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Efficacy and safety of peginterferon beta-1a in relapsing-remitting multiple sclerosis: 2-year data from the ADVANCE study

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INTRODUCTION

- Peginterferon beta-1a, a pegylated form of interferon beta-1a, is a new investigational drug in clinical development as a subcutaneous (SC) treatment for relapsing-remitting multiple sclerosis (RRMS) with a less frequent dosing requirement than currently-available injectable therapies.
  - Pegylation, modification via attachment of polyethylene glycol (PEG) molecules, may increase the half-life and reduce the immunogenicity of drugs by increasing the molecular size, shielding the molecule, and improving chemical stability.[1]
  - Phase 1 data show that peginterferon beta-1a has a longer half-life and prolonged exposure (area under the curve and peak concentration) compared to non-pegylated interferon beta-1a.[2]
- In Year 1 of the Phase 3 ADVANCE study,[3]
  - Peginterferon beta-1a injected every 2 (Q2W) or 4 (Q4W) weeks significantly reduced annualized relapse rate (ARR, primary endpoint), risk of disability progression and relapse, number of new or newly-enlarging T2 lesions, and multiple other MRI measures compared to placebo.
  - Peginterferon beta-1a Q2W provided greater improvements than the Q4W regimen on clinical and MRI endpoints.
  - The safety profile was similar between the Q2W and Q4W dosing regimens and consistent with that of established interferon beta therapies for RRMS.

OBJECTIVE

- To further evaluate the efficacy and safety of investigational peginterferon beta-1a in patients with RRMS in the ADVANCE study, including 24-week confirmed disability progression rates at Year 1 and efficacy and safety data over 2 years.

METHODS

Study design

- ADVANCE is a 2-year, multicenter, randomized, double-blind, parallel-group, Phase 3 study with a 1-year placebo-controlled period (Figure 1).
- Patients were randomized (1:1:1) to self-administered SC injections of placebo or peginterferon beta-1a 125 µg Q2W or Q4W during Year 1 of the study.
  - A dose titration procedure was used for subjects initiating peginterferon beta-1a (63 µg at week 0, 94 µg at week 2, and 125 µg at week 4 and for the remainder of the study).
  - Subjects randomized to Q4W self-administered alternating injections of peginterferon beta-1a 125 µg and placebo to maintain blinding across 2 years.
- At the end of Year 1 of ADVANCE, patients on placebo were re-randomized to peginterferon beta-1a 125 µg Q2W or Q4W.
- Patients who were randomized to treatment with peginterferon beta-1a in Year 1 remained on the same dosing regimen in Year 2.

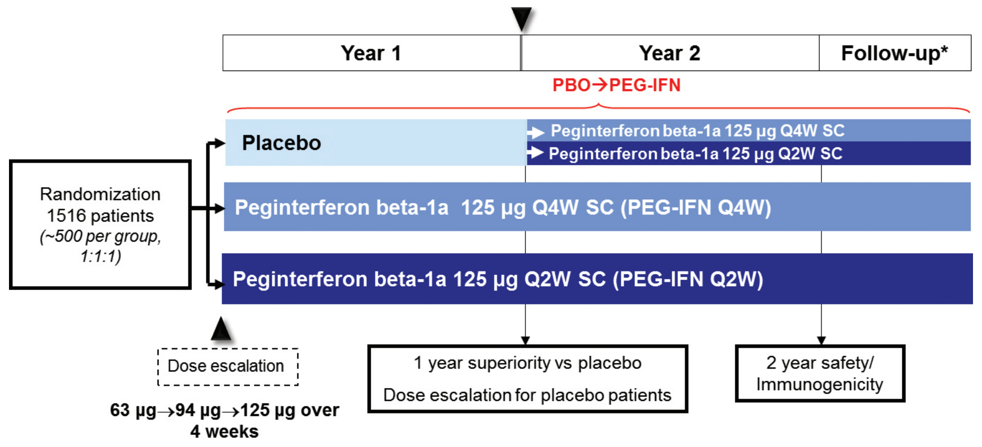
Patients

- Key inclusion criteria:
  - Men and women aged 18–65 years
  - Confirmed diagnosis of RRMS (McDonald criteria 1–4)
  - Expanded Disability Status Scale (EDSS) score ≤5.0
  - ≥2 relapses within the last 3 years, including ≥1 relapse in the 12 months prior to randomization.
- Key exclusion criteria
  - Primary progressive, secondary progressive, or progressive relapsing MS
  - Prior interferon treatment exceeding 4 weeks or within <6 months prior to baseline.

