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Immunogenicity with Peginterferon Beta-1a: 2-year Data from the ADVANCE Study in Relapsing-Remitting Multiple Sclerosis

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Introduction

- The efficacy of IFN betas on clinical and radiological measures may be reduced in patients who become positive for IFN beta NAbs.[1]
- Drug modification by attachment of PEG molecules (pegylation) is a procedure that may increase half-life and reduce immunogenicity.[2]
- Peginterferon beta-1a, a pegylated version of IFN beta-1a, is a SC injectable therapy in clinical development for the treatment of relapsing MS.
- Peginterferon beta-1a may provide efficacy and safety similar to that of approved first-line IFN beta therapies, with a lower dosing frequency than required for other IFN beta therapies.

IFN, interferon; NAbs, neutralizing antibodies; PEG, polyethylene glycol; SC, subcutaneous.
[1]Polman CH, et al. *Lancet Neurol* 2010; 9:740–750; [2]Kieseier BC, Calabresi PA. *CNS Drugs* 2012; 26:205–214.

Introduction

- Phase 1 data show that half-life and exposure (area under the curve and peak concentration) of peginterferon beta-1a at a variety of dose levels (63, 125, 188 µg SC or intramuscular) are increased compared to non-pegylated IFN beta-1a (30 µg).[1]
- Results from the Phase 3 ADVANCE study[2] show that SC peginterferon beta-1a (125 µg) administered every 2 (Q2W) or 4 (Q2W) weeks
  - Provides statistically significant improvements in clinical and radiological outcomes versus placebo.
  - Has a safety profile consistent with that of established IFN beta-1a therapies for relapsing MS.

IFN=interferon; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous .
[1]Hu X, et al. *J Clin Pharmacol* 2012; 5:798–808, [2]Calabresi P, Kieseier B, Arnold DL, et al. *Lancet Neurol*, In press.

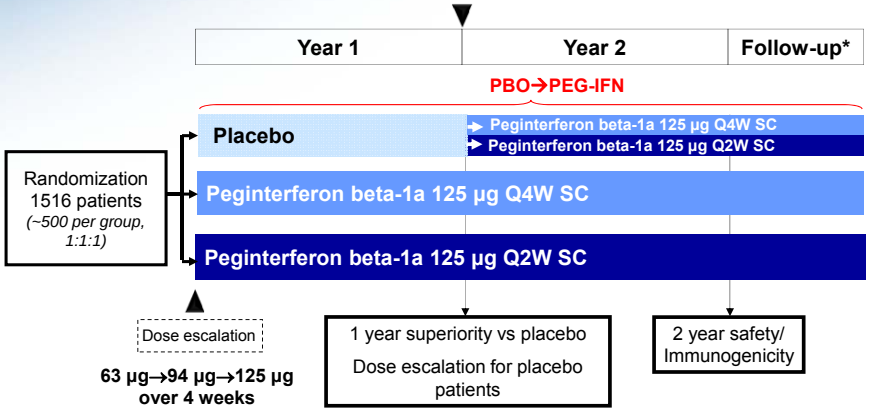
Objectives

- To assess the immunogenicity of SC peginterferon beta-1a in patients with relapsing-remitting MS over 2 years of the Phase 3 ADVANCE study.
- To assess the impact of peginterferon beta-1a immunogenicity on measures of efficacy, safety, and pharmacology.

MS, multiple sclerosis; SC, subcutaneous.

ADVANCE study design

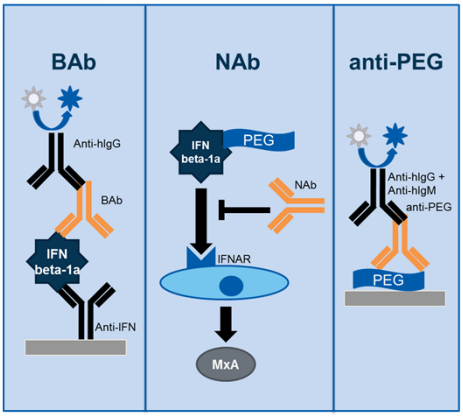
- **Design:** Two-year, multicenter, randomized, double-blind, parallel-group Phase 3 study with a 1-year placebo-controlled period.
- Baseline characteristics were balanced across the three groups.[1]



[1]Calabresi P, Kieseier B, Arnold DL, et al. *Lancet Neurol*, In press.
*12-week safety follow-up period for those patients who do not enter an extension study (ATTAIN); PBO, placebo; PEG-IFN, peginterferon; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous.

