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APPLICATION NUMBER:

125499Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	15 August 2014
From	Ellis F. Unger, MD Director, Office of Drug Evaluation-I
Subject	Office Director Decisional Memo
BLA	125499
Applicant Name	Biogen Idec Inc.
Date of Submission	16 May 2013
PDUFA Goal Date (post-extension)	15 August 2014
Proprietary Name / Established (USAN) Name	Plegridy/ pegylated interferon- β -1a beta-1a
Dosage Forms / Strength	63, 94,125 micrograms subcutaneous, 14 day intervals
Proposed Indication(s)	For treatment of patients with relapsing forms of multiple sclerosis
Action:	Approval

Material Reviewed/Consulted Office of New Drugs Action Package Including:	Names of discipline reviewers:
Cross-discipline Team Leader	John Marler, MD
Clinical Efficacy	Lawrence Rodichok, MD
Statistical Review	Tristan Massie, PhD
Clinical Safety Review	Gerard Boehm, MD, PhD
Clinical Pharmacology Review	Ta-Chen Wu, PhD
Pharmacometrics Review	Xiaofeng Wang, PhD
Pharmacology Toxicology Review	Rick Houghtling, PhD
Office of Biotechnology Products / Division of Therapeutic Proteins Review	Ralph Bernstein, PHD, Ennan Guan, PhD, Serge Beaucage, PhD, Tracy Denison, PhD
Biotechnology Manufacturing Assessment Branch (Office of Compliance)	Bo Chi, PhD, Lakshmi Narasimhan, PhD
CDRH, Office of Compliance	Felicia Brayboy
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CDRH, Office of Device Evaluation/Human Factors	Quynh Nhu Nguyen
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Division of Risk Management	George Neyarapally, PharmD, MPH
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Office of Medical Policy / Division of Medical Policy Programs	Twanda Scales, RN, MSN/Ed.
Office of Prescription Drug Promotion	Aline Moukhtara, RN, MPH

1. Introduction

This biologics license application (BLA) was submitted by Biogen-Idec for pegylated interferon- β -1a, to treat relapsing multiple sclerosis (MS). The members of the review team are unanimous in their support for approval, and I concur with their assessment.

2. Background

There are 3 approved interferon drug products for the treatment of MS: Betaseron/Extavia, Avonex, and Rebif. (Extavia is simply Betaseron with a different brand name and a different needle.) Betaseron/Extavia is interferon β -1b, whereas Rebif and Avonex are different formulations of interferon β -1a. All 3 products have indications to reduce the frequency of exacerbations. Rebif and Avonex have a claim for prevention of progression (disability), whereas Betaseron/Extavia does not.

The pegylated interferon- β -1a drug substance is a pegylated form of the Avonex drug substance, which is produced and marketed by Biogen-Idec. Pegylation is claimed to decrease renal clearance and slow proteolysis, prolonging the biologic's half-life. Whereas the marketed interferons are administered every other day by the subcutaneous (SC) route or weekly by the intramuscular (IM) route, pegylated interferon- β -1a is intended for use every other week, which can be viewed as a major convenience. Pegylated interferon- β -1a will represent the only pegylated interferon for MS.

Biogen requested a Special Protocol Assessment for a phase 3 pivotal trial on December 23, 2008, but we did not agree to their design. Biogen submitted a revised protocol that addressed our concerns and we sent an agreement letter for the revised protocol on May 3, 2010.

At a March 12, 2013, pre-NDA meeting, the Division of Neurology Products (DNP) agreed that the one-year results from a single trial could provide substantial evidence of effectiveness. As explained by Dr. Dunn in his approval memo, based upon extensive accumulated experience with interferons for the treatment of MS, i.e., the probability of effectiveness based on consistent effects observed with other interferons, the Division was prepared to accept the results from a single adequate well controlled study of one year's duration as constituting substantial evidence of effectiveness.

3. CMC/Device

The recombinant human interferon- β -1a is expressed in Chinese hamster ovary (CHO) cells, and the sequence is identical to human interferon- β -1a. The molecule is then pegylated with a single polyethylene glycol molecule to form the drug substance. Biogen will market pegylated interferon- β -1a in two presentations: Plegridy, a pre-filled syringe; and Plegridy Pen, an auto-injector.

