

**The European Medicines Agency's Need for Revision of the Note for Guidance on  
Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis  
(CPMP/EWP/561/98)**

Comments Provided From:

**The Sylvia Lawry Centre for Multiple Sclerosis Research (Munich, Germany)**

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**Introduction**

The Staff and the majority of the scientific and medical advisors of the Sylvia Lawry Centre for Multiple Sclerosis Research (Munich) are pleased to provide comment to EMEA in preparation for its revision of the current "Note for Guidance" on clinical investigation of medicinal products for multiple sclerosis (MS). The current note, in force since January 2002, has served for the past two years to define the need for well-designed and implemented clinical trials for MS. At the same time, the past two years have brought significant changes in the diagnosis of MS, the availability of medications in Europe (and abroad which are likely to find eventual regulatory approval in Europe), and in the prescribing practices of physicians who treat patients with MS. Revisions to the "Note for Guidance" are thus appropriate at this time.

We believe that the current "Note for Guidance" has been appropriately broad and has not been overly restrictive to investigators and sponsors in their efforts to design and undertake MS clinical trials for new therapies. Any revised guidelines should, we

believe, be equally open to reasonable variation in trial design, depending on the nature of agents to be tested and the particular disease sub-type under examination.

Among the changes that have taken place in MS therapeutics in the past several years, which have an impact on clinical trial design are:

- Regulatory approval of agents that are aimed at the earliest stages of what can be assessed for individuals to have a low, moderate, or high likelihood to evolve into MS over a finite interval, i.e., for “clinically isolated syndromes” (CIS).
- Development of new diagnostic criteria that fully incorporate magnetic resonance imaging to help obtain confirmation of the “second attack separated in time and space” that is needed for a traditional MS diagnosis (the McDonald, or International Panel, criteria.).
- Regulatory approval of several partially effective agents to treat relapsing forms of MS, which has seriously limited the practical and ethical use of placebo-controlled trial designs for this form of disease.
- Rapid proliferation of clinical trials of a variety of agents for MS, in all stages of development, which have significantly reduced the availability of treatment-naïve patients for prospective trials.
- A growing sense that there may be value in systematically testing whether combinations of available and new therapeutic approaches may have value in altering the course of the disease. Again, attention to long-term benefit is premium.
- As long term effectiveness of approved agents on measures of disability has still to be convincingly shown there is a clear and growing need for longer-term data on all MS therapies to help project short term safety and benefits from 2-3 year trials onto life-long therapy outcomes.
- Growing consensus among clinical experts that validation of surrogate outcomes, including short term clinical measures, magnetic resonance imaging and biological markers, will be needed to expedite future trials and to better understand the implications of existing studies.

## **Comments and Recommendations**

We believe that the future of MS clinical trials, for all forms of the disease, will depend heavily on the willingness of investigators, sponsors and regulatory agencies to explore together and to accept reasonable innovation in MS trial design. We do not have specific detailed recommendations for how trial design should be changed except to say that we need to work to either validate short term surrogates and/or to move to long term trials with observational data as the underpinning of outcome assessment. Because of the very different considerations that must apply to trial design depending on the type and biological activity of a candidate therapeutic agent, and on the sub-type of MS that will be studied, it is not possible to define closely future trial design. However, cooperation among investigator, sponsor and regulators in the following key aspects of MS trial design, independent of the nature of a putative agent or the disease sub-type of interest, will go far to help provide innovative trial design that results in more efficient and more rapidly gathered information about safety and efficacy of any new product. The areas of focus should include:

### *Utilization of available data sets to help define future trial sample size*

MS trialists should vigorously explore available datasets, including past trials and natural history information, to help define trial sample size and expected size effects in prospective trials. Such datasets, from multiple past studies, have been collected in the SLCMSR data base and can (especially if the existing placebo data are supplemented with those of the active treatment arms) provide more information that could more closely define the absolute minimum sample size needed to detect a desired size effect. In addition, such datasets offer the *potential* to use accumulated placebo performance data from past studies to “model” prospective placebo group performance and might even offer the possibility of replacing some actual placebo subjects with “virtual” placebo subjects. Support from EMEA to help mine such datasets to these ends could have a major impact in increasing efficiency and reducing size and duration of prospective trials but also in better defining responders and non responders to available treatments.

### *Clarification of long-term benefits of “early” treatment*

Recent clinical trials in CIS and in relatively early relapsing-remitting disease have defined safety and efficacy largely related to reduction of rate of relapses, or increase in time to subsequent relapses. Some agents have also been shown to slow progression of disability in patients with relapsing forms of MS. But in all cases, the clinical trials that defined these outcomes were of three or fewer years duration, and there is virtually no interpretable information about the impact of such treatment on future, longer-term disease evolution.

Does treatment of CIS delay not only a second attack (which makes for disease definition) but also reduce the long-term development and progression of disability? Does treatment of relatively early relapsing-remitting MS result in fewer patients developing secondary progressive disease over time, and/or slow ultimate long-term progression of disability?

Such questions can only be answered through innovative trial design that guarantees and incentivizes long-term follow-up of enrolled subjects, perhaps for periods of time up to one decade or more. Key to these questions is the clarification of the relationship between relapses – frequency and severity – to progression of disability, a point of basic clinical knowledge that regulatory agents can assist with gathering.

EMA should consider that ALL future MS clinical trials require high-quality, interpretable follow-up to help define therapeutic impact over the longer-term. It might be considered if continued licensing of any approved product were tied to mandatory follow-up.