Study endpoints and assessment

- Primary endpoint: ARR at Year 1.
- Maintenance of efficacy over 2 years on:
  - ARR
  - Proportion of patients with disability progression measured by ≥1.0-point increase in EDSS from baseline EDSS ≥1.0, or a ≥1.5-point increase from baseline EDSS=0, that is sustained for ≥12 weeks
  - New or newly enlarging T2 hyperintense lesions on brain MRI scans
  - Number of gadolinium-enhancing (Gd+) lesions on brain MRI scans
  - Number of new T1 hypointense lesions on brain MRI scans.
- Maintenance of safety and tolerability over 2 years.

Figure 1. Advance study design



Year 1
Year 2
Follow-up*
PBO→PEG-IFN
Placebo
Peginterferon beta-1a 125 µg Q4W SC
Peginterferon beta-1a 125 µg Q2W SC
Randomization
1516 patients
(~500 per group, 1:1:1)
Peginterferon beta-1a 125 µg Q4W SC (PEG-IFN Q4W)
Peginterferon beta-1a 125 µg Q2W SC (PEG-IFN Q2W)
Dose escalation
63 µg→94 µg→125 µg over 4 weeks
1 year superiority vs placebo
Dose escalation for placebo patients
2 year safety/ Immunogenicity

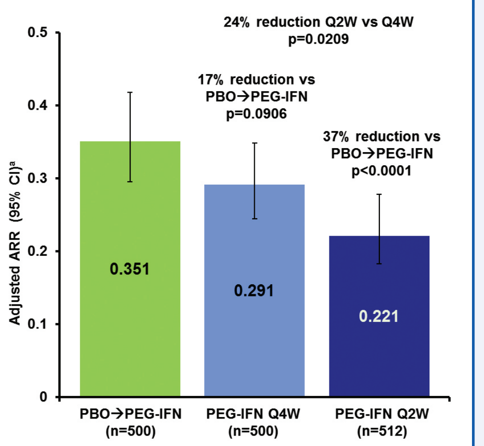
*12-week safety follow-up period for those patients who do not enter an extension study (ATTAIN); Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous

RESULTS

Patients

- In Year 2,
  - 456 patients originally randomized to placebo were re-randomized to Q2W (n=228) or Q4W (n=228).
  - 438 patients originally randomized to Q2W and 438 patients originally randomized to Q4W continued treatment.
- Patient demographics and baseline disease characteristics were generally similar across treatment groups.[3]
- Retention over the 2-year study was similar across groups (patients who received placebo during Year 1 and peginterferon beta-1a in Year 2, 79%; patients who received continuous peginterferon beta-1a Q4W, 78%; patients who received continuous peginterferon beta-1a Q2W, 80%).
- Across treatment groups, 86% to 94% of patients who initiated Year 2 completed Year 2.
- AEs and withdrawal of consent were the most common reasons for discontinuation during Year 2.
  - Discontinuation rates due to AEs were 2% in patients continuing peginterferon beta-1a (both Q2W and Q4W regimens) and 4% in patients re-randomized from placebo to peginterferon beta-1a (both Q2W and Q4W regimens).
  - Rates of discontinuation due to withdrawn consent in Year 2 were 3% in patients continuing Q2W, 6% in patients continuing peginterferon beta-1a Q4W, 7% in patients re-randomized from placebo to Q2W, and 6% in patients re-randomized from placebo to Q4W.

