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# Issues Regarding Use of Placebo in MS Drug Trials

Peter Scott Chin, MD
Novartis Pharmaceuticals Corporation

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# Context of the Guidance

The draft EMA Guidance mentions placebo as a comparator for superiority trials evaluating disease modification of multiple sclerosis (MS), in addition to brief mentions in the context of acute relapses and repair of stable disability.

Current discussion is framed within the scope set by the Guidance.

> ***2. Scope*** *[Lines 118-121]*
> *This Guideline is intended to provide guidance for the evaluation of drugs for the treatment of multiple sclerosis. The guideline primarily focuses on treatments aimed to modify disease progression. In addition some remarks are made concerning the treatment of relapses, repair and restoration of functioning.*

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# Ethics of Placebo

The use of placebo-controlled trials to demonstrate efficacy and safety of new therapeutic interventions must be considered in the context of ethics and human rights protections.

The Declaration of Helsinki allows for placebo study designs under specific conditions (Article 32)* :

> *"Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option."*

With regard to placebo-controlled clinical trials in multiple sclerosis, the consensus position of international expert clinicians has been:

> *"Placebo controlled trials can still be done ethically, with restrictions. In relapsing MS for which established treatments exist, placebo controlled trials should only be offered with rigorous informed consent" ***

***World Medical Association, 2008***

****Polman et al. Neurology 2008: 70;1134-1140***

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# Considerations around placebo in disease modifying MS trials

The scientific merit of placebo-controlled trials for evaluating disease-modifying therapies in multiple sclerosis (MS) is well established.

**Phase 2**

- Placebo-controlled trials in relapsing MS have demonstrated proof of efficacy for novel therapeutic drug candidates and informed dose selection, as well as patient selection, for further evaluation.

**Phase 3**

- Placebo-controlled trials in relapsing MS have demonstrated the efficacy of novel therapeutics on clinical and MRI parameters while characterizing the safety profile, typically over two or more years.

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# Considerations around placebo in disease modifying MS trials

Unmet medical need in MS varies and the appropriateness of placebo control varies accordingly. In all settings where a placebo design is considered, patient protection from harm, rigorous informed consent and patient autonomy need to be emphasized.

**Progressive MS**

- No proven effective therapies are available for modifying disease progression in Primary Progressive MS (PPMS) or Secondary Progressive MS (SPMS).
- Placebo studies remain viable for developing therapies in these indications.

**Relapsing MS**

- Established treatments exist for RRMS, therefore placebo controlled trials should only be proposed in well defined circumstances and offered with rigorous consent; the considerations are complex and should be deliberated case by case
- Limited use of placebo in short-term studies may be acceptable if the scientific value derived offsets a minimal risk of harm to study participants
- Trials in which an experimental therapy complementary to immunomodulation, or its placebo control, is added to an existing effective disease modifying therapy are feasible and acceptable

# Potential for worsening following a relapse

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**Figure 1. Residual disability at initial recovery from relapse**

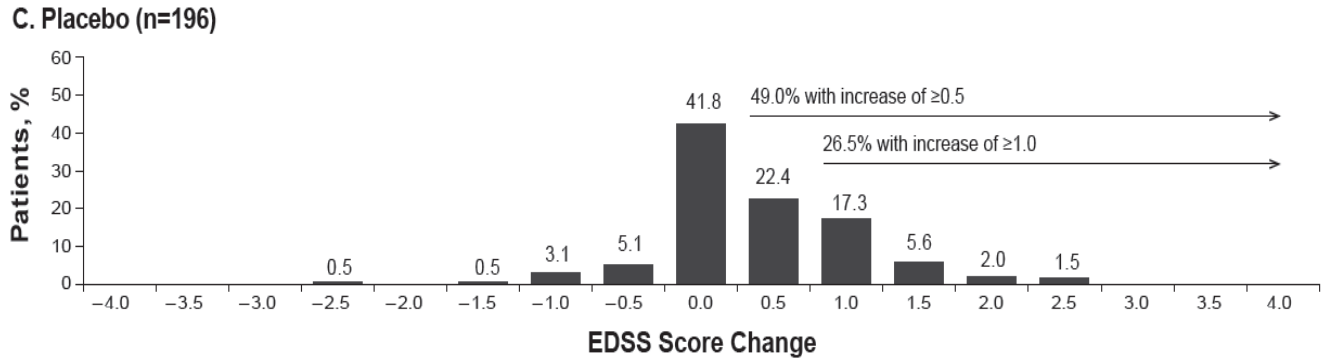
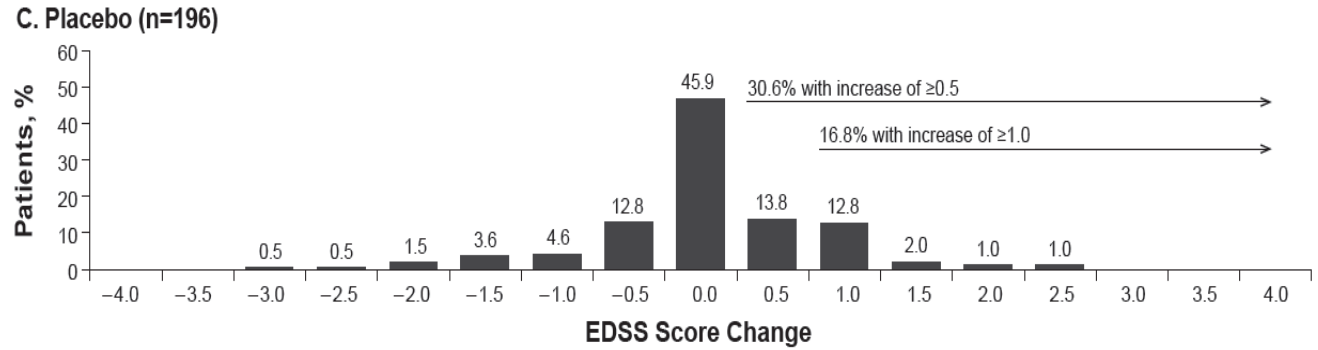