Assessment of immunogenicity

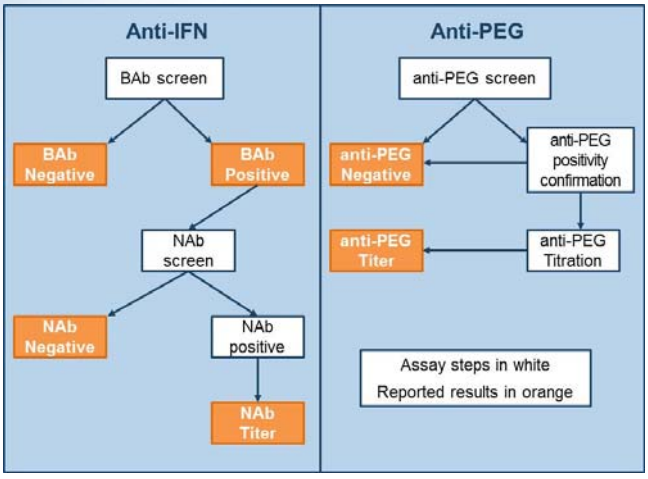
- Immunogenicity was assessed via 3 analytically validated assays:
  - An ELISA for IFN beta-1a binding antibodies (BAbs)
  - A cell-based assay for IFN beta-1a NAbs
  - An ELISA for anti-PEG binding antibodies.
- Clinical serum samples were collected pre-dose on Day 1 and at Weeks 8, 20, 36, 48, 60, 72, and 96.



BAbs, binding antibodies; IFN, interferon; NAbs, neutralizing antibodies; ELISA, enzyme-linked immunosorbent assay; PEG, polyethylene glycol.

Assessment of immunogenicity

- Sera samples were first tested for the presence of BAbs to IFN beta-1a.
- Samples positive for BAbs to IFN beta-1a were then tested for presence and titer of NAbs to IFN beta-1a.
- Samples were also tested for the presence and titer of anti-PEG antibodies.



BAbs, binding antibodies; IFN, interferon; NAbs, neutralizing antibodies; PEG, polyethylene glycol.

Incidence of interferon beta-1a and anti-PEG antibodies at baseline

- Few patients were positive for IFN beta-1a BAbs, IFN beta-1a NAbs, or anti-PEG antibodies at baseline.
- For patients positive for anti-PEG antibodies at baseline, titers increased >3-fold across the study in 2/39 and 4/43 patients receiving peginterferon beta-1a every 4 weeks or every 2 weeks, respectively.

	Placebo→Peginterferon 125 µg		Peginterferon 125 µg	
	Q4W (n=227)	Q2W (n=228)	Q4W (n=501)	Q2W (n=512)
IFN BAb positive, n (%)	7 (3)	1 (<1)	8 (2)	16 (3)
IFN NAb positive, n (%)	3 (1)	0	2 (<1)	8 (2)
Anti-PEG positive, n (%)	12 (5)	18 (8)	27 (5)	25 (5)

BAb, binding antibody; IFN, interferon; NAb, neutralizing antibody; PEG, polyethyleneglycol; Q2W, every 2 weeks; Q4W, every 4 weeks. Year 2 baseline for subjects who received placebo in Year 1; Year 1 baseline for subjects who received peginterferon 125 µg throughout the study.

Incidence of treatment emergent interferon beta-1a binding antibodies over 2 years

- The overall incidence of treatment emergent IFN beta-1a BAbs was 6% among the total study population and generally similar between treatment arms.