The Division of Therapeutic Proteins review team concluded that "the manufacture of Plegridy is well controlled, and leads to a product that is pure and potent. The processes used in manufacturing have been validated, and a consistent product is produced from different production runs..." Inspections of manufacturing sites were acceptable. Stability testing supports an expiry of 36 months at $5 \pm 3^\circ\text{C}$ and $(b)(4)$ months at $(b)(4)^\circ\text{C}$. The manufacturing review team has negotiated postmarketing commitments with the applicant concerning release

and stability specifications, leachables, and sub-visible particulates. There are no outstanding issues.

The CDRH review team concluded that the non-human factors device design is complete and acceptable. There were no apparent deficiencies in a desk review of compliance with medical device regulations.

4. Nonclinical Pharmacology/Toxicology

Nonclinical studies were conducted in guinea pigs and rhesus monkeys. Rhesus monkeys developed high levels of binding and neutralizing antibodies to pegylated interferon- β -1a and interferon- β -1a, and so qualification of biological activity was limited in this species.

Toxicological study results were consistent with prior experience with interferon- β -1a, including increased body temperature, reduced circulating lymphocytes, and increased serum neopterin.

In her secondary non-clinical review, Dr. Lois Freed concluded that additional nonclinical studies would not be useful for evaluating differences between interferon- β -1a and pegylated interferon- β -1a. “The data provided by the sponsor demonstrate that [pegylated interferon- β -1a] exerts effects consistent with its pharmacological activity, and provide sufficient information for labeling.” With reference to Dr. Freed’s comments in her supervisory memo concerning reproductive toxicology and the potential utility of a pregnancy registry, we are imposing a postmarketing requirement for a pregnancy registry.

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted a number of clinical pharmacology studies to characterize the pharmacokinetics (PK) and pharmacodynamics of pegylated interferon- β -1a, including a study in subjects with renal impairment. They compared the PK profiles of the IM and SC routes of administration, and compared the PK profiles of the prefilled syringe and prefilled pen delivery systems.

Important findings include:

- Peginterferon doses from 63 to 188 μ g SC result in a higher exposure than Avonex at the approved 30 μ g IM dose.
- Pegylation approximately doubles the terminal elimination; the terminal half-life in MS patients is approximately 78 hours.
- The time to maximum concentration is 1 to 1.5 days.
- Pegylated interferon- β -1a, 125 μ g, administered every 14 days, does not accumulate.
- Subjects with all degrees of renal impairment have relative increases in the maximum concentration and overall drug exposure compared to normal volunteers, ranging from 26 to 53% higher.
- SC pegylated interferon- β -1a is widely distributed in the body (volume of distribution is 480 liters)
- Clearance occurs primarily through renal elimination, and secondarily through catabolism.
- The PK profiles of the auto-injector pen and pre-filled syringe are not importantly different.
- The emergence of anti-drug antibodies during treatment is infrequent.

The clinical pharmacology team concluded that labeling should note the potential for increased exposure in patients with impaired renal function. They found no reason to adjust the dose on

the basis of body mass index. The label notes that patients with severe renal impairment should be monitored for adverse reactions because of increased exposure.

6. Clinical/Statistical - Efficacy

The evidence of efficacy was primarily reviewed by Drs. Lawrence Rodichok and Marler (clinical) and Tristan Massie (biostatistics).

Study Design: The pivotal trial, 105MS301, “A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects with Relapsing Multiple Sclerosis,” was a 48-week, randomized, double-blind, placebo-controlled clinical trial that compared two regimens of pegylated interferon- β -1a to placebo. The study will be referred to as study 301 in this memo. Subjects were randomized to pegylated interferon- β -1a 125 μ g SC every 2 weeks, pegylated interferon- β -1a 125 μ g SC every 4 weeks, or matching placebo. The dose of pegylated interferon- β -1a was initiated at half the maintenance dose and increased to three-fourths the maintenance dose before it was increased to the full maintenance dose.

At the conclusion of the last follow-up for the first year, subjects in the placebo group were re-randomized to one of the two active treatment groups and followed for an additional year. Although all subjects learned whether they had been receiving pegylated interferon- β -1a after 48 weeks, they were blinded (or remained blinded) to dosing frequency (Q2 or 4 weeks) during the second year of the trial.

