Short title (max. 45 characters): Interferon β-1a: 2017 McDonald criteria applied

Title: Efficacy of subcutaneous interferon β-1a in patients with a first clinical demyelinating event: the REbif FLEXible dosing in early multiple sclerosis (REFLEX) study – outcomes in patients stratified by the 2017 McDonald criteria.

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Introduction: In REFLEX, subcutaneous interferon β-1a (scIFNβ-1a) reduced conversion to multiple sclerosis (MS; McDonald [McD]-2005 criteria) and clinically definite MS (CDMS) vs placebo in patients with a first clinical event suggestive of MS. Retrospective analysis demonstrated overall results were unchanged with application of the McD-2010 MS criteria. The revised McD-2017 MS criteria included the presence of cerebrospinal fluid specific oligoclonal bands.

Objectives: To assess the effects of scIFNβ-1a on time to McD-2005 criteria MS and CDMS, and annualised relapse rate (ARR) during REFLEX, stratified by retrospective diagnosis at baseline in patients that do/do not meet the updated McD-2017 MS criteria.

Methods: During REFLEX, patients were randomised to scIFNβ-1a once (qw) or three times weekly (tiw), or placebo for 2 years. Retrospective analysis stratified patients randomised to the intent-to-treat population into McD-2017-positive (defined as those that retrospectively met the McD-2010 MS criteria at baseline or those with positive oligoclonal bands) and -negative subgroups. Kaplan-Meier curves estimated time to McD-2005 MS and time to CDMS by treatment group and for each McD-2017 subgroup.

Results: Optional detection of oligoclonal bands during REFLEX resulted in a small number of patients added from the McD-2010 analysis. Of 517 patients, 235 were McD-2017-positive at baseline (40 McD-2010-negative but had positive oligoclonal bands). scIFNβ-1a qw or tiw significantly delayed time to McD-2005 MS and CDMS vs placebo in the McD-2017-positive subgroup (hazard ratio [HR] tiw vs placebo=0.47;p<0.001, qw vs placebo=0.58;p=0.002. HR time to CDMS tiw vs placebo=0.46;p=0.010; qw vs placebo=0.42;p=0.003). Treatment with qw or tiw significantly reduced mean ARR vs placebo in McD-2017-positive patients (respectively, 69.1% and 59.3%;p<0.001).

Conclusion: The treatment effects of scIFNβ-1a observed in McD-2010 patients on time to McD-2005 MS and CDMS were maintained in McD-2017-positive patients, although there were only a small number of additional patients when the 2017 criteria were applied.

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