**Title: Assessment of effectiveness of DMD treatment for PwMS in the European Register for Multiple Sclerosis (EUReMS): Study protocol**

Authors: *Jan Hillert[1], Karoline Buckow[2], Otto Rienhoff[2], David Ellenberger[2], Tim Friede[2], Vito Lepore[3], Maria Trojano[4], Anna Glaser[1], Andrius Kavaliunas[1], Ryan Ramanujam[1], Leszek Stawiarz[1], Tsveta Schyns-Liharska[5], Elisabeth Kasilingam[5], Christoph Thalheim[5],*

Acknowledgements:
*Jan Fuge[6] and Dorothea Pitschnau-Michel[6]*

*for the EUReMS Consortium*

1 Karolinska Institute, Stockholm, Sweden;
2 University Medical Center, Georg-August Universität Göttingen, Germany;
3 Mario Negri Sud Fundation, Epidemiology, Chieti, Italy;
4 Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari and Consortium Mario Negri Sud, Bari, Italy;
5 European Multiple Sclerosis Platform, Brussels, Belgium;
6 Deutsche Multiple Sklerose Gesellschaft Bundesverband e.V., DMSG, Hanover, Germany

Conflict of interest / disclosure: Jan Hillert received honoraria for serving on advisory boards for BiogenIdec and Novartis and speaker's fees from BiogenIdec, Merck-Serono, Bayer-Schering, Teva and Sanofi-Aventis. He has served as P.I. for projects sponsored by, or received unrestricted research support from, BiogenIdec, Merck-Serono, TEVA, Novartis and Bayer-Schering.
Tim Friede is a consultant to Novartis and Biogen Idec. This did not result in a conflict of interest.
EMSP (Christoph Thalheim, Elisabeth Kasilingam, Tsveta Schyns-Liharska) ensures that any funding received from the pharmaceutical industry is unconditional grant. Acceptance of those grants does not constitute endorsement by the EMSP of any product of the sponsoring companies.

The other authors did not declare any conflicts of interest.

**Background:** Seven disease modifying (DMD) treatments for MS were approved in the last two decades by FDA, EMA and PMDA, based on efficacy data from randomized controlled trials running against placebo typically for two years. However, MS runs over decades and any analysis of long term effectiveness needs be based on observational data. To date, published studies on long term outcomes of DMD treatment have been limited both in terms of size and outcome measures.

**Objectives:** We have set out to use data from clinical European MS registries to explore the potential of assessing the long-term effectiveness of DMD treatment. The feasibility of such an analysis will be based on quantity, density and quality of data. We will also seek to assess differences in patterns of prescription between countries e.g. due to socioeconomic factors. Disability outcome will be primarily based on expanded disability status scale (EDSS) scores. Since only proportion of patients will have reached EDSS level of 4 or 6 in the first 15 years after start of DMD treatment we anticipate a big initial sample size to be crucial to draw robust conclusions.

**Methods:** A total of 15 European registers were identified and assessed for numbers of patients and types of data registered. Only registers providing longitudinal information of EDSS as outcome and detailed information about DMD treatment were considered possible to include.

**Results:** Only three participating registries were found to likely to contribute information needed for the study, i.e. the MS registries from Germany, Italy and Sweden, altogether containing approximately 62,000 PwMS. These dataset all include the following necessary covariates for analysis: Sex, age at onset, date at diagnosis, disease course at onset, DMD treatments with start and end dates, sequential EDSS scores with dates. Necessarily, the amount of information is expected to vary greatly between patients. If possible also numbers of MRI lesions will be collected. Only patients fulfilling diagnostic criteria of Poser or McDonald will be included. We expect to present data on the number of patients available for analysis as well as which comparisons that are feasible to perform, i.e. treated versus untreated patients, early versus late treatment, and time on treatment.

**Conclusions:** Despite the availability of numerous MS registries and databases it is a big challenge to find comparable registry data giving the information needed in complex settings like assessment of DMD effectiveness. Registry data in Europe is collected with many different scopes and therefore quite heterogeneous in data architecture and data collection. Still they offer a valuable tool for questions which cannot easily be assessed in clinical trials.