

Request for permission for oral testimony at Idaho  
Medicaid's P&T Committee meeting on 05-22-2014.

Submission # 1

As of April 29, 2015, a portion of this request has  
been approved for oral testimony.



Biogen Medical Information  
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April 24, 2015

Idaho Medicaid Pharmacy & Therapeutics Committee  
Attention: Tami Eide, Pharm.D.  
3232 Elder Street  
Boise, Idaho 83705

Dear Dr. Eide,

Thank you for your recent unsolicited request for medical information regarding PLEGRIDY® (peginterferon beta-1a) injection.

PLEGRIDY is an interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis.

*This information is provided as an educational resource for healthcare providers in response to an unsolicited request and should be considered current as of the date listed herein. It is not intended to be a substitute for consultation and review of reference materials and medical literature pertaining to individual clinical circumstances. Healthcare providers should make all treatment decisions based on the context of the situation and their clinical judgment.*

In response to your inquiry, the following information is being provided:

- PLEGRIDY® (peginterferon beta-1a) injection: Summary of Kieseier Mult Scler 2014

Additionally, in response to your inquiry, Biogen is providing you access to published articles and/or Biogen sponsored posters.

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**Federal Physician Payments Sunshine Act. For more information on the Sunshine Act, please visit <http://cms.gov> or e-mail [sunshine@biogen.com](mailto:sunshine@biogen.com) or call 1-866-392-4321.**

Please find your requested information included in the following manner:

- **Attached Articles as PDF Documents:**
  - Kieseier BC, Arnold DL, Balcer LJ, et al. Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE. *Mult Scler*. 2014 Nov 28.

**Summary of Prescribing Information: Multiple Sclerosis**

Please click here: <https://medinfo.biogen.com/medinfo/pdf/secure/pi/PLEGRIDY-pi.pdf> for the full prescribing information or see the appended full prescribing information

**Contact Information**

We hope you find this information helpful. If you have further questions, please contact Medical Information at 866-MED-INFO (866-633-4636), by email at [medinfo@biogen.com](mailto:medinfo@biogen.com), or visit our website at <https://medinfo.biogen.com>.

If this inquiry is related to a suspected adverse event in a specific patient receiving a Biogen product, please contact our Drug Safety and Risk Management department as soon as possible at 800-456-2255 to report relevant details about the event, if you have not done so already.

Sincerely,

Medical Information

Additional Enclosures Attached:

- PLEGRIDY Prescribing Information
- Medical Information Feedback Form

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PLEGRIDY™ safely and effectively. See full prescribing information for PLEGRIDY.

→ PLEGRIDY (peginterferon beta-1a) injection, for subcutaneous injection  
Initial U.S. Approval: 2014

### INDICATIONS AND USAGE

PLEGRIDY is an interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis (1)

### DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2.1)
- Recommended dose: 125 micrograms every 14 days (2.1)
- PLEGRIDY dose should be titrated, starting with 63 micrograms on day 1, 94 micrograms on day 15, and 125 micrograms (full dose) on day 29 (2.1)
- A healthcare professional should train patients in the proper technique for self-administering subcutaneous injections using the prefilled pen or syringe (2.2)
- Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms (2.3)

### DOSAGE FORMS AND STRENGTHS

- Injection: 125 micrograms per 0.5 mL solution in a single-dose prefilled pen (3)
- Injection Starter Pack: 63 micrograms per 0.5 mL solution in a single-dose prefilled pen and 94 micrograms per 0.5 mL solution in a single-dose prefilled pen (3)
- Injection: 125 micrograms per 0.5 mL solution in a single-dose prefilled syringe (3)
- Injection Starter Pack: 63 micrograms per 0.5 mL solution in a single-dose prefilled syringe and 94 micrograms per 0.5 mL solution in a single-dose prefilled syringe (3)

### CONTRAINDICATIONS

History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation (4)

### WARNINGS AND PRECAUTIONS

- Hepatic injury: monitor liver function tests; monitor patients for signs and symptoms of hepatic injury; consider discontinuation of PLEGRIDY if hepatic injury occurs (5.1)
- Depression and suicide: advise patients to report immediately any symptom of depression or suicidal ideation to their healthcare provider; consider discontinuation of PLEGRIDY if depression occurs (5.2)
- Seizure: Seizures are associated with the use of interferon beta. Exercise caution when administering PLEGRIDY to patients with a seizure disorder (5.3)
- Anaphylaxis and other allergic reactions: serious allergic reactions have been reported as a rare complication of treatment with interferon beta. Discontinue PLEGRIDY if a serious allergic reaction occurs (5.4)
- Injection site reactions: change injection site or consider discontinuation of PLEGRIDY if there is necrosis (5.5)
- Congestive heart failure: monitor patients with pre-existing significant cardiac disease for worsening of cardiac symptoms (5.6)
- Decreased peripheral blood counts: monitor complete blood counts (5.7)
- Autoimmune disorders: consider discontinuation of PLEGRIDY if a new autoimmune disorder occurs (5.8)

### ADVERSE REACTIONS

The most common adverse reactions (incidence  $\geq 10\%$  and at least 2% more frequent on PLEGRIDY than on placebo) were injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec at 1-800-456-2255 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Pregnancy: based on animal data, may cause fetal harm (8.1)
- Severe Renal Impairment: monitor for adverse reactions (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 08/2014

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

PLEGRIDY (peginterferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosing Information

PLEGRIDY is administered subcutaneously.

The recommended dosage of PLEGRIDY is 125 micrograms injected subcutaneously every 14 days.

##### Treatment initiation

Patients should start treatment with 63 micrograms on day 1. On day 15 (14 days later), the dose is increased to 94 micrograms, reaching the full dose of 125 micrograms on day 29 (after another 14 days). Patients continue with the full dose (125 micrograms) every 14 days thereafter (see Table 1). A PLEGRIDY Starter Pack is available containing two prefilled pens or syringes: 63 micrograms (dose 1) and 94 micrograms (dose 2).

**Table 1: Schedule for Dose Titration**

Dose	Time*	Amount (micrograms)	Color of Pen or Syringe Label
Dose 1	On day 1	63	Orange
Dose 2	On day 15	94	Blue
Dose 3	On day 29 and every 14 days thereafter	125 (full dose)	Grey

\*Dosed every 14 days

#### 2.2 Important Administration Instructions (All Dosage Forms)

Healthcare professionals should train patients in the proper technique for self-administering subcutaneous injections using the prefilled pen or syringe. Patients should be advised to rotate sites for subcutaneous injections. The usual sites for subcutaneous injections are abdomen, back of the upper arm, and thigh.

Each PLEGRIDY pen and syringe is provided with the needle pre-attached. Prefilled pens and syringes are for a single dose only and should be discarded after use.

### **2.3 Premedication for Flu-like Symptoms**

Prophylactic and concurrent use of analgesics and/or antipyretics may prevent or ameliorate flu-like symptoms sometimes experienced during treatment with PLEGRIDY.

## **3 DOSAGE FORMS AND STRENGTHS**

### *Pen*

- Injection: 125 micrograms of PLEGRIDY per 0.5 mL of solution in a single-dose prefilled pen
- Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled pen and 94 micrograms per 0.5 mL solution in a single-dose prefilled pen

### *Prefilled Syringe*

- Injection: 125 micrograms of PLEGRIDY per 0.5 mL of solution in a single-dose prefilled syringe
- Injection: Starter Pack containing 63 micrograms per 0.5 mL of solution in a single-dose prefilled syringe and 94 micrograms per 0.5 mL of solution in a single-dose prefilled syringe

## **4 CONTRAINDICATIONS**

PLEGRIDY is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation [*see Warnings and Precautions (5.4)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Hepatic Injury**

Severe hepatic injury, including hepatitis, autoimmune hepatitis, and rare cases of severe hepatic failure, have been reported with interferon beta. Asymptomatic elevation of hepatic transaminases has also been reported, and in some patients has recurred upon rechallenge with interferon beta.

Elevations in hepatic enzymes and hepatic injury have been observed with the use of PLEGRIDY in clinical studies. The incidence of increases in hepatic transaminases was greater in patients taking PLEGRIDY than in those taking placebo. The incidence of elevations of alanine aminotransferase above 5 times the upper limit of normal was 1% in placebo-treated patients and 2% in PLEGRIDY-treated patients. The incidence of elevations of aspartate aminotransferase above 5 times the upper limit of normal was less than 1% in placebo-treated patients and less than 1% in PLEGRIDY-treated patients. Elevations of serum hepatic

transaminases combined with elevated bilirubin occurred in 2 patients. Both cases resolved following discontinuation of PLEGRIDY.

Monitor patients for signs and symptoms of hepatic injury.

## **5.2 Depression and Suicide**

Depression, suicidal ideation, and suicide occur more frequently in patients receiving interferon beta than in patients receiving placebo.

In clinical studies, the overall incidence of adverse events related to depression and suicidal ideation in multiple sclerosis patients was 8% in both the PLEGRIDY and placebo groups. The incidence of serious events related to depression and suicidal ideation was similar and less than 1% in both groups.

Advise patients to report immediately any symptom of depression or suicidal ideation to their healthcare provider. If a patient develops depression or other severe psychiatric symptoms, consider stopping treatment with PLEGRIDY.

## **5.3 Seizures**

Seizures are associated with the use of interferon beta.

The incidence of seizures in multiple sclerosis clinical studies was less than 1% in patients receiving PLEGRIDY and placebo.

Exercise caution when administering PLEGRIDY to patients with a seizure disorder.

## **5.4 Anaphylaxis and Other Allergic Reactions**

Anaphylaxis and other serious allergic reactions are rare complications of treatment with interferon beta.

Less than 1% of PLEGRIDY-treated patients experienced a serious allergic reaction such as angioedema or urticaria. Those who did have serious allergic reactions recovered promptly after treatment with antihistamines or corticosteroids.

Discontinue PLEGRIDY if a serious allergic reaction occurs.

## **5.5 Injection Site Reactions**

Injection site reactions, including injection site necrosis, can occur with the use of subcutaneous interferon beta.

In clinical studies, the incidence of injection site reactions (e.g., injection site erythema, pain, pruritus, or edema) was 66% in the PLEGRIDY group and 11% in the placebo group; the incidence of severe injection site reactions was 3% in the PLEGRIDY group and 0% in the placebo group. One patient out of 1468 patients who received PLEGRIDY in clinical studies experienced injection site necrosis. The injury resolved with standard medical treatment.

Decisions to discontinue therapy following necrosis at a single injection site should be based on the extent of the necrosis. For patients who continue therapy with PLEGRIDY after injection

site necrosis has occurred, avoid administration of PLEGRIDY near the affected area until it is fully healed. If multiple lesions occur, discontinue PLEGRIDY until healing occurs.

## **5.6 Congestive Heart Failure**

Congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure occur in patients receiving interferon beta.

In clinical studies, the incidence of cardiovascular events was 7% in both PLEGRIDY and placebo treatment groups. No serious cardiovascular events were reported in the PLEGRIDY group.

Monitor patients with significant cardiac disease for worsening of their cardiac condition during initiation and continuation of treatment with PLEGRIDY.

## **5.7 Decreased Peripheral Blood Counts**

Interferon beta can cause decreased peripheral blood counts in all cell lines, including rare instances of pancytopenia and severe thrombocytopenia.