Patient Selection: Adult patients were enrolled with a confirmed diagnosis of relapsing MS, EDSS score of 0 - 5.0, ≥ 2 relapses in the preceding 3 years, and ≥ 1 relapse within the preceding a year. Key exclusion criteria included 1 $^{\circ}$ or 2 $^{\circ}$ progressive MS, recent (within 6 months) or prolonged (> 1 month) treatment with interferons, history of seizures, suicidal ideation, and severe depression.

Blinding: Given that injection of interferons can cause flu-like symptoms, frequent injection site reactions, and hematological changes, the usual measures were taken to promote blinding: personnel who assessed efficacy assessments were separate from personnel who cared for the patients and recorded adverse events; patients were to take anti-inflammatory agents to blunt flu-like symptoms; efficacy assessors were not permitted to have access to laboratory data.

Concomitant drugs: Additional MS therapies were not permitted during the study. Relapses could be treated with IV methylprednisolone.

Primary endpoint: The 1 $^{\circ}$ endpoint was the annualized relapse rate (ARR). The analysis was a negative binomial regression for the annualized relapse rate at one year. The model included terms for treatment group, age (<40 vs. ≥ 40), and EDSS (4 or ≥ 4). Baseline relapse rate was defined as the number of relapses during the 3 years prior to screening, divided by 3.

Secondary endpoints: There were three 2 $^{\circ}$ endpoints: 1) number of new or newly enlarging T2 hyperintense lesions at 48 weeks; 2) proportion of subjects with relapses through 48 weeks; and 3) progression of disability at Week 48 as measured by EDSS.

Statistical plan: The pre-specified efficacy population was the “intent to treat” population: all subjects who were randomized and received ≥ 1 dose of study drug. For the 1^o efficacy analysis a sequential (closed) procedure was pre-specified as follows: if the first comparison (the Q2W group versus placebo) was statistically significant ($p \leq 0.05$), then the second comparison (the Q4W group versus placebo) would also be made at the 0.05 alpha level. If the first comparison was not statistically significant, then the second comparison would not be considered statistically significant. The 2^o endpoints were rank-prioritized (in the order above), and a sequential closed testing procedure included both the order of the 2^o endpoints and two treatment groups. Specifically, for each 2^o endpoint, a sequential (closed) testing procedure was used to control the overall Type I error rate for both active treatment groups (pegylated interferon- β -1a Q2W vs. versus placebo; pegylated interferon- β -1a Q4W vs. placebo). If statistical significance was not achieved for at least one regimen, none of the endpoint(s) of lower rank could be considered statistically significant.

Interim analysis for futility: An interim futility analysis was planned after the first 210 subjects completed their Month 6 MRI assessments to quantify the number of new or newly enlarged T2 lesions. Because the 1^o endpoint was not evaluated, there was no need to adjust alpha for the interim analysis.

Sample size adjustment: The protocol also included monitoring of the pooled 1-year annualized relapse rate to assure that the trial would not be underpowered. Because the annualized relapse rate was lower than expected, the sample size was increased from 420 to 500 subjects per group in version 4 of the protocol (dated March 14, 2011). Again, because the analysis provided no assessment of efficacy, there was no need to adjust alpha for this.

Results: Investigators at 183 sites in 26 countries randomized 1516 subjects. The highest enrolling countries were Poland (386 subjects), the Ukraine (189 subjects), India (170 subjects), Russian Federation (145 subjects), and Serbia (134 subjects). Other countries enrolled fewer than 100 subjects each. This was essentially a non-US study, with just 3% of subjects from the U.S. and Canada. Of the 1516 subjects randomized, 4 subjects never received study drug; therefore, the modified ITT population included 1512 subjects.

A total of 1332 subjects (88%) completed the placebo-controlled phase of the study. For all 3 treatment groups, withdrawal of consent was the most common reason for discontinuing study treatment and was similar among groups, ranging from 6 to 7%. The second most common reason for patients discontinuing was an adverse event, with 5% of patients in both pegylated interferon- β -1a groups, and 1% of placebo patients discontinuing for an adverse event. Overall, 88% and 86% of subjects in the pegylated interferon- β -1a Q4W and Q2W groups, respectively, completed the study; 91% of placebo subjects completed the study.