**Figure 3. Residual disability at best recovery from relapse**




At the first EDSS assessment 30 or more days from relapse onset, proportions with residual EDSS increases were similar to published findings:

>= 0.5 pt. increase (49.0%)

>= 1.0 pt. increase (26.5%)

At the last EDSS assessment on study (“best recovery”) the proportions with residual increases were reduced:

>= 0.5 pt. increase (30.6%)

>= 1.0 pt. increase (16.8%)

*Cutter G, et al., American Academy of Neurology meeting, #P7.118, March 2013*

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# Limits of study designs in relapsing MS

- Study features to mitigate risks may not avoid worsening in a subject receiving placebo during a study.
  - Rigorous informed consent and re-consent: potential for continued disease activity and progression on placebo remains
  - Escape with rescue therapy: does not prevent worsening accrued from relapse or disability progression that has already occurred on placebo
  - Also applies to large number of patients exposed to an unproven experimental therapy in active control designs
- Active comparator superiority trials pose an execution challenge for evaluating modestly efficacious therapies with favorable safety profiles
  - Such designs favor improvements in benefit-risk on the efficacy side but improvements in safety may be equally valuable
  - Placebo control may remain appropriate in this setting, depending on the detailed specifics of a given study design
- Non-inferiority study designs are also difficult to execute
  - Lack of agreement on non-inferiority margins with resultant very large sample sizes required

# Additional contexts beyond MS disease modification

- Brief reference to placebo study designs is made in other contexts
- Placebo could be envisaged as a control or reference arm in evaluating treatments within these settings, but it would depend on the details of the study designs

**4.3. Treatments intended to improve apparently stable residual impairment** l235-241]
Products that may potentially facilitate remyelination or improve nerve conduction

- Randomised double blind placebo controlled parallel group trial to establish efficacy.
- Maintenance of treatment effect should be clear and in case of products improving nerve conduction, overstimulation should be excluded.

**5.1. Treatments for acute relapses** [257-269]
Duration and severity of relapses and overall recovery or prevention of their sequelae

- Clinical trials with methylprednisolone as a positive control and a placebo arm for the internal validation of the study.

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# Recommendations

1. The field is moving toward active comparator superiority studies of immunomodulators for demonstrating disease modification in relapsing MS. However, real unsolved challenges exist in designing executable superiority or non-inferiority trials using an active comparator.
   - Active comparator superiority studies for demonstrating disease modification in relapsing MS are appropriate for highly efficacious therapies
   - Active comparator superiority studies for immunomodulatory agents with modest efficacy and mild safety profiles are not viable; placebo designs may have to be carefully considered in this instance
   - Non-inferiority studies against an active comparator are challenging to conduct; however further exploration of such approaches may prove beneficial in MS
   - Placebo control in RRMS could remain appropriate, with restrictions, when proposed in well defined circumstances and offered with rigorous consent; the complex considerations involved should be carefully deliberated case by case

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# Recommendations

2. Placebo control remains appropriate in superiority trials evaluating therapies to slow or prevent progression in SPMS and PPMS.

3. Further elaboration in the Guidance for evaluating treatments for acute relapses and improvement of an apparently stable residual disability would enable more informed review on the use of placebo in these contexts.

4. The MS treatment landscape will continue to evolve and the ethics of placebo in each therapeutic context must be re-evaluated on a continuing basis.