In clinical studies, decreases in white blood cell counts below  $3.0 \times 10^9/L$  occurred in 7% of patients receiving PLEGRIDY and in 1% receiving placebo. There is no apparent association between decreases in white blood cell counts and an increased risk of infections or serious infections. The incidence of clinically significant decreases in lymphocyte counts (below  $0.5 \times 10^9/L$ ), neutrophil counts (below  $1.0 \times 10^9/L$ ), and platelet counts (below  $100 \times 10^9/L$ ) were all less than 1% and similar in both placebo and PLEGRIDY groups. Two serious cases were reported in patients treated with PLEGRIDY: one patient (less than 1%) experienced severe thrombocytopenia (defined as a platelet count less than or equal to  $10 \times 10^9/L$ ), and another patient (less than 1%) experienced severe neutropenia (defined as a neutrophil count less than or equal to  $0.5 \times 10^9/L$ ). In both patients, cell counts recovered after discontinuation of PLEGRIDY. Compared to placebo, there were no significant differences in red blood cell counts in patients treated with PLEGRIDY.

Monitor patients for infections, bleeding, and symptoms of anemia. Monitor complete blood cell counts, differential white blood cell counts, and platelet counts during treatment with PLEGRIDY. Patients with myelosuppression may require more intensive monitoring of blood cell counts.

## **5.8 Autoimmune Disorders**

Autoimmune disorders of multiple target organs including idiopathic thrombocytopenia, hyper- and hypothyroidism, and autoimmune hepatitis have been reported with interferon beta.

In clinical studies, the incidence of autoimmune disorders was less than 1% in both PLEGRIDY and placebo treatment groups.

If patients develop a new autoimmune disorder, consider stopping PLEGRIDY.

## 6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of labeling:

- Hepatic Injury [*see Warnings and Precautions (5.1)*]
- Depression and Suicide [*see Warnings and Precautions (5.2)*]
- Seizures [*see Warnings and Precautions (5.3)*]
- Anaphylaxis and Other Allergic Reactions [*see Warnings and Precautions (5.4)*]
- Injection Site Reactions [*see Warnings and Precautions (5.5)*]
- Congestive Heart Failure [*see Warnings and Precautions (5.6)*]
- Decreased Peripheral Blood Counts [*see Warnings and Precautions (5.7)*]
- Autoimmune Disorders [*see Warnings and Precautions (5.8)*]

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of PLEGRIDY cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

In clinical studies (Study 1 and Study 2), a total of 1468 patients with relapsing multiple sclerosis received PLEGRIDY for up to 177 weeks (41 months), with an overall exposure equivalent to 1932 person-years. A total of 1093 patients received at least 1 year, and 415 patients at least 2 years of treatment with PLEGRIDY. A total of 512 and 500 patients, respectively, received PLEGRIDY 125 micrograms every 14 days or every 28 days during the placebo-controlled phase of Study 1 (year 1). The experience in year 2 of Study 1 and in the 2-year safety extension study (Study 2) was consistent with the experience in the 1-year placebo-controlled phase of Study 1.

In the placebo-controlled phase of Study 1, the most common adverse drug reactions for PLEGRIDY 125 micrograms subcutaneously every 14 days were injection site erythema, influenza-like illness, pyrexia, headache, myalgia, chills, injection site pain, asthenia, injection site pruritus, and arthralgia (all had incidence more than 10% and at least 2% more than placebo). The most commonly reported adverse event leading to discontinuation in patients treated with PLEGRIDY 125 micrograms subcutaneously every 14 days was influenza-like illness (in less than 1% of patients).

Table 2 summarizes adverse reactions reported over 48 weeks from patients treated in the placebo-controlled phase of Study 1 who received subcutaneous PLEGRIDY 125 micrograms (n=512), or placebo (n=500), every 14 days.

**Table 2: Adverse reactions in the 48-week placebo-controlled phase of Study 1 with an incidence 2% higher for PLEGRIDY than for placebo**

	<b>PLEGRIDY (N=512) %</b>	<b>Placebo (N=500) %</b>
<b>Nervous System Disorders</b>		
Headache	44	33
<b>Gastrointestinal Disorders</b>		
Nausea	9	6
Vomiting	5	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Myalgia	19	6
Arthralgia	11	7
<b>General Disorders and Administration Site Conditions</b>		
Injection site erythema	62	7
Influenza like illness	47	13
Pyrexia	45	15
Chills	17	5
Injection site pain	15	3
Asthenia	13	8
Injection site pruritus	13	1
Hyperthermia	4	1
Pain	5	3
Injection site edema	3	0
Injection site warmth	3	0
Injection site hematoma	3	1
Injection site rash	2	0
<b>Investigations</b>		
Body temperature increased	6	3
Alanine aminotransferase increased	6	3
Aspartate aminotransferase increased	4	2
Gamma-glutamyl-transferase increased	3	1
<b>Skin and Subcutaneous Tissue Disorder</b>		
Pruritus	4	1

### *Immunogenicity*

For therapeutic proteins, there is a potential for immunogenicity. In Study 1, fewer than 1% of patients treated with PLEGRIDY every 14 days for 1 year developed neutralizing antibodies. Approximately 7% of PLEGRIDY-treated patients developed antibodies to PEG.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PLEGRIDY with the incidence of antibodies to other products may be misleading.

### *Flu-Like Symptoms*

Influenza-like illness was experienced by 47% of patients receiving PLEGRIDY 125 micrograms every 14 days and 13% of patients receiving placebo. Fewer than 1% of PLEGRIDY-treated patients in Study 1 discontinued treatment due to flu-like symptoms.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### **Pregnancy Category C**

There are no adequate and well-controlled studies in pregnant women. PLEGRIDY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PLEGRIDY has not been tested for developmental toxicity in pregnant animals. In monkeys given interferon beta by subcutaneous injection every other day during early pregnancy, no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses.

### **8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PLEGRIDY is administered to a nursing woman.

### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

### **8.5 Geriatric Use**

Safety and effectiveness in geriatric patients have not been established.

### **8.6 Renal Impairment**

Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment [*see Clinical Pharmacology (12.3)*].

## 11 DESCRIPTION

PLEGRIDY (peginterferon beta-1a) is an interferon beta-1a to which a single, linear 20,000 dalton (Da) methoxy poly(ethyleneglycol)-O-2-methylpropionaldehyde molecule is covalently attached to the alpha amino group of the N-terminal amino acid residue.

The interferon beta-1a portion of PLEGRIDY is produced as a glycosylated protein using genetically-engineered Chinese hamster ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of the recombinant interferon beta-1a is identical to that of the human interferon beta counterpart. The molecular mass of PLEGRIDY is approximately 44,000 Da, consistent with the mass of the protein (approximately 20,000 Da), the carbohydrate moieties (approximately 2,500 Da), and the attached poly(ethylene glycol). However, because of the extended and flexible nature of the attached poly(ethylene glycol) chain, the apparent mass of PLEGRIDY in solution is greater than 300,000 Da. The more than 10-fold increase in apparent mass of PLEGRIDY compared to interferon beta-1a has been shown to contribute to the reduced clearance *in vivo*.

PLEGRIDY 125 micrograms contains 125 micrograms of interferon beta-1a plus 125 micrograms of poly(ethylene glycol). Using the World Health Organization International Standard for interferon beta, PLEGRIDY has a specific antiviral activity of approximately 100 million International Units (MIU) per mg of protein as determined using an *in vitro* cytopathic effect assay. PLEGRIDY 125 micrograms contains approximately 12 MIU of antiviral activity. PLEGRIDY contains no preservative.

### 11.1 PLEGRIDY PEN Single-Dose Prefilled Pen

PLEGRIDY PEN is composed of an autoinjector that surrounds a prefilled glass syringe containing 0.5 mL of a sterile solution in water for injection of 63, 94, or 125 micrograms of peginterferon beta-1a, 15.8 mg of L-arginine HCl, 0.79 mg of sodium acetate trihydrate, 0.25 mg of glacial acetic acid, and 0.025 mg of polysorbate 20. The pH is approximately 4.8.

### 11.2 PLEGRIDY Single-Dose Prefilled Syringe

A prefilled syringe of PLEGRIDY for subcutaneous injection contains 0.5 mL of a sterile solution in water for injection of 63, 94, or 125 micrograms of peginterferon beta-1a, 15.8 mg of L-arginine HCl, 0.79 mg of sodium acetate trihydrate, 0.25 mg of glacial acetic acid, and 0.025 mg of polysorbate 20. The pH is approximately 4.8.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism by which PLEGRIDY exerts its effects in patients with multiple sclerosis is unknown.

### 12.2 Pharmacodynamics

There is no biochemical or physiologic effect known to relate directly to the clinical effect of PLEGRIDY.

## 12.3 Pharmacokinetics

After single-dose or multiple-dose subcutaneous administration of PLEGRIDY to healthy subjects, serum PLEGRIDY peak concentration ( $C_{max}$ ) and total exposure over time (area under the curve, or AUC) increased in proportion to doses from 63 to 188 micrograms. PLEGRIDY did not accumulate in the serum after multiple doses of 125 micrograms every 14 days. Pharmacokinetic parameters for PLEGRIDY, including  $C_{max}$  and AUC, did not differ significantly between healthy volunteers and multiple sclerosis patients or between single-dose and multiple-dose administrations. However, the coefficient of variation between individual patients for AUC,  $C_{max}$ , and half-life was high (41% to 68%, 74% to 89%, and 45% to 93%, respectively).

### *Absorption*

After 125 microgram subcutaneous doses of PLEGRIDY in multiple sclerosis patients, the maximum concentration occurred between 1 and 1.5 days, the mean  $C_{max}$  was 280 pg/mL, and the AUC over the 14 day dosing interval was 34.8 ng.hr/mL.

### *Distribution*

In multiple sclerosis patients taking 125 microgram subcutaneous doses of PLEGRIDY every 14 days, the estimated volume of distribution was 481 liters.

### *Metabolism and Elimination*

Clearance mechanisms for PLEGRIDY include catabolism and excretion. The major pathway of elimination is renal. The half-life is approximately 78 hours in multiple sclerosis patients. The mean steady state clearance of PLEGRIDY is approximately 4.1 L/hr. PLEGRIDY is not extensively metabolized in the liver.

### *Specific Populations*

Body weight, gender, and age do not require dosage adjustment.

Renal impairment can increase the  $C_{max}$  and AUC for PLEGRIDY. Results of a pharmacokinetic study in patients with mild, moderate, and severe renal impairment (creatinine clearance 50 to 80, 30 to 50, and less than 30 mL/minute, respectively) showed increases above normal for  $C_{max}$  of 27%, 26%, and 42%, and for AUC, increases of 30%, 40%, and 53%. The half-life was 53, 49, and 82 hours in patients with mild, moderate, and severe renal impairment, respectively, compared to 54 hours in normal subjects.

In the same study, subjects with end stage renal disease requiring hemodialysis two or three times weekly had AUC and  $C_{max}$  of PLEGRIDY values that were similar to those of normal controls. Each hemodialysis session removed approximately 24% of circulating PLEGRIDY from the systemic circulation [see *Use in Specific Populations (8.6)*].

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenesis*

The carcinogenic potential of PLEGRIDY has not been tested in animals.

#### *Mutagenesis*

PLEGRIDY was not mutagenic when tested in an *in vitro* bacterial reverse mutation (Ames) test and was not clastogenic in an *in vitro* assay in human lymphocytes.

#### *Impairment of Fertility*

In monkeys administered interferon beta by subcutaneous injection over the course of one menstrual cycle, menstrual irregularities, anovulation, and decreased serum progesterone levels were observed. These effects were reversible after discontinuation of drug.

## **14 CLINICAL STUDIES**

The efficacy of PLEGRIDY was demonstrated in the randomized, double-blind, and placebo-controlled phase (year 1) of Study 1. The trial compared clinical and MRI outcomes at 48 weeks in patients who received PLEGRIDY 125 micrograms (n=512) or placebo (n=500) by the subcutaneous route, once every 14 days.