Figure 2. ARR over 2 years



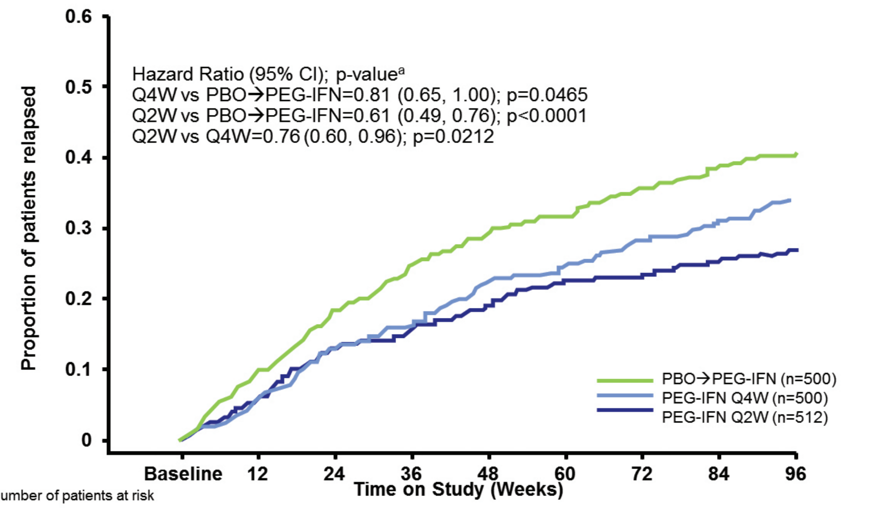
[a]Based on negative binomial regression, adjusted for baseline EDSS (<4 vs. ≥4), baseline relapse rate, and age (<40 vs. ≥40). ARR = annualized relapse rate; PBO→PEG-IFN = patients receiving placebo in Year 1 and peginterferon in Year 2; PEG-IFN = peginterferon; Q2W = every 2 weeks; Q4W = every 4 weeks.

Table 1. Lesions on brain MRI over 2 years

Endpoint	PBO→PEG-IFN (n=393)	PEG-IFN Q4W (n=389)	PEG-IFN Q2W (n=407)
New or newly-enlarged T2-weighted hyperintense lesions			
Adjusted mean number of lesions[a]	14.8	12.5	5.0
Lesion mean ratio (Q2W:Q4W) (95% CI)[a]	—	—	0.40 (0.32, 0.49)
p value (Q2W vs Q4W)[a]	—	—	<0.0001
Number of Gd+ lesions			
Mean number of lesions (SE)	0.5 (0.08)	0.7 (0.12)	0.2 (0.06)
Percent reduction (Q2W vs Q4W)[b]	—	—	71
p value (Q2W vs Q4W)[b]	—	—	<0.0001
T1 hypointense lesions			
Mean number of lesions (SE)	5.6 (0.47)	4.9 (0.47)	2.3 (0.27)
Percent reduction (Q2W vs Q4W)[c]	—	—	53
p value (Q2W vs Q4W)[c]	—	—	<0.0001

[a]Based on negative binomial regression, adjusted for baseline number of new or newly-enlarging T2 lesion; [b]Percent reduction based on group mean and p-value based on multiple logit regression, adjusted for baseline number of Gd+ lesions; [c]Percent reduction based on group mean and p-value based on multiple logit regression, adjusted for baseline number of T1 lesions. CI = confidence interval; Gd+ = gadolinium enhancing; MRI = magnetic resonance imaging; PBO = placebo; PEG-IFN = peginterferon beta-1a; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error

Figure 3. Proportion of patients relapsed over 2 years



Hazard Ratio (95% CI); p-value[a]
Q4W vs PBO→PEG-IFN=0.81 (0.65, 1.00); p=0.0465
Q2W vs PBO→PEG-IFN=0.61 (0.49, 0.76); p<0.0001
Q2W vs Q4W=0.76 (0.60, 0.96); p=0.0212

Number of patients at risk	Baseline	12	24	36	48	60	72	84	96
PBO→PEG-IFN	500	448	398	363	335	314	289	269	217
PEG-IFN Q4W	500	457	412	389	350	330	308	293	212
PEG-IFN Q2W	512	458	414	389	368	341	333	321	262

[a]Based on Cox proportional hazards model, adjustment for baseline EDSS (<4 vs. ≥4), age (<40 vs. ≥40), baseline relapse rate, and baseline Gd+ lesions (presence vs. absence). Analyses were conducted by combining patients who received placebo in Year 1 and either peginterferon beta-1a Q2W or Q4W in Year 2 as one group (PBO→PEG-IFN). PEG-IFN = peginterferon; Q2W = every 2 weeks; Q4W = every 4 weeks

