ADVANCE Trial: PEG-IFN-β-1a Every 2 Weeks Significantly Improved Outcomes Over 2 Years in RRMS

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The 1-year results of the Efficacy and Safety Study of Peginterferon Beta-1a in Participants With Relapsing Multiple Sclerosis [ADVANCE; Calabresi PA et al. *Lancet Neurol.* 2014] demonstrated superior clinical and magnetic resonance imaging (MRI) outcomes as compared with placebo in patients with relapsing-remitting multiple sclerosis (RRMS). Post hoc analyses showed that significantly more patients treated with peginterferon beta-1a (PEG-IFN-β-1a) versus placebo had no evidence of disease activity (NEDA) at year 1 [Calabresi PA et al. ACTRIMS/ECTRIMS. 2013 (poster P514)]. The aim of this analysis of the ADVANCE trial, presented by Douglas L. Arnold, MD, McGill University, Montreal, Canada, was to evaluate MRI outcomes and NEDA over 2 years.

The phase 3 ADVANCE trial randomized 1516 patients with RRMS to PEG-IFN-β-1a (125 µg, Q4W), PEG-IFN-β-1a (125 µg, Q2W), or placebo for year 1 [Calabresi PA et al. *Lancet Neurol.* 2014]. After 1 year, patients in the placebo group were randomized to 1 of the 2 PEG-IFN-β-1a regimens (delayed treatment group), and the original PEG-IFN-β-1a groups continued the same treatment. The year 2 tertiary MRI end points were the mean number of new or newly enlarging T2 hyperintense lesions, new T1 hypointense lesions, and gadolinium-enhancing (Gd+) lesions.

Analyses were performed in the intention-to-treat (ITT) population [Calabresi PA et al. CTRIMS/ECTRIMS. 2013 (poster P514)]. Post hoc analyses of clinical and MRI NEDA status were performed from baseline to week 96 and from week 48 to week 96 in the ITT population.

Over 2 years, as compared with delayed treatment and PEG-IFN (Q4W), there was a significant reduction in the mean number of new T1 hypointense lesions and the adjusted mean number of new or newly enlarging T2 hyperintense lesions in the PEG-IFN-β-1a (Q2W) group (14.8, 12.5, and 5.0, respectively; $P < .0001$).

Over 2 years, patients receiving continuous PEG-IFN-β-1a (Q2W vs Q4W) had significantly fewer Gd+ lesions (0.2 vs 0.7; 71% reduction; $P < .0001$). Patients treated with continuous PEG-IFN-β-1a (Q2W and Q4W) had improvement in the occurrence of new or newly enlarging T2 hyperintense lesions (1.9 vs 4.1 and 5.6 vs 9.4, respectively) and new T1 hypointense lesions at year 2 relative to year 1 (0.7 vs 1.8 and 1.8 vs 3.2, respectively).

Over 2 years, significantly more patients treated with continuous PEG-IFN-β-1a (Q2W) achieved NEDA, clinical NEDA, and MRI NEDA versus patients in the delayed treatment and continuous PEG-IFN-β-1a (Q4W) groups (Table 1).

NEDA is an emerging trial end point but is highly dependent on definitions and analytic methods. The sensitivity of automated lesion identification methods may vary across studies and sites. Patients treated with continuous PEG-IFN-β-1a (Q2W) had improved outcomes over 2 years when compared with patients in the delayed treatment group. When considered with the full efficacy and safety results [Calabresi PA et al. ACTRIMS/ECTRIMS. 2014; Kieseier BC et al. ACTRIMS/ECTRIMS. 2014 (poster P085)], these findings confirm that PEG-IFN-β-1a offers an effective treatment for RRMS with a favorable safety profile.

Table 1. Percentage of Patients Who Achieved NEDA Over 2 Years by Original Randomization Group

	PEG-IFN, 125 µg		Delayed Treatment[a]	OR (*P* Value)	
	Q2W	Q4W		vs PEG-IFN Q4W	vs Delayed Treatment
NEDA	36.7	23.0	15.8	1.94 (< .001)	3.09 (< .0001)
Clinical	71.3	64.2	56.6	1.39 (.0160)	1.90 (< .0001)
MRI	40.7	24.8	21.2	2.08 (< .0001)	2.56 (< .0001)

NEDA, no evidence of disease activity; OR, odds ratio; PEG-IFN, peginterferon beta-1a.

[a]Delayed treatment patients received placebo in year 1 and PEG-IFN (Q2W or Q4W) in year 2.