Study 1 enrolled patients who had a baseline Expanded Disability Status Scale (EDSS) score from 0 to 5, who had experienced at least 2 relapses within the previous three years, and had experienced at least 1 relapse in the previous year. The trial excluded patients with progressive forms of multiple sclerosis. The mean age of the study population was 37 years, the mean disease duration was 3.6 years, and the mean EDSS score at baseline was 2.46. The majority of the patients were women (71%).

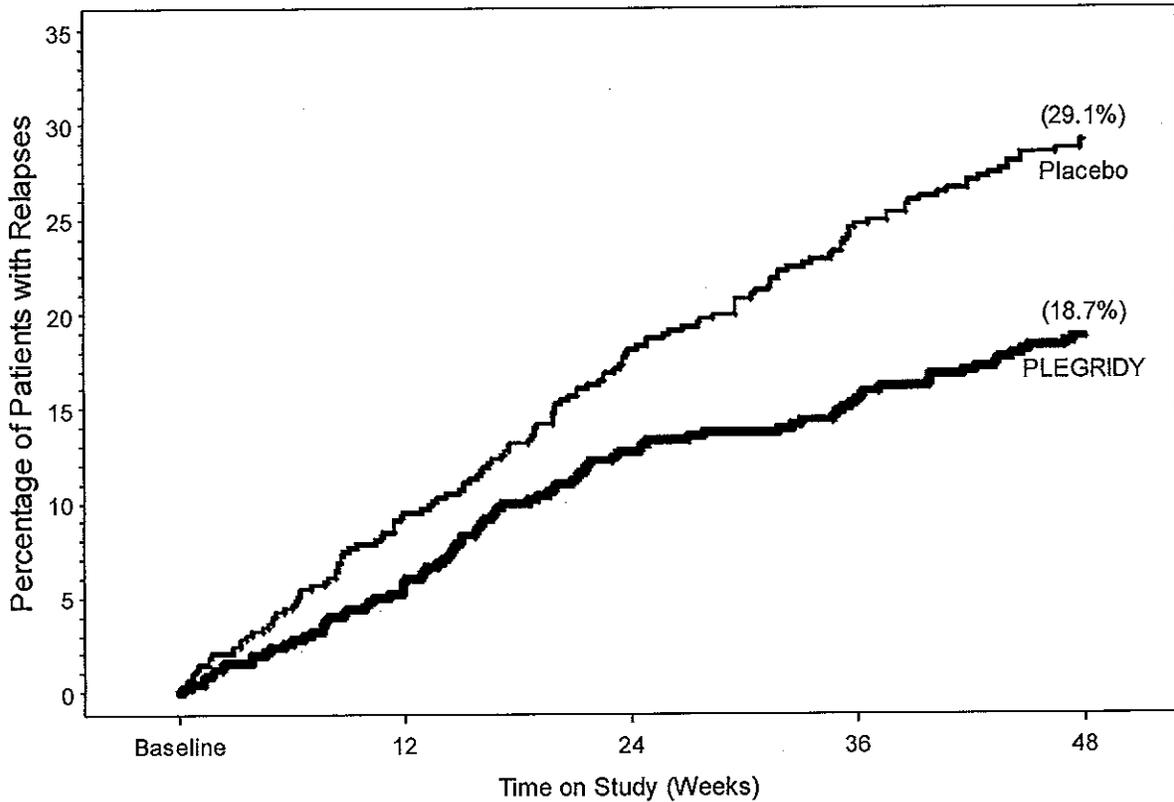
The trial scheduled neurological evaluations at baseline, every 12 weeks, and at the time of a suspected relapse. Brain MRI evaluations were scheduled at baseline, week 24, and week 48.

The primary outcome was the annualized relapse rate over 1 year. Secondary outcomes included the proportion of patients relapsing, number of new or newly enlarging T2 hyperintense lesions, and time to confirmed disability progression. Confirmed disability progression was defined as follows: if the baseline EDSS score was 0, a sustained 12-week increase in EDSS score of 1.5 points was required; if the baseline EDSS score was greater than 0, a sustained 12-week increase in EDSS score of 1 point was required. Table 3 and Figure 1 show the results of Study 1.

**Table 3: Clinical and MRI Results of Study 1**

<b>Endpoint</b>	<b>PLEGRIDY 125 micrograms every 14 days</b>	<b>Placebo</b>	<b>p-value</b>
<b>Clinical outcomes at 48 weeks</b>	<b>N=512</b>	<b>N=500</b>	
Annualized relapse rate	0.26	0.40	0.0007
Relative reduction	36%		
Proportion of patients with relapses	0.19	0.29	0.0003
Relative risk reduction	39%		
Proportion of patients with disability progression	0.07	0.11	0.0383
Relative risk reduction	38%		
<b>MRI outcomes at 48 weeks</b>	<b>N=457</b>	<b>N=476</b>	
Mean number of new or newly enlarging T2 hyperintense lesions	3.6	10.9	<0.0001
Relative reduction	67%		
Mean number of Gd enhancing lesions	0.2	1.4	<0.0001
Relative reduction	86%		

**Figure 1: Time to first relapse**



Number of Subjects at Risk

Placebo	500	448	398	363	280
PLEGRIDY	512	458	414	389	318

PLEGRIDY 125 mcg every 14 days (n=512) versus placebo (n=500) Hazard Ratio (95% CI)=0.61(0.47, 0.80), p=0.0003

## 16 HOW SUPPLIED/STORAGE AND HANDLING

PLEGRIDY is supplied as a sterile, clear liquid for subcutaneous injection in two presentations, a prefilled pen and a prefilled syringe.

### 16.1 PLEGRIDY PEN Single-Dose Prefilled Pen

Each dose of PLEGRIDY is stored in a 1 mL capacity glass syringe with a rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single prefilled syringe contains 0.5 mL of solution of PLEGRIDY containing 63 micrograms, 94 micrograms, or 125 micrograms of peginterferon beta-1a. The glass syringe is contained within

a single-dose, disposable, injection device (prefilled pen). The following packaging configurations are available:

- A carton containing two single-dose prefilled pens, each providing 125 micrograms of PLEGRIDY. The NDC is 64406-011-01.
- A Starter Pack carton containing two single-dose prefilled pens; dose 1 provides 63 micrograms of PLEGRIDY, and dose 2 provides 94 micrograms of PLEGRIDY. The NDC is 64406-012-01.

## **16.2 PLEGRIDY Single-Dose Prefilled Syringe**

Each dose of PLEGRIDY is stored in a 1 mL capacity glass syringe with a rubber stopper and rigid needle shield. A 29 gauge, 0.5 inch staked needle is pre-affixed to the syringe. A single prefilled syringe contains 0.5 mL of solution of PLEGRIDY containing 63 micrograms, 94 micrograms, or 125 micrograms of peginterferon beta-1a. The following packaging configurations are available:

- A carton containing two single-dose prefilled syringes, each providing 125 micrograms of PLEGRIDY. The NDC is 64406-015-01.
- A Starter Pack carton containing two single-dose prefilled syringes; dose 1 provides 63 micrograms of PLEGRIDY, and dose 2 provides 94 micrograms of PLEGRIDY. The NDC is 64406-016-01.

## **16.3 Storage and Handling**

Store in the closed original carton to protect from light until ready for injection.

Store in a refrigerator between 2°C to 8°C (36°F to 46°F). Do not freeze. Discard if frozen. Once removed from the refrigerator, PLEGRIDY should be allowed to warm to room temperature (about 30 minutes) prior to injection. Do not use external heat sources such as hot water to warm PLEGRIDY.

If refrigeration is unavailable, PLEGRIDY may be stored between 2°C to 25°C (36°F to 77°F) for a period up to 30 days, protected from light. PLEGRIDY can be removed from, and returned to, a refrigerator if necessary. The total combined time out of refrigeration, within a temperature range of 2°C to 25°C (36°F to 77°F), should not exceed 30 days.

## **16.4 Instructions for Disposal**

Dispose in a sharps-bin container or other hard plastic or metal sealable container. Always follow local regulations for disposal.

## **17 PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

Instruct patients to carefully read the supplied PLEGRIDY Medication Guide and Instructions for Use, and caution patients not to change the PLEGRIDY dose or schedule of administration without medical consultation.

### **Instructions for Self-Injection Technique and Procedures**

Provide appropriate instruction for methods of self-injection, including careful review of the PLEGRIDY Medication Guide and Instructions for Use. Instruct patients in the use of aseptic technique when administering PLEGRIDY.

Inform patients that a healthcare provider should show them or their caregiver how to prepare to inject PLEGRIDY before administering the first dose. Tell patients not to re-use needles or syringes, and instruct patients on safe disposal procedures. Inform patients to dispose of used needles and syringes in a puncture-resistant container, and instruct patients regarding safe disposal of full containers.

#### **Advise patients:**

- to rotate areas of injection with each dose to minimize the likelihood of injection site reactions
- NOT to inject into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred in any way
- to check the injection site after 2 hours for redness, swelling, and tenderness
- to contact their healthcare professional if they have a skin reaction and it does not clear up in a few days

### **Pregnancy**

Advise patients that PLEGRIDY should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

### **Liver Disease**

Advise patients that severe hepatic injury, including rare cases of hepatic failure, has been reported during the use of interferon beta. Advise patients of symptoms of hepatic dysfunction, and instruct patients to report them immediately to their physician.

### **Depression and Suicide**

Advise patients that depression, suicidal ideation, and suicide have been reported with the use of interferon beta. Instruct patients to report symptoms of depression or thoughts of suicide to their physician immediately.

**Seizure**

Advise patients that seizures have been reported in patients using PLEGRIDY. Instruct patients to report seizures immediately to their physician.

**Anaphylaxis and Other Allergic Reactions**

Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur.

**Injection Site Reactions**

Advise patients that injection site reactions can occur and that the reactions can include injection site necrosis. Instruct patients to report promptly any break in the skin that is associated with blue-black discoloration, swelling, or drainage of fluid from the injection site.

**Cardiac Disease**

Advise patients that worsening of significant cardiac disease has been reported in patients using interferon beta. Advise patients of symptoms of worsening cardiac condition, and instruct patients to report them immediately to their physician.

**Flu-like Symptoms**

Inform patients that flu-like symptoms are common following initiation of therapy with PLEGRIDY. Prophylactic and concurrent use of analgesics and/or antipyretics may prevent or ameliorate flu-like symptoms sometimes experienced during interferon treatment.

43643-01

Manufactured by:

Biogen Idec Inc.

Cambridge, MA 02142

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# Multiple Sclerosis Journal

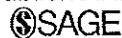
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European Committee for Treatment and Research in Multiple Sclerosis

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What is This?

## → Peginterferon beta-1a in multiple sclerosis: 2-year results from ADVANCE

Bernd C Kieseier, Douglas L Arnold, Laura J Balcer, Alexey A Boyko, Jean Pelletier, Shifang Liu, Ying Zhu, Ali Seddighzadeh, Serena Hung, Aaron Deykin, Sarah I Sheikh and Peter A Calabresi

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### Abstract

**Objective:** To evaluate the efficacy and safety of subcutaneous peginterferon beta-1a over 2 years in patients with relapsing–remitting multiple sclerosis in the ADVANCE study.

**Methods:** Patients were randomized to placebo or 125 µg peginterferon beta-1a every 2 or 4 weeks. For Year 2 (Y2), patients originally randomized to placebo were re-randomized to peginterferon beta-1a every 2 weeks or every 4 weeks. Patients randomized to peginterferon beta-1a in Year 1 (Y1) remained on the same dosing regimen in Y2.