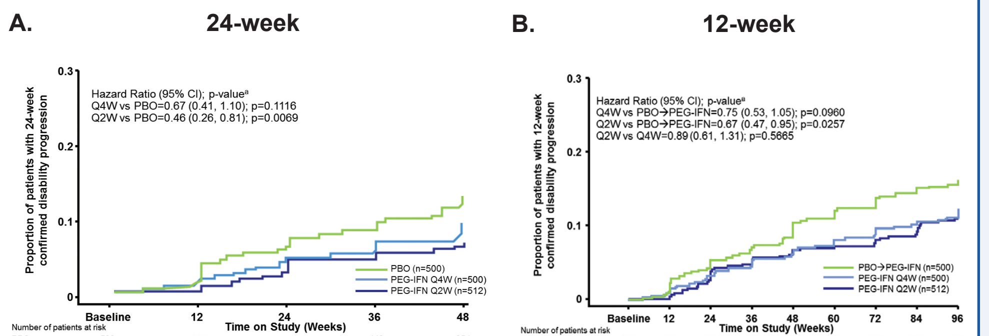
Relapses

- Reduction in ARR over 2 years was greater in patients who received continuous peginterferon beta-1a versus those who received placebo in Year 1 (Figure 2).
  - This difference was statistically significant for the Q2W group but not the Q4W group.
- Reduction in ARR over 2 years was significantly greater among patients continuing peginterferon beta-1a Q2W compared to patients continuing peginterferon beta-1a Q4W (Figure 2).
- Risk of relapse over 2 years was significantly lower among patients who received continuous peginterferon beta-1a compared to patients who received placebo in Year 1 (Q2W, 39% reduction vs patients who received placebo in Year 1 and peginterferon beta-1a in Year 2; Q4W, 19% reduction vs patients who received placebo in Year 1 and peginterferon beta-1a in Year 2; Figure 3).

Disability

- In year 1, patients who received peginterferon beta-1a had a reduced risk of 24-week confirmed disability progression versus those receiving placebo (Q2W by 54%; Q4W by 33%) (Figure 4A); data on 24-week confirmed disability progression in Year 2 will be reported in a future presentation.
- Over 2 years, patients who received continuous peginterferon beta-1a had a reduced risk of 12-week confirmed disability progression versus those who received placebo in Year 1 (Q2W by 33%; Q4W by 25%); Q2W provided favorable outcomes versus Q4W (11% reduction) (Figure 4B).

Figures 4A and 4B. Time to sustained 24-week and 12-week confirmed disability progression.



A. Hazard Ratio (95% CI); p-value[a]
Q4W vs PBO=0.67 (0.41, 1.10); p=0.1116
Q2W vs PBO=0.46 (0.26, 0.81); p=0.0069

Number of patients at risk	Baseline	12	24	36	48
PBO	500	483	460	443	354
PEG-IFN Q4W	500	475	457	333	355
PEG-IFN Q2W	512	480	455	437	362

B. Hazard Ratio (95% CI); p-value[a]
Q4W vs PBO→PEG-IFN=0.75 (0.53, 1.05); p=0.0960
Q2W vs PBO→PEG-IFN=0.67 (0.47, 0.95); p=0.0257
Q2W vs Q4W=0.89 (0.61, 1.31); p=0.5665

Number of patients at risk	Baseline	12	24	36	48	60	72	84	96
PBO→PEG-IFN	500	483	458	440	419	401	383	362	254
PEG-IFN Q4W	500	474	455	433	416	395	380	358	252
PEG-IFN Q2W	512	482	453	431	420	407	398	391	293

[a]Based on a Cox proportional hazards model, adjustment for baseline EDSS and age (<40 v s. ≥40).
Analyses were conducted by combining patients who received placebo in Year 1 and either PEG-IFN Q2W or Q4W in Year 2 as one group (PBO → PEG-IFN). PEG-IFN = peginterferon; Q2W = every 2 weeks; Q4W = every 4 weeks.

MRI endpoints

- In Year 2, the number of new or newly-enlarging T2 lesions, Gd+ lesions, and T1 hypointense lesions were significantly lower in the Q2W group than in the Q4W group (p<0.0001 for all lesion types, Table 1).

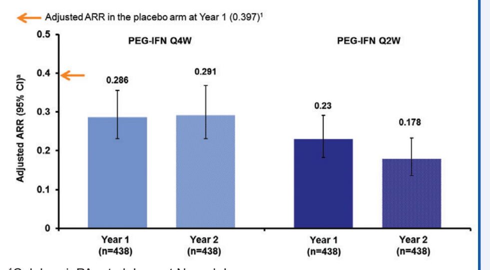
Maintenance of efficacy

- In Year 2, ARR was maintained in patients continuing peginterferon beta-1a Q4W and further reduced in patients continuing peginterferon beta-1a Q2W (Figure 5).
- Relative to Year 1, the number of new or newly-enlarging T2 lesions was lower in both peginterferon beta-1a groups (Figure 6).