Baseline demographic and disease-specific characteristics were similar among treatment groups. Mean age was 37, and 71% of subjects were female. Europeans constituted 78% of the population, North Americans 3.5%, and others 18%. The mean number of relapses in the three years prior to study entry was 2.5 and the mean EDSS score was 2.5.

Primary endpoint: For the pegylated interferon- β -1a Q4W and Q2W groups, there were statistically significant reductions in the annualized relapse rate of 27.5% and 35.6% compared to placebo, respectively, with p-values of 0.011 and 0.0007 (**Table 1**).

The effects of pegylated interferon- β -1a Q2W and Q4W on annualized relapse rate were examined in various subgroups by the applicant (**Figure 1** – adapted from the applicant’s study report). For pegylated interferon- β -1a Q2W, results were reasonably similar when analyzed by subgroups based on gender, age, time since most recent pre-study relapse, McDonald Criteria, prior MS treatment, and various baseline MRI parameters.

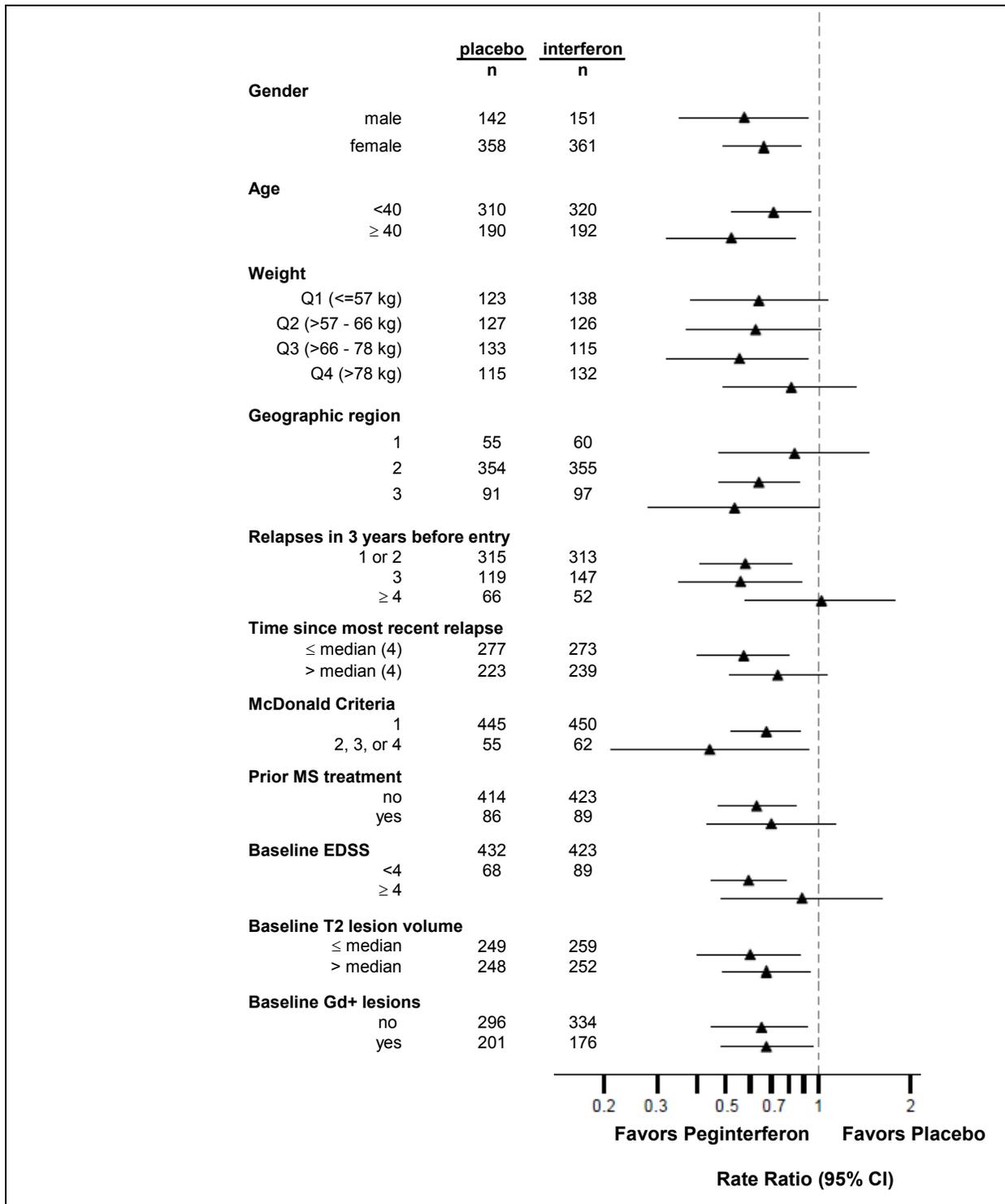
The treatment effect within subgroups based on baseline weight, geographic region, baseline relapse rate, and baseline EDSS are less consistent; however, the analogous subgroup analysis comparing Q4W administration of pegylated interferon- β -1a to placebo shows more consistency within these subgroups (data not shown). The single exception is patients with ≥ 4 relapses within the 3 years prior to study entry. For this subset of patients, the point estimates are close to 1 for both regimens, suggesting that pegylated interferon- β -1a is less effective in such patients.