**Results:** Compared with Y1, annualized relapse rate (ARR) was further reduced in Y2 with every 2 week dosing (Y1: 0.230 [95% CI 0.183–0.291], Y2: 0.178 [0.136–0.233]) and maintained with every 4 week dosing (Y1: 0.286 [0.231–0.355], Y2: 0.291 [0.231–0.368]). Patients starting peginterferon beta-1a from Y1 displayed improved efficacy versus patients initially assigned placebo, with reductions in ARR (every 2 weeks: 37%,  $p < 0.0001$ ; every 4 weeks: 17%,  $p = 0.0906$ ), risk of relapse (every 2 weeks: 39%,  $p < 0.0001$ ; every 4 weeks: 19%,  $p = 0.0465$ ), 12-week disability progression (every 2 weeks: 33%,  $p = 0.0257$ ; every 4 weeks: 25%,  $p = 0.0960$ ), and 24-week disability progression (every 2 weeks: 41%,  $p = 0.0137$ ; every 4 weeks: 9%,  $p = 0.6243$ ). Over 2 years, greater reductions were observed with every 2 week versus every 4 week dosing for all endpoints and peginterferon beta-1a was well tolerated.

**Conclusions:** Peginterferon beta-1a efficacy is maintained beyond 1 year, with greater effects observed with every 2 week versus every 4 week dosing, and a similar safety profile to Y1.

**Clinicaltrials.gov Registration Number:** NCT00906399.

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**Keywords:** Interferon, pegylated, peginterferon beta-1a, relapse, multiple sclerosis, relapse-remitting multiple sclerosis, MRI, phase 3

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### Introduction

Interferon (IFN) beta has been an effective treatment for relapsing–remitting multiple sclerosis (RRMS) for many years. However, some currently available IFN beta therapies require injection several times a week because they are rapidly degraded or cleared by the kidney.<sup>1</sup> Frequent injections may have an impact on treatment initiation or adherence among patients with RRMS. Peginterferon beta-1a was developed by attaching a poly(ethylene glycol) chain to the parent IFN beta-1a molecule,<sup>2</sup> an established process known as pegylation, and is in development for the treatment of RRMS. Pegylation of IFN beta-1a has been shown to improve pharmacokinetic (PK) and pharmacodynamic (PD) properties in

humans compared with non-pegylated IFN beta-1a,<sup>3</sup> resulting in prolonged exposure, increased biologic activity, and a longer half-life.<sup>4,5</sup>

ADVANCE is a 2-year Phase 3, multicenter, randomized, double-blind study with a 1-year placebo-controlled period evaluating the efficacy and safety of subcutaneous (SC) peginterferon beta-1a administered every 2 or 4 weeks in patients with RRMS.

Year 1 results have been previously reported.<sup>6</sup> Briefly, peginterferon beta-1a every 2 weeks and every 4 weeks significantly improved clinical and magnetic resonance imaging (MRI) endpoints versus placebo

(with reductions in annualized relapse rate [ARR; primary endpoint], risk of relapse and disability progression, and the number of new or newly enlarging T2 lesions [secondary endpoints]), with a safety profile consistent with that of established IFN beta-1a therapies. During Year 1, every 2 week dosing provided numerically greater reductions relative to every 4 week dosing across relapse and MRI endpoints.

After Year 1, patients randomized to placebo were re-randomized to peginterferon beta-1a (every 2 or 4 weeks) for Year 2 and patients randomized to active treatment in Year 1 remained on the same dosing regimen in Year 2. Here we report the 2-year efficacy and safety results from ADVANCE.

## Methods

### *Study design and participants*

Patients were recruited between June 2009 and November 2011 for ADVANCE, a randomized, multicenter, double-blind, Phase 3 study to investigate peginterferon beta-1a in patients with RRMS. Full details of the study design and eligibility criteria have been previously reported.<sup>6</sup> Briefly, eligible patients had a diagnosis of RRMS as defined by the McDonald criteria,<sup>7</sup> were aged 18–65 years, had a score of 0–5 on the Expanded Disability Status Scale (EDSS)<sup>8</sup> and  $\geq 2$  clinically documented relapses in the previous 3 years, with  $\geq 1$  of these relapses having occurred within the 12 months prior to randomization. Key exclusion criteria were progressive forms of multiple sclerosis (MS), pre-specified laboratory abnormalities, and prior IFN treatment for MS exceeding 4 weeks or discontinuation  $< 6$  months prior to baseline.

During Year 1 of ADVANCE, patients were randomly assigned 1:1:1 to SC injections of placebo, peginterferon beta-1a 125  $\mu\text{g}$  every 2 weeks, or peginterferon beta-1a 125  $\mu\text{g}$  every 4 weeks (starting dose 63  $\mu\text{g}$ , 94  $\mu\text{g}$  at Week 2, target dose 125  $\mu\text{g}$  at Week 4 and thereafter). At the end of Year 1 (Week 48), patients randomized to placebo were re-randomized to peginterferon beta-1a 125  $\mu\text{g}$  every 2 weeks or every 4 weeks (1:1) with the same dose titration as described above (i.e. during Year 2 all patients received dose-blinded peginterferon beta-1a).

The protocol was approved by each site's institutional review board and was conducted according to the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. Every patient provided written informed consent prior to study entry.

### *Study procedures and endpoints*

Methods for ADVANCE have been previously published.<sup>6</sup> Briefly, standardized neurologic assessments, including determination of EDSS score by a blinded, EDSS-certified non-treating physician, were carried out every 12 weeks and at the time of suspected relapse (evaluated during unscheduled visits). MRI scans were obtained at Weeks 24, 48, and 96, and were evaluated in a blinded manner at a central MRI reading center.

Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting for  $\geq 24$  hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days, which were confirmed by the independent neurologic evaluation committee (INEC). Disability progression was defined as an increase in the EDSS score of  $\geq 1.0$  point in patients with a baseline score of  $\geq 1.0$ , or an increase of  $\geq 1.5$  points in patients with a baseline score of 0, confirmed after 12 and 24 weeks.

Assessments of the following key clinical and MRI measures in patients with available 2-year data were tertiary endpoints of ADVANCE: ARR, proportion of patients relapsed, disability progression (12-week and 24-week), mean number of new or newly enlarging T2 hyperintense lesions, and gadolinium enhancing (Gd+) lesions.

Safety assessments included monitoring and recording of adverse events (AEs), physical examination, vital signs, and clinician assessment of injection sites, and subject assessment of injection pain. Laboratory assessments included electrocardiography, hematology, blood chemistry, and urinalysis. To assess immunogenicity, patient serum samples were collected pre-dose on Day 1 and Weeks 8, 20, 36, 48, 60, 72, and 96.

### *Statistical analysis*

All efficacy analyses were performed on data from the intent-to-treat (ITT) population (all randomized patients who received at least one dose of active study treatment over 2 years). Statistical tests were two-sided, and  $p < 0.05$  was considered significant.

To assess efficacy over 2 years in patients who received peginterferon beta-1a starting from Year 1 versus those who received placebo in Year 1, patients who switched from placebo to peginterferon beta-1a in Year 2 were combined as one group (the "delayed treatment" group) and statistical comparisons versus those receiving continuous peginterferon beta-1a were made: ARR (post-hoc), proportion of patients

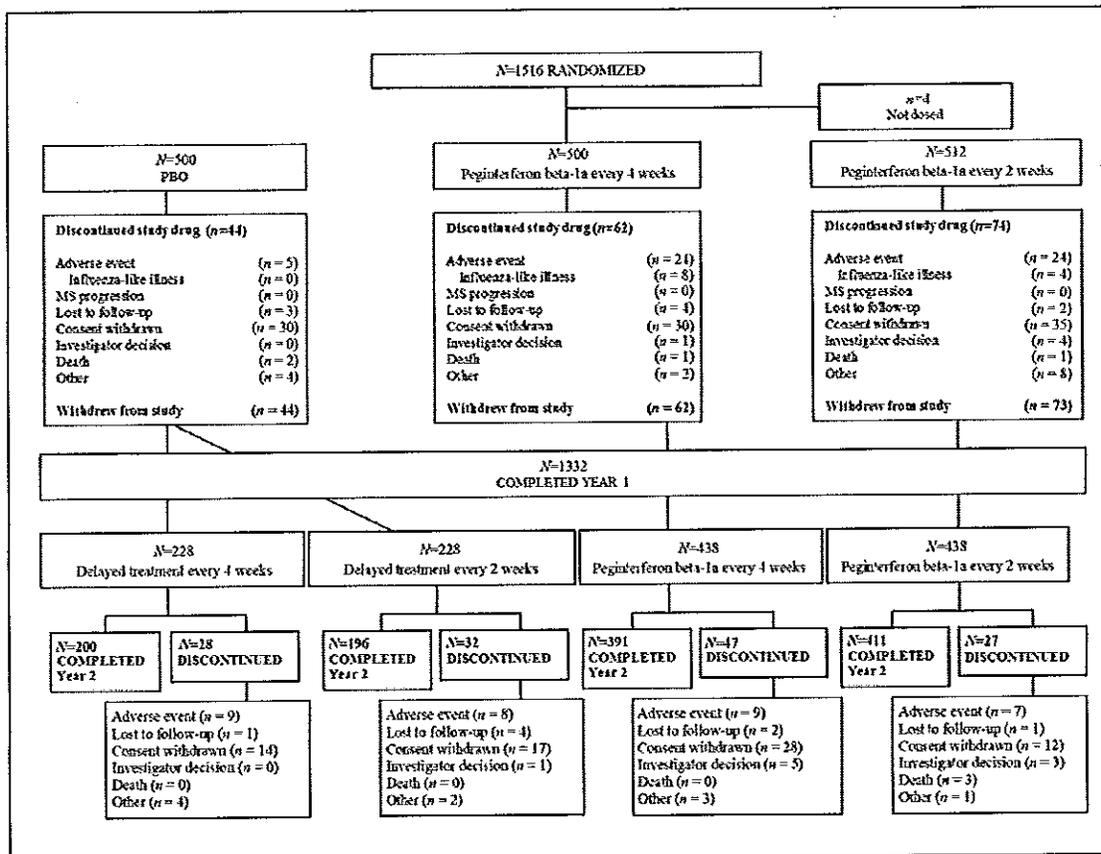


Figure 1. Patient disposition – over 2 years.  
N, n = number of subjects.

relapsed (post-hoc), and proportion of patients with disability progression (pre-specified) over 2 years.

ARR, defined as total number of relapses divided by patient-years in the study, excluding data obtained after patients switched to alternative MS medications, was analyzed with the use of a negative binomial regression model adjusted for baseline EDSS score (<4 versus  $\geq 4$ ), baseline relapse rate (number of relapses in 3 years prior to study entry divided by three), and age (<40 versus  $\geq 40$  years); adjusted ARRs were presented for each group. MRI results are based on all patients with available MRI data. Negative binomial regression was used for analysis of new or newly enlarging hyperintense lesions on T2-weighted images (adjusted for baseline number of T2 lesions) and multiple logit regression was used for the analysis of Gd<sup>+</sup> lesions (adjusted for baseline number of Gd<sup>+</sup> lesions). Time to first clinical relapse (adjusted for baseline EDSS, age, baseline relapse rate, and baseline presence/absence of Gd<sup>+</sup> lesions) and time to first disability progression (adjusted for baseline EDSS and age) were analyzed

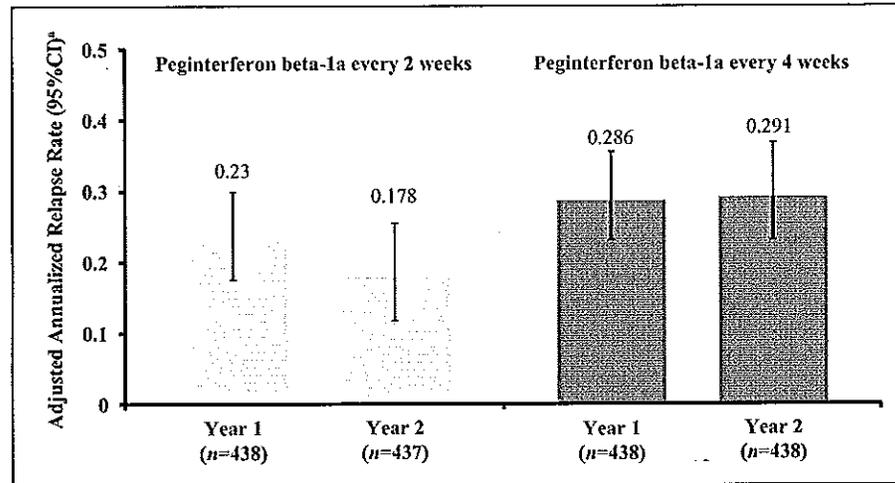
using a Cox proportional hazards model. Post-hoc analyses compared the efficacy of every 2 week versus every 4 week regimens over 2 years.