Safety

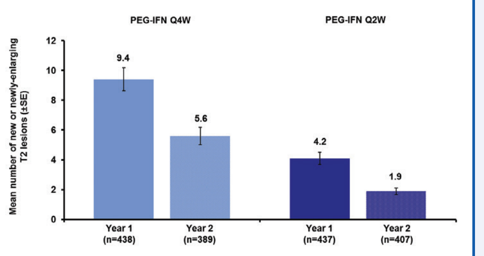
- The overall incidence of adverse events (AEs) was similar between patients treated at any time with peginterferon-beta 1 Q2W (94%) and Q4W (94%) (Table 2).

Figure 5. ARR in year 1 and 2



[1]Calabresi, PA. et al. Lancet Neurol; In press
*Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs ≥4), baseline relapse rate and age (<40 vs ≥40).
ARR = annualized relapse rate; CI = confidence interval; PEG-IFN = peginterferon beta-1a; Q2W = every 2 weeks; Q4W = every 4 weeks

Figure 6. New or newly-enlarging T2 lesions in year 1 and 2



PEG-IFN = peginterferon beta-1a; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error

Table 2. Safety and tolerability data over 2 years

Event, n (%)	PEG-IFN Q4W (n=728)	PEG-IFN Q2W (n=740)
Any AE	687 (94)	699 (94)
Most common AEs (≥20% in any treatment group)		
Injection site erythema	433 (59)	470 (64)
Influenza like illness	365 (50)	377 (51)
Pyrexia	298 (41)	320 (43)
Headache	296 (41)	308 (42)
Multiple sclerosis relapse	222 (30)	185 (25)
Myalgia	137 (19)	140 (19)
AEs related to study treatment	644 (88)	668 (90)
AEs leading to discontinuation	42 (6)	41 (6)
AEs leading to discontinuation (≥1% in any active treatment group)		
Influenza like illness	12 (2)	8 (1)
Any serious adverse events	107 (21)	80 (16)
Deaths	3 (<1)	4 (<1)

Along with all safety data, deaths were reviewed by an independent data safety monitoring board which concluded that these events were not likely related to study drug and did not change the risk-benefit profile of PEG-IFN. Further details will be reported in the manuscript. AE = adverse event; PEG-IFN = peginterferon beta-1a; Q2W = every 2 weeks; Q4W = every 4 weeks.

- The most common AEs (incidence ≥20% in any treatment group) in the Q2W and Q4W groups were injection site erythema, influenza-like illness, pyrexia, and headache. AEs considered related to treatment were similar between the Q2W (88%) and Q4W (90%) groups.
- Influenza-like illness was the most common AE leading to study discontinuation in the Q2W (1%) and Q4W (2%) groups.
- There were no differences in serious AEs beyond MS relapses between patients receiving peginterferon beta-1a Q2W and those receiving peginterferon beta-1a Q4W.
- Over 2 years, 4 deaths were reported in the Q2W group and 3 deaths in the Q4W group. The incidence of deaths in Q2W group and Q4W groups were similar to that in the placebo group in Year 1, and none of the deaths were considered related to treatment by an independent data safety monitoring committee. Further details will be reported in the manuscript.
- Development of neutralizing antibodies occurred in a low percentage of patients over 2 years (Q2W, n=7 [<1%]; Q4W, n=6 [<1%]).
- No clinically significant changes in liver enzymes or hematology laboratory abnormalities were observed in patients treated with peginterferon beta-1a over 2 years.
  - The majority of hepatic transaminase elevations were <3 times the upper limit of normal.

CONCLUSIONS

- In Year 1, 24-week confirmed disability progression was reduced by 54% in the Q2W group vs placebo and by 33% in the Q4W group vs placebo.
- The efficacy of peginterferon beta-1a was maintained or further improved over 2 years on both clinical and MRI measures beyond the 1-year placebo controlled study period.
- Treatment effects on multiple clinical and MRI endpoints were significantly greater with peginterferon beta-1a Q2W compared to the Q4W regimen over 2 years.
- The safety and tolerability profiles of peginterferon beta-1a Q2W and Q4W over 2 years were consistent with data from Year 1.[3]

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Disclosures

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