Eighty-seven percent (87%) of all relapses were confirmed.

Table 1: 1° Endpoint – Annualized Relapse Rate by Treatment Group, Trial 301

Outcome Measure	Placebo N=500	Peginterferon beta-1a 125 μ g		Total	%
		q4w n=500	q2w n=512		
All relapses	213	142	132	487	
Protocol-defined relapses	204	134	126	464	95%
Confirmed relapses	181	125	116	422	87%
Adjusted annualized relapse rate - 1° endpoint (95% CI)	0.40 (0.33 to 0.48)	0.29 (0.23 to 0.36)	0.26 (0.21 to 0.32)		
Rate reduction		27.5%	35.6%		
<i>p</i> -value		0.011	0.0007		

Figure 1: Ratio of Annualized Relapse Rates for Peginterferon 125 µg Q2W vs. Placebo – Subgroup Analysis, Trial 301



Secondary endpoints: All of the secondary analyses showed a statistically significant effect with both treatment regimens (**Table 2**).

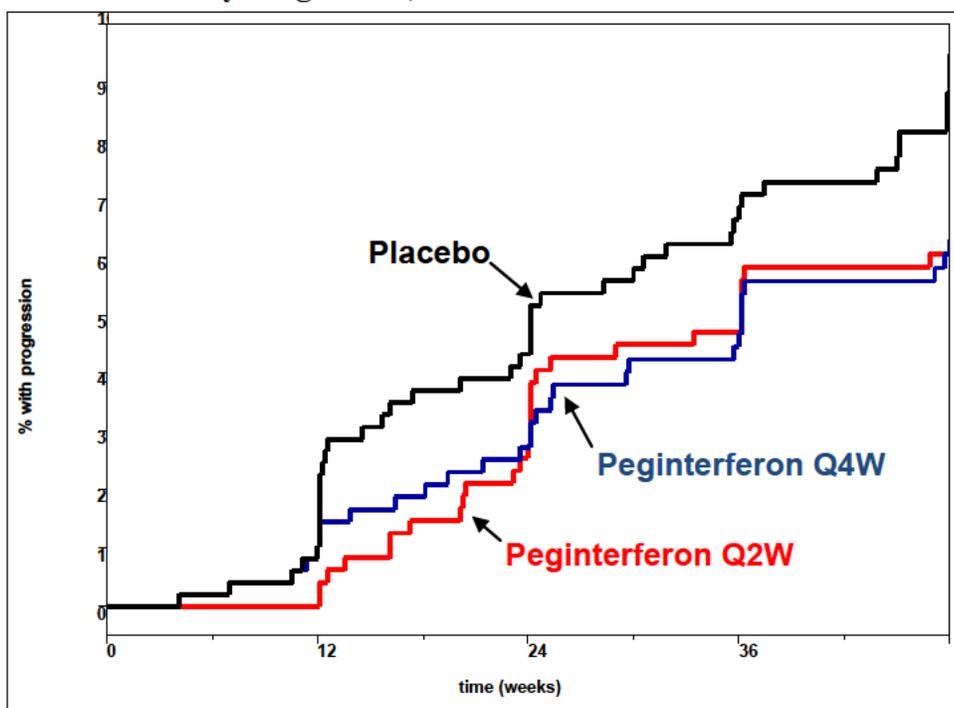
Table 2: Applicant's Analysis of 2° Endpoints, Trial 301