### *Innovation with regard to placebo controlled trial design*

The “gold standard” for MS clinical trial design has been a randomized, double blinded placebo-controlled study and this model has served the field well in the past. The advent of multiple agents that have been shown to have an acceptable safety and efficacy profile,

particularly for relapsing forms of disease, has made the use of placebo controlled trials impractical and for some even unethical . While there is still likely a role for such studies especially in primary and secondary progressive disease, where proven treatments have remained elusive, innovation in trial design for CIS and relapsing forms of MS – to include reduction or even elimination of need for placebo controls – is a critical current consideration.

For such studies, investigators, sponsors and regulators need to consider the potential of active comparative treatment arms (superiority or non-inferiority trials); dosing studies that eliminate a non-treatment group but use a lower-dose of the active agent as the comparator; creative randomization schemes, such as adaptive or delayed randomization to minimize the amount of time that any given patient is exposed to a “non-treatment” arm of the study; and other potential innovations. The EMEA needs to be an ACTIVE partner with investigators and sponsors in considering such design innovation and, where appropriate, in facilitating their use in prospective trials that the agency is considering.

#### *Need for surrogate outcomes*

Use of validated surrogates for clinical outcomes has the potential to speed clinical trials in MS in the future. The clinical investigator community is more and more convinced about the potential for magnetic resonance imaging outcomes, in particular development of gadolinium-enhancing lesions and new / enlarging T2 lesions, to serve as a surrogate for clinical relapses. But there is still an urgent need to perform the necessary long-term validation studies to determine whether both short term clinical measures (e.g., relapse behavior, disability measures over 1-3 years ) and magnetic resonance imaging outcomes can be shown to serve as bona fide outcome for late clinical behaviours (e.g., persistent disability) . EMEA needs to be proactive in working with investigators and sponsors in exploring these important issues and mining other kinds of imaging data to detect potential surrogates for other aspects of MS.

### *Innovation in statistical analysis*

MS clinical trials have traditionally been designed to support a “frequentist” analytic plan, where the frequency of event after treatment is the analytic path to determine efficacy and safety. Novel trial designs incorporating Bayesian, or adaptive, analytic schemes have not been applied to MS, but offer the possibility to potentially shorten trials and reduce sample size. Because such analytic schemes have not yet been incorporated in prospective MS trials, EMEA should work actively with investigators and sponsors to explore and model such approaches for future trials, and be willing, when appropriate, to consider such designs as appropriate for future pivotal studies.

### *Refining patient selection and stratification*

Recent MS trials experience has shown that careful patient ascertainment and stratification can be vital to the success and interpretation of a trial. EMEA should work with investigators and sponsors to mine available data for all possible covariants in patient ascertainment that could have a potential impact on differential outcomes in a trial, and work to design appropriately stratified and powered studies so that such variables can be studied in detail for their impact on efficacy and safety.

In addition, for each prospective trial, EMEA should require the most current clinical community consensus about disease diagnosis and disease course, to ensure that the most appropriate definitions are being applied to patient selection and randomization.

### *Detecting “improvement”*

Past MS clinical trials have largely been designed to test the impact of a treatment in slowing disease progress and/or deterioration. In this regard, measures of relapses and progression of disability have served reasonably well to define outcomes. Worldwide interest in neural repair, however, is being applied rapidly to MS and putative agents that are intended to actually repair damage and result in recovery of function are in pre-

clinical testing stages for MS today. EMEA should work with investigators and sponsors to define appropriate and achievable clinical and non-clinical outcomes that can provide valid measure of repair and functional recovery, and should do so rapidly so as to position the community in advance to take advantage of this growing biological revolution.

### *Development of biomarkers*

The discovery of valid biological markers of disease activity could have the most profound impact on the future of MS clinical trials. Such markers have revolutionized all aspects of trial design in cardiac disease, HIV and others. However, to date, such are lacking in MS. EMEA can assist in the discovery of appropriate biomarkers by *requiring* that all prospective trials under its auspices allow for a standardized collection and banking of biological materials (e.g., immune, genetic, possibly electrophysiological, depending on the nature of the putative agent and disease sub-type), and the provision by sponsors of adequate funds to explore the potential marker-status of such materials after the completion of such trials. Such requirement will do much to help ensure the eventual application of such information to speed future trial conduct.

### **Conclusion**

The past decade has seen approval of a number of partially effective agents for relapsing forms of MS but, importantly, there remains no data to establish long-term benefit nor are there efforts in place to address this key research and practice issue. There is now a mandate to learn from past experience and move forward understanding the complexities of the MS trial environment. EMEA guidance in MS clinical trials needs to be broad and flexible, reflecting the well-known variability of the disease and the many current unknowns about how to achieve the most efficient and practical future clinical trials designs.

EMEA, clinical trials investigators and pharmaceutical/biotech sponsors need to combine their expertise and work together to create innovative clinical trials design, analysis and

interpretation strategies to help move the next generation of MS therapeutics ahead more rapidly even than the last.

To this end, we at the Sylvia Lawry Center propose that EMEA initiates an international Multiple Sclerosis Clinical Trials Innovation Task Force, including experts representative of the major stakeholders in the MS therapeutics arena. The points noted in these comments are only a starting position for the discussions and innovation that need to happen. This unique partnership will help advance the implementation of future MS clinical trials, will help ensure that future trials are rapidly adaptive to changes in the field, and will help solidify the worldwide influence of the European MS community in MS treatment evolution.