AEs were summarized with the use of descriptive statistics for all patients who received at least one dose of active study treatment, excluding data obtained after patients switched to alternative MS medications. Immunogenicity was measured by an analytically validated cell-based assay to characterize neutralizing antibodies (NAbs) to IFN beta-1a.

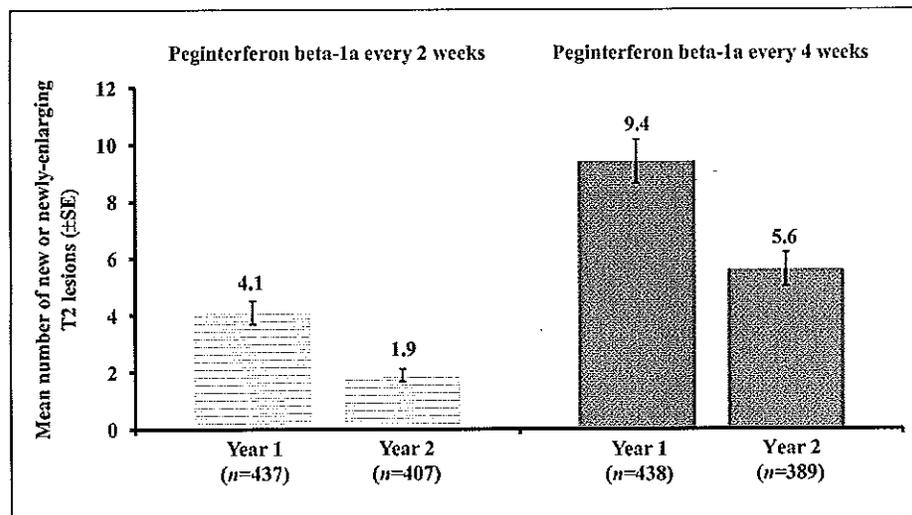
## Results

### Patients

In the overall study population, patient demographics and baseline disease characteristics were generally well balanced across treatment groups.<sup>6</sup> Baseline characteristics were similar among the original treatment groups at randomization (Table S1, supplementary materials). Of the 1332 patients completing Year 1, the percentage who completed Year 2 was similar



**Figure 2.** Annualized relapse rate by study year.  
 \*Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. ≥4), baseline relapse rate and age (<40 vs. ≥40).  
 CI: confidence interval.



**Figure 3.** New or newly enlarging T2 lesions by study year.  
 Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are imputed based on previous visit data assuming the constant rate of lesion development or group mean at same visit.  
 SE: standard error.

across the continuous peginterferon beta-1a treatment groups and across the placebo-to-active treatment groups (Figure 1). Over 2 years, the rate of discontinuation due to AEs was similar between dosing regimens (6% for each peginterferon beta-1a group).

*Efficacy*

*Maintenance of efficacy.* Maintenance of efficacy over 2 years was evaluated by comparing ARR and

the number of new or newly enlarging T2 lesions from Year 1 (Baseline to Week 48) and Year 2 (Week 48 to Week 96) for patients receiving peginterferon beta-1a both years. ARR was further reduced with peginterferon beta-1a every 2 weeks or maintained with peginterferon beta-1a every 4 weeks in Year 2 relative to Year 1; for the peginterferon beta-1a every 2 weeks group, ARR was 0.230 (95% CI 0.183–0.291) in Year 1 and 0.178 (0.136–0.233) in Year 2 (Figure 2). In the peginterferon beta-1a every 4 weeks group, the ARR was 0.286 (95% CI 0.231–0.355) in Year 1

and 0.291 (0.231–0.368) in Year 2 (Figure 2). The mean number of new or newly enlarging T2 lesions was numerically lower in Year 2 (1.9 every 2 weeks; 5.6 every 4 weeks) versus Year 1 for both dosing regimens (4.1 every 2 weeks; 9.4 every 4 weeks) (Figure 3).

*Efficacy in patients who received peginterferon beta-1a for 2 years versus those who switched from placebo in Year 1 to peginterferon beta-1a in Year 2.* Analysis of clinical endpoints among patients on continuous peginterferon beta-1a and patients originally assigned to placebo showed that peginterferon beta-1a had numerically greater effects. The ARR (95% CI) was 0.351 (0.295–0.418) for the delayed treatment group, 0.221 (0.183–0.267) for the peginterferon beta-1a every 2 weeks group and 0.291 (0.244–0.348) for the peginterferon beta-1a every 4 weeks group (Table 1). A post-hoc analysis of continuous peginterferon beta-1a versus the delayed treatment group showed a reduction of 37% ( $p < 0.0001$ ) and 17% ( $p = 0.0906$ ) with peginterferon beta-1a every 2 weeks and every 4 weeks, respectively. The estimated proportion of patients who relapsed over 2 years was 0.402 for the delayed treatment group, 0.265 for the peginterferon beta-1a every 2 weeks group, and 0.344 for the peginterferon beta-1a every 4 weeks group, representing reductions versus the delayed treatment group of 39% ( $p < 0.0001$ ) and 19% ( $p = 0.0465$ ), respectively (Table 1; Figure 4). The estimated proportion of patients with 12-week confirmed disability progression was 0.162 for the delayed treatment group, 0.112 for the peginterferon beta-1a every 2 weeks group, and 0.123 for the peginterferon beta-1a every 4 weeks group, representing reductions versus the delayed treatment group of 33% ( $p = 0.0257$ ) and 25% ( $p = 0.0960$ ), respectively (Table 1; Figure 5). The estimated proportion of patients with 24-week confirmed disability progression was 0.119 for the delayed treatment group, 0.077 for the peginterferon beta-1a every 2 weeks group, and 0.113 for the peginterferon beta-1a every 4 weeks group, corresponding to a 41% ( $p = 0.0137$ ) and 9% ( $p = 0.6243$ ) reduction versus the delayed treatment group, respectively (Table 1; Figure 6). Patients treated with continuous peginterferon beta-1a every 2 weeks and peginterferon beta-1a every 4 weeks had fewer newly enlarging T2 lesions over 2 years than patients in the delayed treatment group, by 67% ( $p < 0.0001$ ) and 16% ( $p = 0.0973$ ), respectively. Statistically significant reductions in the number of Gd+ lesions were also observed in the every 2 weeks group versus the delayed treatment group ( $p = 0.0002$ ) (Table 1).

*Peginterferon beta-1a every 2 weeks versus every 4 weeks.* Post-hoc analyses of the efficacy of peginterferon beta-1a every 2 weeks versus every 4 weeks were conducted for clinical and MRI endpoints over 2 years (Table 1). Over 2 years, peginterferon beta-1a every 2 weeks produced favorable outcomes compared with peginterferon beta-1a every 4 weeks. The ARR was 0.221 and 0.29 in the every 2 week and every 4 week groups respectively, representing a 24% ([95% CI (4.1–40)];  $p = 0.0209$ ) reduction versus the every 4 week group (Table 1). Relative to peginterferon beta-1a every 4 weeks, the risk of relapse was reduced by 24% ([4–40],  $p = 0.0212$ ). Hazard ratios (Table 1) indicated that peginterferon beta-1a every 2 weeks reduced the risk of 12-week confirmed disability progression by 11% ([95% CI (31–39)];  $p = 0.5665$ ) and the risk of 24-week disability progression by 36% ([95% CI (1–58)];  $p = 0.0459$ ) relative to every 4 week dosing.

Patients treated with peginterferon beta-1a every 2 weeks had 60% ( $p < 0.0001$ ) fewer new or newly enlarging hyperintense T2 lesions over 2 years than patients in the every 4 weeks group (Table 1). Relative to the peginterferon beta-1a every 4 weeks group, the number of Gd+ lesions over 2 years was reduced by 71% ( $p < 0.0001$ ) in the peginterferon beta-1a every 2 weeks group.

#### *Safety*

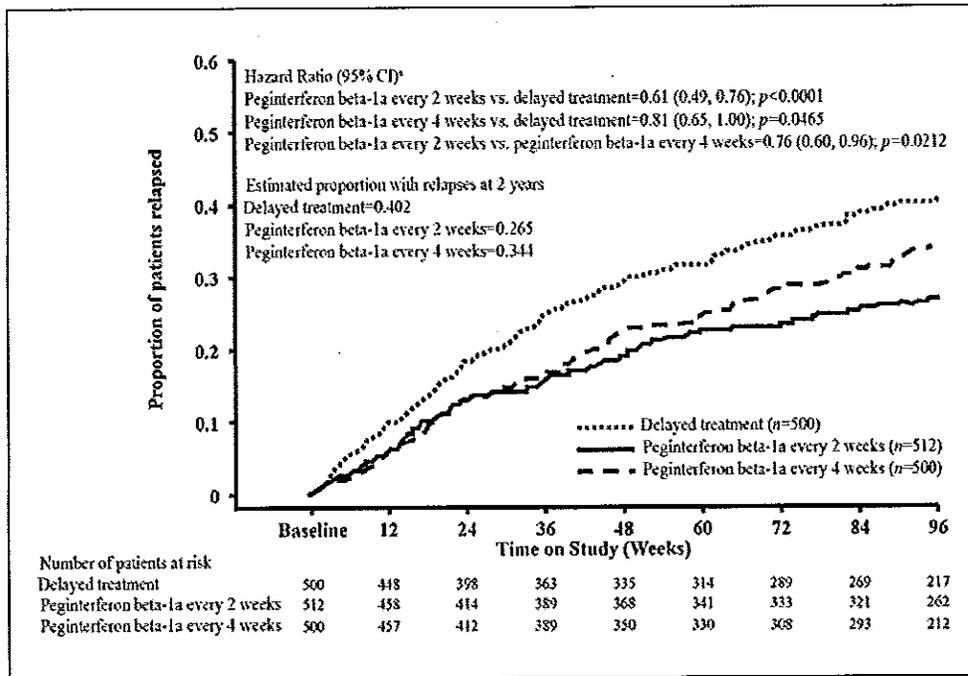
Over 2 years, in patients who received at least one dose of peginterferon beta-1a, the incidence of AEs was similar between treatment groups (94% for each peginterferon beta-1a group) (Table 2). The most commonly reported AEs over 2 years were injection site erythema, influenza-like illness, pyrexia, and headache (Table 2). The majority of AEs were mild or moderate in severity; incidence of severe AEs was similar between peginterferon beta-1a dosing groups (21% for every 2 weeks and 20% for every 4 weeks). The incidence of AEs, most common AEs, and severity of AEs in Year 2 were similar to Year 1 (Table S2, supplementary materials).<sup>6</sup> The incidence of AEs considered related to treatment by the Investigator in peginterferon beta-1a groups was 90% in the every 2 weeks group and 88% in the every 4 weeks group. The incidence of discontinuation of study treatment due to AEs was 6% in each peginterferon beta-1a group. The incidence of serious AEs was higher in the peginterferon beta-1a every 4 weeks group (22%) than the every 2 weeks group (16%), with MS relapse the most frequently reported event (Table 2).