Secondary Outcomes	Placebo N=500	Peginterferon 125 µg	
		q4w n=500	q2w n=512
New or Enlarging T2 Hyperintense Lesions at 48 Weeks (mean)	13.3	9.2	4.1
Median new lesion number	6	3	1
Risk reduction based on mean		28%	67%
<i>p</i> -value		0.0008	0.0001
Proportion with relapses through Week 48 (Year 1)	0.291	0.22	0.19
Reduction in risk of relapse		26%	39%
<i>p</i> -value		0.020	0.0003
Disability progression by EDSS at Week 48 – Number of Subjects	50	31	31
Percent of subjects	10%	6%	6%
Risk reduction		38%	38%
<i>p</i> -value		0.038	0.038

The 2° endpoint, progression of disability, as assessed by worsening EDSS, (b) (4)

Through 48 weeks of the study, 10.5% of placebo patients experienced progression of disability, whereas for both pegylated interferon-β-1a groups, progression occurred in 6.8% of subjects. Thus, for both pegylated interferon-β-1a groups, the relative risk reduction was 38% (p = 0.04 for both comparisons). The Kaplan-Meier survival plot is shown in **Figure 2**.

Figure 2: Time to Disability Progression, Trial 301



A number of tertiary MRI outcomes were statistically significantly positive. For the Q2W pegylated interferon-β-1a group, there were statistically significant differences in the numbers of

new active lesions, Gd-enhancing lesions, and new T1 hypointense lesions. There were also statistically significant differences in the volume of T2 hyperintense lesions, T1 hypointense lesions, and Gd-enhancing lesions.

Brain atrophy and the magnetic transfer ratio were not statistically significantly different in the pegylated interferon- β -1a and placebo groups.

Given the distinctly different rates of injection site reactions (63% of patients in the pegylated interferon- β -1a groups vs. 11% of patients in the placebo group), there was considerable likelihood of unblinding, which could have influenced the results on exacerbations and disability. Conversely, MRI scans, if read by a blinded reader, are not susceptible to bias. Thus, although these MRI endpoints are not as clinically meaningful as exacerbations and progression of disability, the persuasive results on the MRI endpoints are salient here, even if the clinical meaningfulness is less important.

7. Safety

Dr. Gerald Boehm provided the primary safety review and Dr. Sally Yasuda provided the supervisory team leader review. Peginterferon's safety profile was consistent with the approved interferons for MS, and there were no apparent issues with respect to pegylation per se.

Exposure: The applicant conducted 6 clinical trials in which 1664 subjects were exposed to pegylated interferon- β -1a. The vast majority of exposure occurred in study 301.

During the placebo-controlled portion of study 301, there were 4 deaths: 2 in the placebo group (2 of 500, 0.4%) and 2 in the pegylated interferon- β -1a groups (2 of 1012, 0.2%).

There were 4 deaths in the second year of study 301, with all subjects on pegylated interferon- β -1a. None of these deaths was suspicious for a drug-related mechanism.

In the first year of study 301, where pegylated interferon- β -1a was compared to placebo, there were only 4 serious adverse events that occurred in at least 2 pegylated interferon- β -1a-treated subjects and at a greater frequency than placebo, and none of these were plausibly drug-related.

The applicant and review staff paid particular attention to adverse events that are known to be of interest with interferons, including: hepatic disorders, depression/suicide, seizures, hypersensitivity events, injection site reactions, cardiovascular disorders, leukopenia, autoimmune disorders, flu-like symptoms, infections, and malignancies.

Hepatic disorders: The approved beta interferons for MS carry warnings for hepatic injury, and the risk seems similar with pegylated interferon- β -1a. Transaminase elevations were more frequent in patients in the pegylated interferon- β -1a groups, and there were two "Hy's law" cases in the pegylated interferon- β -1a groups. There were no deaths from liver failure and no liver transplants. The pegylated interferon- β -1a label will include a warning for hepatic injury in 5.1, with instructions to monitor patients for signs and symptoms of hepatic injury.

Depression/suicide: All of the interferon labels include warnings about depression and suicide: at 5.1 in the Rebif and Avonex labels; at 5.3 in the Betaseron label. With respect to pegylated interferon- β -1a, there were no completed suicides and no reports of suicide attempts in any patients reported in the BLA. Depression- and suicide-related adverse events were similar in

frequency in the placebo and pegylated interferon- β -1a groups (8% in each). Depression and suicide will be presented in the label in 5.2, based on the history with this class of drugs.

