life
- Rehabilitation and Comprehensive Care
- Reproductive Aspects and Pregnancy
- Symptom Management