Nine deaths were reported over the 2-year study. Deaths occurring in patients receiving at least one

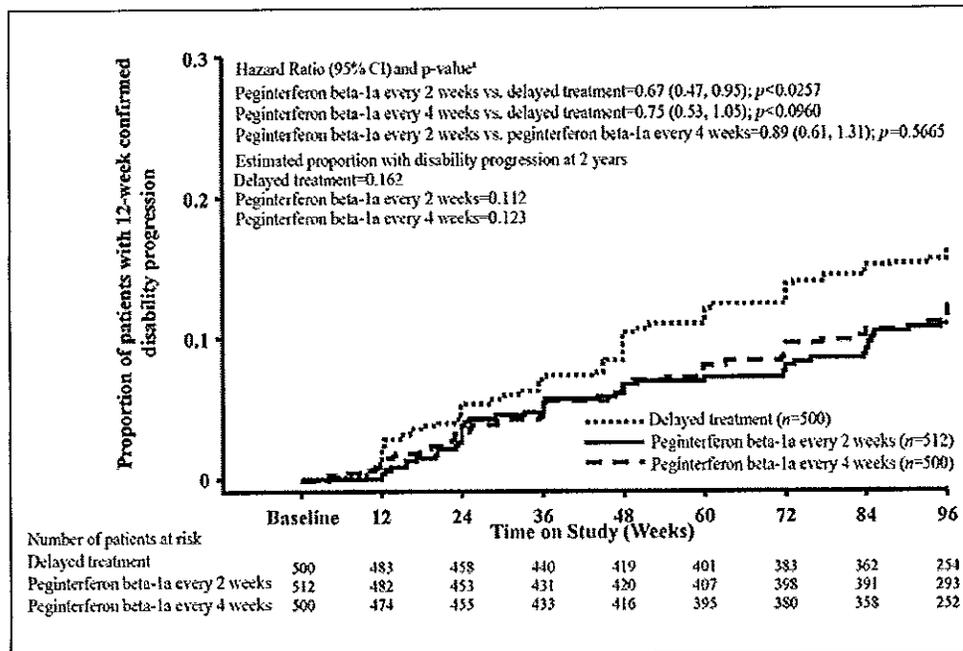
Table 1. Summary of clinical and MRI endpoints over 2 years by original randomization group.

Endpoint	Delayed treatment <sup>h</sup> (n=500)	Peginterferon beta-1a every 2 weeks (n=512)	Peginterferon beta-1a every 4 weeks (n=500)
<b>Annualized relapse rate at 2 years</b>			
Annualized relapse rate (95% CI) <sup>a</sup>	0.351 (0.295, 0.418)	0.221 (0.183, 0.267)	0.291 (0.244, 0.348)
Rate ratio vs. delayed treatment (95% CI) <sup>a</sup>		0.629 (0.500, 0.790)	0.829 (0.666, 1.030)
p-value vs. delayed treatment <sup>a</sup>		<0.0001	0.0906
Rate ratio every 2 weeks vs. every 4 weeks (95% CI) <sup>a</sup>		0.759 (0.600, 0.959)	
p-value (every 2 weeks vs. every 4 weeks) <sup>a</sup>		0.0209	
<b>Estimated proportion of patients with a relapse at 2 years</b>			
Number of patients relapsed	192	124	158
Proportion relapsed <sup>b</sup>	0.402	0.265	0.344
Hazard ratio vs. delayed treatment <sup>c</sup>		0.61 (0.49, 0.76)	0.81 (0.65, 1.00)
p-value vs. delayed treatment <sup>c</sup>		<0.0001	0.0465
Hazard ratio every 2 weeks vs. every 4 weeks (95% CI) <sup>c</sup>		0.76 (0.60, 0.96)	
p-value (every 2 weeks vs. every 4 weeks) <sup>c</sup>		0.0212	
<b>Disability progression at 2 years (12-week confirmed)</b>			
Number of patients with disability progression	75	51	56
Estimated proportion with disability progression <sup>d</sup>	0.162	0.112	0.123
Hazard ratio vs. delayed treatment (95% CI) <sup>e</sup>		0.67 (0.47, 0.95)	0.75 (0.53, 1.05)
p-value vs. delayed treatment <sup>e</sup>		0.0257	0.0960
Hazard ratio every 2 weeks vs. every 4 weeks (95% CI) <sup>e</sup>		0.89 (0.61, 1.31)	
p-value (every 2 weeks vs. every 4 weeks) <sup>e</sup>		0.5665	
<b>Disability progression at 2 years (24-week confirmed)</b>			
Number of patients with disability progression	57	34	52
Estimated proportion with disability progression <sup>d</sup>	0.119	0.077	0.113
Hazard ratio vs. delayed treatment (95% CI) <sup>e</sup>		0.59 (0.38, 0.90)	0.91 (0.63, 1.33)
p-value vs. delayed treatment <sup>e</sup>		0.0137	0.6243
Hazard ratio every 2 weeks vs. every 4 weeks (95% CI) <sup>e</sup>		0.64 (0.42, 0.99)	
p-value (every 2 weeks vs. every 4 weeks) <sup>e</sup>		0.0459	
<b>New or newly enlarging T2-weighted hyperintense lesions at 2 years</b>			
Number of patients evaluated	393	407	389
Adjusted mean number of lesions <sup>f</sup>	14.8	5.0	12.5
Lesion mean ratio (peginterferon beta-1a:delayed treatment) (95% CI) <sup>f</sup>		0.33 (0.27, 0.41)	0.84 (0.69, 1.03)
p-value (peginterferon beta-1a:delayed treatment) <sup>f</sup>		<0.0001	0.0973
Lesion mean ratio (every 2 weeks:every 4 weeks) (95% CI) <sup>f</sup>		0.40 (0.32, 0.49)	
p-value (every 2 weeks vs. every 4 weeks) <sup>f</sup>		<0.0001	
<b>Gd+ lesions at 2 years</b>			
Number of patients evaluated	393	407	389
Mean number of lesions (SE)	0.5 (0.08)	0.2 (0.06)	0.7 (0.12)
p-value (peginterferon beta-1a vs. delayed treatment) <sup>g</sup>		0.0002	0.2169
Percent reduction (every 2 weeks vs. every 4 weeks) <sup>g</sup>		71	
p-value (every 2 weeks vs. every 4 weeks) <sup>g</sup>		<0.0001	

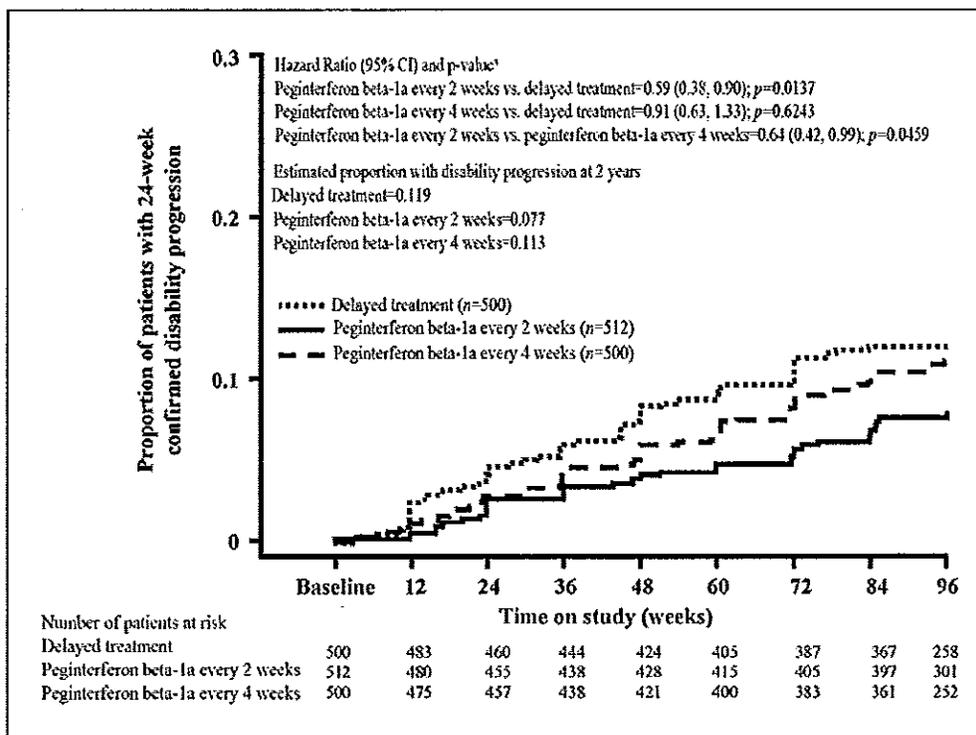
<sup>a</sup>Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. ≥4), baseline relapse rate, age (<40 vs. ≥40).  
<sup>b</sup>Based on Kaplan-Meier product limit method.  
<sup>c</sup>Based on Cox proportion hazards model, adjusted for baseline EDSS (<4 vs. ≥4), age (<40 vs. ≥40), baseline relapse rate, and baseline Gd+ lesions (presence vs. absence).  
<sup>d</sup>Estimated proportion of patients with progression based on the Kaplan-Meier product limit method.  
<sup>e</sup>Based on Cox proportional hazards model, adjusted for baseline EDSS and age (<40 vs. ≥40).  
<sup>f</sup>Based on negative binomial regression, adjusted for baseline number of new or newly enlarging T2 lesions.  
<sup>g</sup>Percent reduction based on group mean and p-value based on multiple logit regression, adjusted for baseline number of Gd+ lesions.  
<sup>h</sup>Delayed treatment group: Patients who received placebo in Year 1 and switched to peginterferon beta-1a in Year 2.



**Figure 4.** Proportion of patients relapsed over 2 years (time to first relapse over 2 years).  
<sup>a</sup>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 every 2 or 4 weeks in Year 2 as one group (delayed treatment).



**Figure 5.** Proportion of patients with 12-week confirmed disability progression over 2 years (time to disability progression).  
<sup>a</sup>Based on a Cox proportional hazards model, adjustment for baseline EDSS and age (<40 vs. ≥40). Disability progression is defined as ≥1.0 point increase on the EDSS from a baseline EDSS ≥1.0 sustained for 12 weeks or ≥1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks. Analyses were conducted by combining patients who received placebo in Year 1 and either peginterferon beta-1a every 2 or 4 weeks in Year 2 as one group (delayed treatment group).



**Figure 6.** Proportion of patients with 24-week confirmed disability progression over 2 years (time to disability progression).

Disability progression is defined as  $\geq 1.0$  point increase on the EDSS from a baseline EDSS  $\geq 1.0$  sustained for 24 weeks or  $\geq 1.5$  point increase on the EDSS from a baseline EDSS of 0 sustained for 24 weeks. Analyses were conducted by combining patients who received placebo in Year 1 and either peginterferon beta-1a every 2 or 4 weeks in Year 2 as one group (delayed treatment).