	Peginterferon beta-1a Q4W n=706	Peginterferon beta-1a Q2W n=706
Subjects with ≥1 positive BAb result, n (%)	36 (5)	54 (8)
Transient BAb positive, n (%)*	17 (2)	25 (4)
Persistent BAb positive, n (%)*	19 (3)	29 (4)

BAb, binding antibody against IFN beta-1a; IFN, interferon; Q2W, every 2 weeks; Q4W, every 4 weeks.
*Transient positive defined as a single positive evaluation or >1 positive evaluation occurring <74 days apart; persistent positive defined as ≥2 consecutive positive evaluations that occurred ≥74 days apart or a positive evaluation at the final assessment.

Incidence and titer of treatment emergent interferon beta-1a neutralizing antibodies over 2 years

- The incidence of treatment emergent NAbs was <1% in both treatment arms; most positive patients had low/medium titer levels.

	Peginterferon beta-1a Q4W n=716	Peginterferon beta-1a Q2W n=715
Subjects with ≥1 positive NAb result, n (%)	6 (<1)	7 (<1)
Transient NAb positive, n (%)*	5 (<1)	2 (<1)
Persistent NAb positive, n (%)*	1 (<1)	5 (<1)
Low NAb titer, n (%)	3 (<1)	2 (<1)
Medium NAb titer, n (%)†	6 (<1)	
High NAb titer, n (%)†	1 (<1)	

NAb, neutralizing antibody against IFN beta-1a; Q2W, every 2 weeks; Q4W, every 4 weeks; NAb titer levels: low (≤50), medium (>50 and ≤700), high (>700); set empirically based on titer distributions of all samples.
*Transient positive defined as a single positive evaluation or >1 positive evaluation occurring <74 days apart; persistent positive defined as ≥2 consecutive positive evaluations that occurred ≥74 days apart or a positive evaluation at the final assessment.
†Combined total for Q4W and Q2W.

Incidence and titer of treatment emergent anti-polyethylene glycol antibodies over 2 years

- The incidence of treatment emergent anti-PEG antibodies was 7% across 2 years in the total study population, with no apparent difference between the Q2W and Q4W groups; most positive patients had low/medium titer levels.

	Peginterferon beta-1a Q4W n=682	Peginterferon beta-1a Q2W n=681
Subjects with ≥1 positive anti-PEG result, n (%)	55 (8)	40 (6)
Transient positive, n (%)*	20 (3)	22 (3)
Persistent positive, n (%)*	35 (5)	18 (3)
Low titer, n (%)	32 (5)	26 (4)
Medium titer, n (%)	21 (3)	13 (2)
High titer, n (%)	2 (<1)	1 (<1)

PEG, polyethylene glycol; Q2W, every 2 weeks; Q4W, every 4 weeks. Results reported as "Positive-titer not determinable" (TND) were considered low titer. Anti-PEG titer levels: low (≤100), medium (>100 and <800), or high (≥800).
*Transient positive defined as a single positive evaluation or >1 positive evaluation occurring <74 days apart; persistent positive defined as ≥2 consecutive positive evaluations that occurred ≥74 days apart or a positive evaluation at the final assessment.

Impact of immunogenicity on the efficacy of peginterferon beta-1a over Year 1

- ARR (primary endpoint) was lower for patients treated with peginterferon beta-1a versus placebo, regardless of antibody status.

		Placebo n=500	Peginterferon beta-1a Q4W n=500		Peginterferon beta-1a Q2W n=512	
			Never positive	Ever positive	Never positive	Ever positive
Anti-IFN BAbs	n	500	472	28	458	54
	ARR	0.41	0.30	0.12	0.28	0.19
Anti-IFN NAbs	n	500	496	4	500	12
	ARR	0.41	0.29	0.00	0.27	0.00
Anti-PEG antibodies	n	500	430	70	456	56
	ARR	0.41	0.29	0.25	0.27	0.24

ARR = annualized relapse rate; BAb = IFN beta-1a binding antibodies; NAb = IFN beta-1a neutralizing antibodies; Q2W = every 2 weeks; Q4W = every 4 weeks.

