CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Plegridy (Peginterferon) for Relapsing Multiple Sclerosis

Date	August 13, 2014
From	John Marler, MD
Subject	Cross-Discipline Team Leader Review
NDA	BLA 125499
Applicant	Biogen-Idec, Inc.
Date of Submission	May 16, 2013
PDUFA Goal Date	August 15, 2014
Proprietary Name / Established (USAN) names	Plegridy
Dose Regimen	125 micrograms every 14 days subcutaneously
Dosage forms / Strength	125 micrograms in pre-filled syringe configuration 125 micrograms in pen configuration
Proposed Indication(s)	Relapsing Multiple Sclerosis
Recommended:	Approval of pre-filled syringe configuration Approval of pen configuration

1. Introduction

Biogen-Idec, the sponsor, submitted a biologics license application (BLA) for **peginterferon** 125 µg injected every 14 days subcutaneously to treat relapsing forms of multiple sclerosis (RMS) using a pre-filled pen or autoinjector.

Peginterferon, a PEGylated interferon-β-1a, is a new medical entity that has not been previously approved. It is directly related to two interferon-β-1a drugs that are approved to treat multiple sclerosis. Avonex, approved in 1996, is interferon-β-1a for

administration intramuscularly 30 μg once per week and Rebif, approved in 2002, is interferon-β-1a for administration subcutaneously 44 μg or 22 μg three times per week. Peginterferon beta-1a is intended to maintain efficacy for MS while increasing convenience and reducing adverse effects due to frequent injections seen with other interferon products.

This review summarizes the primary and secondary reviews of all the disciplines that contributed to the review of the application. The members of the review team are listed in Table 1, below. The cross-discipline team leader recommendation for approval and risk benefit assessment are presented at the end of this document in section 13 below beginning on page 24.

Table 1 Review Team for Peginterferon for Relapsing Multiple Sclerosis

Reviewers		
Review Discipline or Group		**Reviewer**
Clinical Efficacy Review		Lawrence Rodichok, MD
Clinical Safety Review		Gerard Boehm, MD
Statistical Review		Tristan Massie, PhD
Clinical Pharmacology Review		Ta-Chen Wu, PhD
Pharmacology Toxicology Review		Richard Houghtling, PhD
Office of Biological Products/Division of Therapeutic Proteins		Ralph Bernstein, PhD; Enan Guan, PhD
Office of Compliance/Biotech Manufacturing Assessment Branch		Bo Chi, PhD; Lakshmi Narasimhan, PhD
CDRH/Office of Compliance		Felicia Brayboy
CDRH/Office of Device Evaluation		Ryan McGowan
CDRH/Office of Device Evaluation/Human Factors		Quynh Nhu Nguyen
Pediatric and Maternal Health Staff/Pediatric		Ethan Hausman, MD
Pediatric and Maternal Health/Maternal Health		Leyla Sahin, MD
Controlled Substance Staff		Lori Love, MD, PhD; Stephen Sun, MD
Office of Prescription Drug Promotion		Aline Moukhtara, RN, MPH
Office of Surveillance & Epidemiology	Division of Medication Error Prevention and Analysis	Justine Harris, RN; Liu Liu, PharmD
	Division of Drug Risk Evaluation	N/A
	Division of Risk Management	George Neyarapally, PharmD, MPH
CDER/Office of Medical Policy/Division of Medical Policy Programs		Shawna Hutchins, MPH, BSN, RN

2. Background

There are 4 interferon drug products with FDA approval to treat multiple sclerosis: Betaseron, Avonex, Rebif, and Extavia. Betaseron and Extavia are interferon beta-*1b* products while Rebif and Avonex are different formulations of interferon beta-*1a*, the same interferon pegylated to form peginterferon beta-1a (Plegridy), the subject of this review. During development peginterferon was referred to as BIIB017.