\*Based on a Cox proportional hazards model, adjustment for baseline EDSS and age ( $<40$  vs.  $\geq 40$ ).

dose of active treatment ( $n=7$ ) are listed in Table 2 and deaths by study year are listed in Table S2. Of the nine deaths reported over 2 years, four occurred in Year 1 ( $n=2$  in the placebo group and one in each peginterferon beta-1a group) and five occurred in Year 2 ( $n=3$  in the peginterferon beta-1a every 2 weeks group and  $n=2$  in the delayed treatment every 4 weeks group) (Table S2). None of the deaths during Year 1 ( $n=4$ ) were assessed as related to study treatment by the Investigator<sup>6</sup> ( $n=2$  in the placebo group [ $n=1$  sudden death of unknown cause,  $n=1$  subarachnoid hemorrhage] and  $n=1$  in each peginterferon beta-1a group [every 2 weeks, cause unknown; every 4 weeks, septicemic shock]). Of the five deaths in Year 2, three were considered related to study treatment by the Investigator ( $n=1$  pneumonia/septicemia [every 2 weeks group],  $n=1$  squamous cell carcinoma [delayed treatment to every 4 weeks group] and  $n=1$  aspiration pneumonia [delayed treatment to every 4 weeks group]) (Table S2). An independent data safety monitoring board concluded that these events were not likely related to study drug and did not change the risk-benefit profile of peginterferon beta-1a.

In Year 2, the incidence of potentially clinically significant abnormalities in white blood cell counts (defined as  $<3.0 \times 10^9/l$ ), lymphocyte counts (defined as  $<0.8 \times 10^9/l$ ), and absolute neutrophil count (defined as  $\leq 1.0 \times 10^9/l$ ) remained low ( $\leq 10\%$  of patients) across peginterferon beta-1a dosing groups (Table S3 in the supplementary materials). The majority of hepatic transaminase elevations were  $<3$  times the upper limit of normal (ULN) (Table S4 in the supplementary materials). During Year 2, one patient had asymptomatic concurrent elevation of alanine transaminase (ALT) and aspartate transaminase (AST)  $\geq 3 \times$  ULN and elevation of total bilirubin  $>2 \times$  ULN. For both dosing regimens, in majority of subjects who reported hepatic or hematological laboratory abnormalities, the abnormal values returned to normal at the end of Year 2. Lab abnormalities over 2 years are presented in Tables S5 and S6 in the online supplementary materials.

Over 2 years, the incidence (number of patients at risk) of NABs against IFN (anti-IFN NABs) ( $<1\%$  every 4 weeks;  $<1\%$  every 2 weeks), binding

**Table 2.** Adverse events, serious adverse events, and discontinuations over 2 years – all patients who received peginterferon beta-1a any time over 2 years.

Event, n (%)	Peginterferon beta-1a every 2 weeks (n=740)	Peginterferon beta-1a every 4 weeks (n=728)
<b>Any adverse event</b>	699 (94)	687 (94)
<b>Most common adverse events (≥10% in any treatment group)</b>		
Injection site erythema	470 (64)	433 (59)
Influenza-like illness	377 (51)	365 (50)
Pyrexia	320 (43)	298 (41)
Headache	308 (42)	296 (41)
MS relapse	185 (25)	222 (30)
Myalgia	140 (19)	137 (19)
Chills	124 (17)	123 (17)
Injection site pain	125 (17)	105 (14)
Nasopharyngitis	97 (13)	109 (15)
Asthenia	90 (12)	108 (15)
Injection site pruritus	108 (15)	82 (11)
Back pain	92 (12)	89 (12)
Arthralgia	81 (11)	91 (13)
Fatigue	87 (12)	72 (10)
Pain in extremity	71 (10)	74 (10)
Nausea	73 (10)	63 (9)
<b>Adverse events related to study treatment</b>	668 (90)	644 (88)
<b>Adverse events leading to discontinuation</b>	41 (6)	42 (6)
<b>Adverse events leading to discontinuation (≥1% in any active treatment group)</b>		
Influenza-like illness	8 (1)	12 (2)
<b>Any serious adverse events</b>	120 (16)	158 (22)
<b>Severe adverse events</b>	152 (21)	149 (20)
<b>Deaths</b>	4 (<1)	3 (<1)
Severe adverse events were defined as symptom(s) that cause severe discomfort; incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) could be given and/or subject.		

antibodies to IFN moieties (5% every 4 weeks; 8% every 2 weeks), and antibodies against peginterferon (anti-PEG Abs) (8% every 4 weeks; 6% every 2 weeks), were similar for both peginterferon beta-1a dosing groups (Table S7 in the supplementary materials).

### Discussion

The results from ADVANCE show that the clinical and neuroradiologic efficacy of peginterferon beta-1a was maintained beyond 1 year of treatment. Compared with Year 1, further reductions in ARR were observed with peginterferon beta-1a every 2 weeks and the same level of reductions was achieved with peginterferon beta-1a every 4 weeks in Year 2. The number of new or newly enlarging T2 lesions was further reduced in Year 2 compared with Year 1 in the continuous peginterferon beta-1a groups, with greater reductions observed for peginterferon beta-1a every 2

weeks. The safety profile of peginterferon beta-1a over 2 years was consistent with that in Year 1.<sup>6</sup>

Assessment of endpoints by original randomization group generally showed that peginterferon beta-1a had greater effects relative to delayed treatment. Importantly, these results demonstrated that the benefits of earlier therapy initiation remain significant for a minimum of 1 year following treatment delay. However, due to the nature of the comparator group, results should be interpreted with caution as the effect sizes are likely underestimates of those against a "true" placebo group. While the every 2 weeks dosing group demonstrated superiority over the delayed treatment group for all endpoints, the every 4 weeks dosing group only demonstrated significant improvement at one endpoint (proportion of relapsed patients). Although comparisons between dosing groups were not pre-specified, assessment of peginterferon beta-1a every 2 weeks versus every 4 weeks over 2 years

showed that peginterferon beta-1a administered every 2 weeks provided larger statistically significant treatment effects over 2 years versus every 4 weeks administration on ARR, proportion of relapse patients, 24-week disability progression, and all MRI endpoints (12-week disability progression was numerically but not significantly superior).

Comparison of safety results over 2 years with Year 1 showed that the nature, type, and frequency of AEs remained consistent with the longer duration of treatment. The overall incidence of AEs was similar between Year 1 (94% for each peginterferon beta-1a dosing group) and over 2 years (94% for each peginterferon beta-1a dosing group). The most common AEs reported over 2 years were similar to those in Year 1 (injection site erythema, influenza-like illness, pyrexia, and headache). Incidence of severe and serious AEs and rate of infections and serious infections were higher over 2 years than in Year 1 due to the longer duration of follow-up. Safety profiles of peginterferon beta-1a by study year (Year 1 and Year 2) were similar.

The incidence of AEs, serious AEs, and discontinuations due to AEs was also similar across dose regimens (the incidence of serious AEs was slightly higher in the every 4 week dosing group than every 2 week dosing group) and are consistent with the known profiles of IFN beta therapies in MS. For the deaths occurring in Year 1, there was no specific pattern. In Year 2, the nature of deaths was consistent with those expected in the MS population and an independent data safety monitoring board concluded that they did not change the risk-benefit profile of peginterferon beta-1a. The incidence of potentially clinically significant lab abnormalities was low across treatment groups in Year 1 and in Year 2.<sup>6</sup>

Development of NAbS against IFN beta has been associated with reduced levels of efficacy based on clinical and MRI variables.<sup>9-11</sup> Immunogenicity remained low over 2 years; the development of NAbS to IFN beta-1a in Year 1 was similar to that over 2 years (<1%). The development of binding antibodies to IFN beta-1a in Year 1 and over 2 years was also similar (6%) as well as binding antibodies against PEG (7-8%).

Although this study did not directly compare peginterferon beta-1a with other MS therapies, our data are consistent with clinical and MRI findings observed with currently available first-line injection therapies (e.g. 29-34% ARR<sup>12-15</sup> 12-37% of patients with disability progression,<sup>12-14,16</sup> and mean number of new or newly enlarging T2 lesions<sup>12,14,17</sup> in 2-year trials). Although direct comparisons are not possible, results suggest that peginterferon beta-1a may provide

similar efficacy and safety to that of approved first-line therapies, with the added benefit of a more convenient SC dosing regimen.

Two-year results from ADVANCE showed that clinical and MRI benefits were maintained with SC peginterferon beta-1a beyond the placebo-controlled first year of the study and numerically better efficacy was observed in patients receiving continuous peginterferon beta-1a than those originally randomized to placebo in Year 1. Greater efficacy was observed with every 2 week versus every 4 week administration, and safety results show that peginterferon beta-1a is well tolerated over 2 years. Peginterferon beta-1a offers an effective and safe treatment option with the benefit of less frequent administration.

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#### Conflict of interest

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Supplementary Appendix

Table S1. Baseline demographics and clinical characteristics<sup>6</sup>

Characteristic	Placebo (n=500)	Peginterferon beta-1a every 2 weeks (n=512)	Peginterferon beta-1a every 4 weeks (n=500)
Age, years	36.3 (9.7)	36.9 (9.8)	36.4 (9.9)
Gender, n (%) female	358 (72)	361 (71)	352 (70)
Race, n (%) Caucasian	412 (82)	416 (81)	409 (82)
Geographic regions, n (%)			
India	56 (11)	58 (11)	56 (11)
North America	17 (3)	19 (4)	16 (3)
Western Europe	38 (8)	41 (8)	39 (8)
Eastern Europe	354 (71)	355 (69)	355 (71)
Rest of World	35 (7)	39 (8)	34 (7)
Time since first MS symptoms, years	6.3 (6.3)	6.9 (6.6)	6.5 (6.1)
Time since MS diagnosis, years	3.5 (4.6)	4.0 (5.1)	3.4 (4.4)
Relapses within the previous 3 years	2.6 (1.00)	2.6 (0.99)	2.5 (0.77)
Relapses within the previous 12 months	1.6 (0.67)	1.6 (0.67)	1.5 (0.62)
EDSS Score	2.44 (1.18)	2.47 (1.26)	2.48 (1.24)
EDSS <4, n (%)	432 (86)	423 (83)	413 (83)
EDSS ≥4, n (%)	68 (14)	89 (17)	87 (17)
Patients absent Gd+ lesions, n (%)	296 (59)	334 (65)	297 (59)
Number of Gd+ lesions	1.6 (3.8)	1.2 (3.4)	1.8 (5.4)
Number of new or newly-enlarging T2	50.6 (35.7)	48.7 (36.8)	51.4 (36.0)

Characteristic	Placebo (n=500)	Peginterferon beta-1a every 2 weeks (n=512)	Peginterferon beta-1a every 4 weeks (n=500)
lesions			
Prior medication, n (%)			
Glatiramer acetate	24 (5)	27 (5)	28 (6)
IFN beta-1b	6 (1)	8 (2)	5 (1)
IFN beta-1a	5 (1)	4 (<1)	6 (1)

Data are presented as mean (standard deviation), unless otherwise stated.

EDSS=Expanded Disability Status Scale. Gd+=gadolinium-enhancing. IFN=interferon. MS=multiple sclerosis.