Seizures: During the placebo controlled phase of study 301, 4 pegylated interferon- β -1a subjects (0.4%) and 1 placebo subject (0.2%) experienced a seizure. All five subjects had histories of seizure disorders. Two seizures in the pegylated interferon- β -1a group were serious adverse events, but none led to discontinuation. Dr. Boehm comments that the numbers are too small to lead to a meaningful interpretation. Nevertheless, he believes that the warning for seizures in the labels of other interferons for MS should apply to pegylated interferon- β -1a, and I agree.

Hypersensitivity events: Peginterferon did not appear to be associated with an increased risk of hypersensitivity adverse events in year 1 of study 301. The label will note (in section 5.4) that anaphylaxis and other serious allergic reactions are rare complications of treatment with interferon β .

Injection site reactions: The incidence of injection site reactions (e.g., erythema, pain, pruritus, or edema) was 66% in the pegylated interferon- β -1a group and 11% in the placebo group; the incidence of severe injection site reactions was 3% in the pegylated interferon- β -1a group and 0% in the placebo group. Two reactions were serious. One patient developed pain, erythema, and pruritus in a 10 X 20 cm area on the thigh. Another developed gangrenous cellulitis and required hospitalization for treatment with intravenous antibiotics. The incidence of injection site reactions is comparable to that with the other interferons and will be described in section 5.5 of the label.

Cardiovascular disorders: There were few cardiovascular adverse events in study 301, and the frequencies of serious and non-serious adverse events were similar in the pegylated interferon- β -1a and placebo groups. Because of prior experience with interferon β , the label will carry a warning for congestive heart failure and cardiomyopathy in section 5.6.

Leukopenia: In clinical studies, decreases in white blood cell counts below $3.0 \times 10^9/L$ were reported in 7% of patients receiving pegylated interferon- β -1a and 1% of patients receiving placebo. There was no apparent association between decreases in white blood cell counts and an increased risk of serious infections. The label will include instructions to monitor complete blood counts in the decreased peripheral blood count section of Warnings (5.7).

Autoimmune disorders: During the placebo-controlled phase of study 301, 3 of 500 placebo subjects (0.6%) and 1 of 1012 pegylated interferon- β -1a subjects (0.1%) experienced autoimmune adverse events. The adverse event in the pegylated interferon- β -1a patient was autoimmune thyroiditis. The placebo subjects experienced autoimmune thyroiditis (n=2) and rheumatoid arthritis. The numbers are too small to either confirm risk or rule it out. Section 5.8 of Warnings will suggest stopping pegylated interferon- β -1a in patients who develop a new autoimmune disorder.

Flu-like symptoms: Almost half of pegylated interferon- β -1a treated patients experienced flu-like symptoms, but none were categorized as serious adverse events. About 1% of pegylated interferon- β -1a treated patients discontinued because of flu-like symptoms.

Infections: The percentages of patients with infections (reported as both serious and non-serious adverse events) were similar among the 3 treatment groups. The label will include instructions to monitor patients for infections in section 5.7 of warnings.

Malignancies: There were 6 malignancies reported in the pegylated interferon- β -1a groups of studies 301 and 302. Dr. Boehm comments that this number is too low to make comparisons to standardized rates. He makes no conclusions about the association of pegylated interferon- β -1a with the incidence of cancer, and the label will be silent on malignancies.

Immunogenicity: The presence of antibodies at baseline was similar in all groups: $\leq 3\%$ for binding antibodies, $\leq 2\%$ for neutralizing antibodies, and $\leq 8\%$ for anti-PEG antibodies. As noted by Dr. Boehm, the applicant attributed the positive anti-IFN antibody results to false positivity or prior interferon exposure, and expected some patients to have anti-PEG antibodies at baseline given the presence of PEG in foods and medicines.