Impact of immunogenicity on the efficacy of peginterferon beta-1a over Year 1

- Improvements in secondary endpoints were also observed for patients treated with peginterferon beta-1a versus placebo, regardless of antibody status.

		Placebo n=500	Peginterferon beta-1a Q4W n=500		Peginterferon beta-1a Q2W n=512	
			Never positive	Ever positive	Never positive	Ever positive
Anti-IFN BAbs	n (%) subjects	500 (100)	472 (94.4)	28 (5.6)	458 (89.4)	54 (10.5)
	Number of new or newly enlarging T2 lesions, mean (SD)	13.3 (19.51)	9.5 (16.18)	5.2 (7.50)	3.9 (8.11)	5.3 (11.44)
	Relapse-free subjects, %	72	78	89	82	87
Anti-IFN NAbs	n (%) subjects	500 (100)	496 (99.2)	4 (0.8)	500 (97.7)	12 (2.3)
	Number of new or newly enlarging T2 lesions, mean (SD)	13.3 (19.51)	9.2 (15.88)	9.7 (10.26)	4.1 (8.60)	4.7 (6.12)
	Relapse-free subjects, %	72	79	100	82	100
Anti-PEG antibodies	n (%) subjects	500 (100)	430 (86.0)	70 (14.0)	456 (89.1)	56 (10.9)
	Number of new or newly enlarging T2 lesions, mean (SD)	13.3 (19.51)	8.9 (15.19)	11.4 (19.40)	4.1 (8.76)	4.4 (6.77)
	Relapse-free subjects, %	72	79	80	82	86

BAb = IFN beta-1a binding antibodies; NAb = IFN beta-1a neutralizing antibodies; Q2W = every 2 weeks; Q4W = every 4 weeks.

Impact of immunogenicity on the safety of peginterferon beta-1a over Year 1

- Although analysis was limited by the low incidence of treatment-emergent antibodies, no discernible impact on safety and tolerability was observed.
- Incidence of adverse events, including injection site reactions, did not differ by antibody status or titer.

Impact of immunogenicity on the pharmacology of peginterferon beta-1a over Year 1

- None of the 25 subjects from an intensive PK/PD sampling group tested positive for anti-IFN NAbs.
- Two subjects were positive for anti-IFN BAbs (Q2W, n=1 at Week 24; Q4W, n=1 at Weeks 4 and 24), and two separate subjects tested positive for anti-PEG antibodies.
- PD parameters in the 4 subjects that tested positive for anti-IFN BAbs or anti-PEG antibodies were similar to the group medians, including
  - C_{max}
  - AUC for the dosing interval (AUC_{tau})
  - Peak neopterin concentration after baseline correction (E_{peak})
  - AUC from time 0 to 336 hours post-dosing, after correcting for baseline (E_{AUC336})

PD=pharmacodynamics; PK=pharmacokinetics.

Summary and Conclusions

- The incidence of IFN beta-1a BAbs* was low in patients who received 2 years of treatment with peginterferon beta-1a Q2W or Q4W or 1 year of treatment with placebo followed by 1 year of treatment with peginterferon beta-1a Q2W or Q4W.
- The incidence of IFN beta-1a NAbs* was <1% across 2 years in both peginterferon beta-1a treatment arms.
- The incidence of anti-PEG antibodies* was 7% in the total study population across 2 years, with no difference between peginterferon beta-1a treatment arms.
- Titers of IFN beta-1a NAbs and anti-PEG antibodies were low across 2 years in both peginterferon beta-1a treatment arms.
- There was no discernible effect of antibody status or antibody titer level on clinical efficacy, safety, or pharmacodynamics observed in this study, although these analyses were limited by the low incidence of treatment-emergent antibodies.

BAbs=binding antibodies; IFN=interferon; NAbs=neutralizing antibodies; PEG=polyethylene glycol; Q2W=every 2 weeks; Q4W=every 4 weeks.
* Antibodies formed after patients began treatment with peginterferon beta-1a

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