**Table S2. Adverse events, serious adverse events, and discontinuations – Year 1 and Year 2**

Event, n (%)	Year 1 (Calabresi et al 2014)			Year 2				
	Placebo (n=500)	Peginterferon beta-1a every 2 weeks (n=512)	Peginterferon beta-1a every 4 weeks (n=500)		Delayed treatment: peginterferon beta-1a every 2 weeks <sup>a</sup> (n=228)	Delayed treatment: peginterferon beta-1a every 4 weeks <sup>a</sup> (n=227)	Peginterferon beta-1a every 2 weeks (n=438)	Peginterferon beta-1a every 4 weeks (n=439)
<b>Any adverse event</b>	417 (83)	481 (94)	472 (94)		210 (92)	206 (91)	392 (89)	391 (89)
<b>Most common adverse events (≥10% in any treatment group)</b>								
Injection site erythema	33 (7)	315 (62)	282 (56)	Injection site erythema	135 (59)	119 (52)	212 (48)	211 (48)
Influenza like illness	63 (13)	239 (47)	234 (47)	Influenza like illness	106 (46)	95 (42)	192 (44)	199 (45)
Pyrexia	76 (15)	228 (45)	218 (44)	Pyrexia	66 (29)	66 (29)	136 (31)	138 (31)
Headache	165 (33)	224 (44)	204 (41)	Headache	64 (28)	70 (31)	126 (29)	122 (28)
MS relapse	159 (32)	96 (19)	111 (22)	MS relapse	52 (23)	52 (23)	64 (15)	101 (23)
Myalgia	30 (6)	97 (19)	97 (19)	Myalgia	27 (12)	27 (12)	58 (13)	60 (14)

Chills	23 (5)	88 (17)	92 (18)	Chills	29 (13)	28 (12)	41 (9)	52 (12)
Injection site pain	15 (3)	77 (15)	67 (13)	Nasopharyngitis	17 (7)	22 (10)	47 (11)	45 (10)
Asthenia	38 (8)	68 (13)	70 (14)	Injection site pain	25 (11)	25 (11)	45 (10)	32 (7)
Back pain	57 (11)	61 (12)	64 (13)	Injection site pruritus	26 (11)	17 (7)	47 (11)	24 (5)
Injection site pruritus	6 (1)	68 (13)	56 (11)	Asthenia	10 (4)	24 (11)	40 (9)	39 (9)
Nasopharyngitis	77 (15)	53 (10)	69 (14)	Arthralgia	14 (6)	23 (10)	33 (8)	33 (8)
Arthralgia	35 (7)	57 (11)	54 (11)	--		--		
Fatigue	49 (10)	51 (10)	55 (11)	--		--		
Pain in extremity	49 (10)	44 (9)	54 (11)	--		--		
Severe adverse events <sup>b</sup>	53 (11)	90 (18)	82 (16)	Severe adverse events <sup>b</sup>	39 (17)	34 (15)	56 (13)	62 (14)
AEs related to study treatment	266 (53)	459 (90)	449 (90)	AEs related to study treatment	198 (87)	179 (79)	350 (80)	357 (81)

<b>AEs leading to discontinuation</b>	7 (1)	25 (5)	24 (5)	<b>AEs leading to discontinuation</b>	8 (4)	9 (4)	8 (2)	9 (2)
<b>Any serious adverse events</b>	76 (15)	55 (11)	71 (14)	<b>Any serious adverse events</b>	36 (16)	42 (19)	39 (9)	67 (15)
<b>Deaths</b>	2 (<1) <sup>c</sup>	1 (<1) <sup>d</sup>	1 (<1) <sup>e</sup>	<b>Deaths</b>	0 (0)	2 (<1) <sup>f</sup>	3 (<1) <sup>g</sup>	0 (0)

<sup>a</sup>Delayed treatment groups: patients who received placebo in Year 1 and switched to peginterferon beta-1a in Year 2.

<sup>b</sup>Severe adverse events were defined as symptom(s) that cause severe discomfort; incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptom(s) could be given and/or subject hospitalized.

<sup>c</sup>n=1 sudden death of unknown cause, n=1 subarachnoid hemorrhage.

<sup>d</sup>n=1 cause unknown.

<sup>e</sup>n=1 septicemic shock.

<sup>f</sup>n=1 squamous cell carcinoma oral cavity, n=1 aspiration pneumonia

<sup>g</sup>n=1 sudden death, cause unknown, n=1 car accident, n=1 pneumonia/septicaemia

Table S3: Potentially clinically significant hematology lab abnormalities – Year 2

Parameters/criterion	Delayed treatment: peginterferon beta-1a every 2 weeks <sup>a</sup> (n=228 <sup>b</sup> )	Delayed treatment: peginterferon beta-1a every 4 weeks <sup>a</sup> (n=227 <sup>b</sup> )	Peginterferon beta-1a every 2 weeks (n=438 <sup>b</sup> )	Peginterferon beta-1a every 4 weeks (n=439 <sup>b</sup> )
Patients with any post-baseline value, total n	227	227	438	438
WBC, n (%)				
<3 x 10 <sup>9</sup> /L	23 (10)	7 (3)	42 (10)	22 (5)
Lymphocytes, n (%)				
<0.8 x 10 <sup>9</sup> /L	13 (6)	7 (3)	35 (8)	23 (5)
PMN, n (%)				
≤1.0 x 10 <sup>9</sup> /L	2 (<1)	0 (0)	4 (<1)	6 (1)
Hemoglobin, n (%)				
≤100 g/L	15 (7)	9 (4)	19 (4)	20 (5)
Platelet count, n (%)				
≤100 x 10 <sup>9</sup> /L	3 (1)	2 (<1)	5 (1)	4 (<1)

PMN=polymorphonuclear leukocytes. WBC=white blood cell.

<sup>a</sup>Delayed treatment groups: patients who received placebo in Year 1 and switched to peginterferon beta-1a in Year 2.

<sup>b</sup>Total n is the number of patients in the safety population dosed in year 2 with at least one post-baseline value. This is the denominator for percentages in parentheses.

Table S4: Maximum post-baseline liver transaminases – Year 2

Parameters/Criterion	Delayed treatment: peginterferon beta-1a every 2 weeks <sup>a</sup> (n=228 <sup>b</sup> )	Delayed treatment: peginterferon beta-1a every 4 weeks <sup>a</sup> (n=227 <sup>b</sup> )	Peginterferon beta-1a every 2 weeks (n=438 <sup>b</sup> )	Peginterferon beta-1a every 4 weeks (n=439 <sup>b</sup> )
Patients with any post-baseline value, total n	227	227	438	438
ALT, n (%)				
>1 x ULN	111 (49)	70 (31)	162 (37)	124 (28)
≥3x ULN	9 (4)	8 (4)	14 (3)	15 (3)
>5 x ULN	2 (<1)	2 (<1)	7 (2)	7 (2)
AST, n (%)				
>1 x ULN	72 (32)	36 (16)	119 (27)	73 (17)
≥3x ULN	4 (2)	1 (<1)	9 (2)	10 (2)
>5 x ULN	2 (<1)	0 (0)	6 (1)	5 (1)

ALT=alanine transaminase. AST=aspartate transaminase. ULN=upper limit of normal.

<sup>a</sup>Delayed treatment groups: patients who received placebo in Year 1 and switched to peginterferon beta-1a in Year 2.

<sup>b</sup>Total n is the number of patients in the safety population dosed in year 2 with at least one post-baseline value. This is the denominator for percentages in parentheses. Baseline is Year 1 baseline for patients previously treated with peginterferon beta-1a, and year 2 baseline for patients previously treated with placebo, during year 1.

**Table S5.** Potentially clinically significant hematology lab abnormalities over 2 years – All patients who received peginterferon beta-1a any time over 2 years

<b>Parameters/criterion</b>	<b>Peginterferon beta-1a every 2 weeks (n=740)</b>	<b>Peginterferon beta-1a every 4 weeks (n=728)</b>
<b>WBC, n (%)</b>		
<3 x 10 <sup>9</sup> /L	80 (11)	43 (6)
<b>Lymphocytes, n (%)</b>		
<0.8 x 10 <sup>9</sup> /L	64 (9)	48 (7)
<b>PMN, n (%)</b>		
≤1.0 x 10 <sup>9</sup> /L	11 (1)	11 (2)
<b>Hemoglobin, n (%)</b>		
≤100 g/L	42 (6)	35 (5)
<b>Platelet count, n (%)</b>		
≤100 x 10 <sup>9</sup> /L	13 (2)	7 (<1)

PMN=polymorphonuclear leukocytes. WBC=white blood cell.

**Table S6. Maximum post-baseline liver transaminases over 2 years – All patients who received peginterferon beta-1a any time over 2 years**

<b>Parameters/Criterion</b>	<b>Peginterferon beta-1a every 2 weeks (n=740)</b>	<b>Peginterferon beta-1a every 4 weeks (n=728)</b>
<b>ALT, n (%)</b>		
>1 x ULN	399 (54)	292 (40)
≥3x ULN	56 (8)	38 (5)
>5 x ULN	21 (3)	17 (2)
<b>AST, n (%)</b>		
>1 x ULN	293 (40)	171 (24)
≥3x ULN	23 (3)	21 (3)
>5 x ULN	11 (1)	8 (1)

ALT=alanine transaminase. AST=aspartate transaminase. ULN=upper limit of normal.

**Table S7: Incidence of positive antibody tests over 2 years – All patients who received peginterferon beta-1a any time over 2 years**

Antibody type	Peginterferon beta-1a every 2 weeks (n=740)	Peginterferon beta-1a every 4 weeks (n=728)	Total (n=1468)
<b>Number of antibody positive/number at risk (%)– Post-baseline to Week 96</b>			
IFN binding (BAbs) positive	54/706 (8)	36/706 (5)	90/1412 (6)
IFN neutralizing (NAbs) positive	7/715 (<1)	6/716 (<1)	13/1431 (<1)
Anti-PEG positive	40/681 (6)	55/682 (8)	95/1363 (7)

IFN=interferon. PEG=polyethylene glycol.

Entries are number of antibody positive/number at risk. Number at risk is the number of patients whose baseline antibody was not positive and who had at least one post-baseline antibody value for any time post baseline. Numbers in parentheses are percentages based on number at risk.



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→ **PLEGRIDY® (peginterferon beta-1a) injection: Summary of Kieseier, et al, *Mult Scler*, 2014**

Year 2 results are reported from a 2-year, phase III, multicenter, randomized, double-blind study with 1 year placebo-controlled period that evaluated efficacy and safety of PLEGRIDY 125 µg administered subcutaneously to patients with RRMS every 2 weeks (Q2W) or 4 weeks (Q4W) (page 1, paragraph 2, lines 1-5). Patients were randomized to placebo or 125 µg PLEGRIDY Q2W or Q4W (page 2, paragraph 4, lines 1-11). For Year 2 (Y2), patients originally randomized to placebo were re-randomized to PLEGRIDY Q2W or Q4W (page 2, paragraph 4, lines 1-11). Patients randomized to PLEGRIDY in Year 1 (Y1) remained on the same dosing regimen in Y2 (page 2, paragraph 4, lines 1-11). Compared with Y1, annualized relapse rate (ARR) was further reduced in Y2 with Q2W dosing and maintained with Q4W dosing (page 4, paragraph 2, lines 6-13 and page 5, paragraph 1, line 1). Patients starting PLEGRIDY Q2W from Y1 displayed improved efficacy versus patients initially assigned placebo, with reductions in ARR (Q2W: 37%,  $p < 0.0001$ ) (page 5, paragraph 2, lines 9-14), risk of relapse (Q2W: 39%  $p < 0.0001$ ) (page 5, paragraph 2, lines 14-21), 12 week disability progression (Q2W: 33%,  $p = 0.0257$ ) (page 5, paragraph 2, lines 21-28), and 24-week disability progression (Q2W: 41%,  $p = 0.0137$ ) (page 5, paragraph 2, lines 29-36). Over 2 years, greater reductions were observed with Q2W versus Q4W dosing for all endpoints (page 5, paragraph 3, lines 1-18). PLEGRIDY was well tolerated and the most commonly reported AEs over 2 years were injection site erythema, influenza-like illness, pyrexia, and headache (page 5, paragraph 5, lines 4-6). The majority of AEs were mild or moderate in severity (page 5, paragraph 5, lines 7-10). Over 2 years, the incidence (number of patients at risk) of NABs against IFN (anti-IFN NABs), binding antibodies to IFN moieties, and antibodies against peginterferon (anti-PEG Abs), were similar for both PLEGRIDY dosing groups (page 8, paragraph 3, lines 1-3 and page 9, paragraph 1, lines 1-6).

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