Subjects in study 301 who were antibody negative at baseline and exposed to pegylated interferon- β -1a developed antibodies infrequently during the first year: $\leq 8\%$ in each group for binding antibodies, $< 1\%$ in each group for neutralizing antibodies, and $\leq 9\%$ in each group for anti-PEG antibodies. Few additional subjects developed antibodies after the first year. Although comparisons across clinical trials have obvious limitations, the applicant noted that these percentages compare to 2 to 8% of subjects developing neutralizing antibodies during Avonex clinical trials, and 12-46% of subjects developing neutralizing antibodies in Rebif clinical trials. The labeling will state that fewer than 1% of patients developed neutralizing antibodies.

The applicant did not find that the probability of injection site reactions was increased in subjects who developed anti-pegylated interferon- β -1a or anti-PEG antibodies, although these analyses were limited by the small number of subjects with antibodies.

In summary, Drs. Boehm, Yasuda, and Marler present careful analyses of the safety of pegylated interferon- β -1a. Pegylation, a unique property of interferons for MS, does not appear to cause any safety issues; the adverse events associated with pegylated interferon- β -1a are generally consistent with those of other β interferons approved for MS.

8. Advisory Committee Meeting

Although this BLA is for a new molecular entity, there is nothing novel about the molecule, there were no concerns regarding the efficacy or safety profiles, and so there was no controversy regarding the approvability of the application. For these reasons, we decided not to take the application to an advisory committee meeting.

9. Pediatrics

There will be a waiver the pediatric study requirement 0 to <10 year-olds because such studies would be impossible or highly impracticable given the demographics of the disease. We will defer a study for patients 10 to 17 because the biologic is ready for approval for use in adults and the pediatric study has not been completed. There will be a post-marketing requirement to conduct a randomized, controlled, parallel group superiority trial to evaluate the safety and efficacy of pegylated interferon- β -1a compared to an active appropriate control for the treatment of relapsing forms of MS.

10. Pregnancy

Biogen did not study pegylated interferon- β -1a in pregnant women. The applicant will be required to conduct a prospective, observational, exposure cohort study in the United States that compares the maternal, fetal, and infant outcomes of women with MS exposed to pegylated interferon- β -1a during pregnancy to unexposed control populations – a population of women with MS who have not been exposed to pegylated interferon- β -1a in pregnancy, and a second population of women without MS. The registry will record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, and other adverse pregnancy outcomes. Infant outcomes will be assessed through at least the first year of life.

11. Recommendations

The review team has the unanimous opinion that pegylated interferon- β -1a 125 μ g SC once every 14 days should be approved for the treatment of relapsing forms of multiple sclerosis, and I agree.

A single adequate and well controlled study, study 301, provides substantial evidence of effectiveness. Peginterferon, 125 μ g SC, administered Q2W by either pre-filled syringe or auto-injector, decreased the annualized relapse rate by 36%, relative to placebo. The *p*-value for the 1^o endpoint was 0.0007, which is persuasive. Examination of various subgroups showed that the results were by-and-large generalizable, with the exception of patients with 4 or more relapses in the 3 years prior to study entry, where there was no mean treatment effect. The trial also showed evidence of effectiveness on all the pre-specified 2^o outcomes including disability progression and a number of MRI parameters.

The Division agreed to accept the results from a single adequate well controlled study, one year in duration, to constitute substantial evidence of effectiveness. This thinking is based upon the extensive accumulated experience with the effectiveness of interferons as a class, and the consistency of results between one and two years.

(b) (4)



As noted by the review team, there are no safety concerns that preclude approval. The safety of pegylated interferon- β -1a is generally consistent with that of the approved interferons, although we recognize the inherent limitations of cross-study comparisons. Pegylation does not appear to alter the risk profile of the biologic. Although some of the uncommon adverse events attributed to interferons were not reported in this development program, i.e., suicide attempts, or not reported in excess in the pegylated interferon- β -1a groups, e.g., depression, hypersensitivity reactions, cardiovascular disorders, it seems reasonable for pegylated interferon- β -1a to “inherit” various warnings extant in the other interferon labels.

A study in pediatric MS patients aged 10 to 17 years and a pregnancy registry will be conducted as postmarketing requirements. In addition, we will impose several post-marketing commitments to assure manufacturing quality.

No specific postmarketing risk management activities are needed at this time.

We have agreed with the applicant on product labeling that describes the effectiveness and safety of pegylated interferon- β -1a 125 μ g Q2W for the treatment of relapsing forms of MS, and this BLA will be approved on this date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
08/15/2014