The peginterferon drug substance is a pegylated form of the Avonex drug substance, which is produced and marketed by Biogen-Idec, the applicant and manufacturer for peginterferon. Avonex is approved for treatment of relapsing MS at a dose of 30μg

per week administered intramuscularly. Peginterferon has longer duration than other forms of interferon beta. For peginterferon, the sponsor proposes subcutaneous injection of 125µg once every two weeks (for labeling, "every 14 days" is preferred by FDA instead of q 2 weeks).

In his primary clinical review, Dr. Rodichok summarized the pre-NDA regulatory activity. Biogen Idec submitted the IND to develop peginterferon for MS on April 23, 2007. After completing a single dose study (105HV101) and a multiple dose study (105HV102) in healthy volunteers, Biogen requested a Special Protocol Assessment for a phase 3 pivotal trial on December 23, 2008. FDA did not agree to the design. Biogen submitted a revised protocol that addressed FDA concerns and FDA sent an agreement letter for the revised protocol on May 3, 2010.

3. CMC/Device

Peginterferon is a biological product, a pegylated form of recombinant human interferon-β-1a expressed in Chinese hamster ovary (CHO) cells. The interferon amino acid sequence is identical to the human interferon-β-1a. The interferon molecule is pegylated with a single polyethylene glycol molecule to form the peginterferon drug substance. Biogen plans to market peginterferon in two presentations: as pre-filled syringe (Plegridy) and as an autoinjector Plegridy Pen).

The Division of Therapeutic Proteins review team consisted of Ralph Bernstein, Ennan Guan, Serge Beaucage, Tracy Denison, Juhong Liu, Amy Rosenberg, and Susan Kirchner. They have concluded that the manufacture of Plegridy and Plegridy Pen is well controlled and leads to a product that is pure and potent. The manufacturing processes are valid and consistent product is produced from different production runs. They recommend approval for human use and recommend that FDA grant the 4-year and 12-year periods of exclusivity that Biogen requests in the application.

The CMC reviewers are proposing 4 post-marketing requirements/commitments to ensure the maintenance of manufacturing quality.

Lakshmi Rani Narashimhan and team leader Patricia Hughes in the Biotech Manufacturing Assessment Branch reviewed the BLA agreed with approval from the product quality microbiology perspective.

Three CDRH review teams evaluated the pre-filled syringes and autoinjectors: engineering, compliance, and human factors. Ryan McGowan concluded that the non-human factors device design is complete and acceptable. Felicia Brayboy, in CDRH compliance found no apparent deficiencies in her desk review of compliance with medical device regulations. An inspection of the manufacturing site is pending.

4. Nonclinical Pharmacology/Toxicology

Rick A. Houghtling, Ph.D., performed the primary non-clinical pharmacology and toxicology reviews.

Peginterferon binds to the human interferon receptor subunit, IFNAR2, with an affinity similar to interferon-β-1a. Nonclinical studies tested peginterferon in guinea pigs and rhesus monkeys because they showed evidence of biological activity including increased temperature, induction of 2'-5"-oligoadenylate synthetase activity, or increased serum neopterin. Non-clinical PK studies comparing peginterferon to interferon-β-1a demonstrated higher C_{max} and AUC_{inf}, reduced clearance, reduced volume of distribution, and prolonged half life ($t_{½}$). Spleen, kidney, liver and lung had high concentrations of both pegylated and non-pegylated interferon-β-1a while muscle, brain, and spinal cord had low concentrations.

Rhesus monkeys developed high levels of binding and neutralizing antibodies to peginterferon and interferon-β-1a in tests for immunogenicity.

Toxicological study results are consistent with prior experience testing interferon-β-1a. Findings included increased body temperature and reduced circulating lymphocytes.

Interferon-β-1a as Avonex is not mutagenic. In vitro studies revealed a potential alert for genotoxicity for the pegylated form of interferon; however Ames tests and an in vitro cytogenetic assay in human lymphocytes did not demonstrate genotoxic effects.

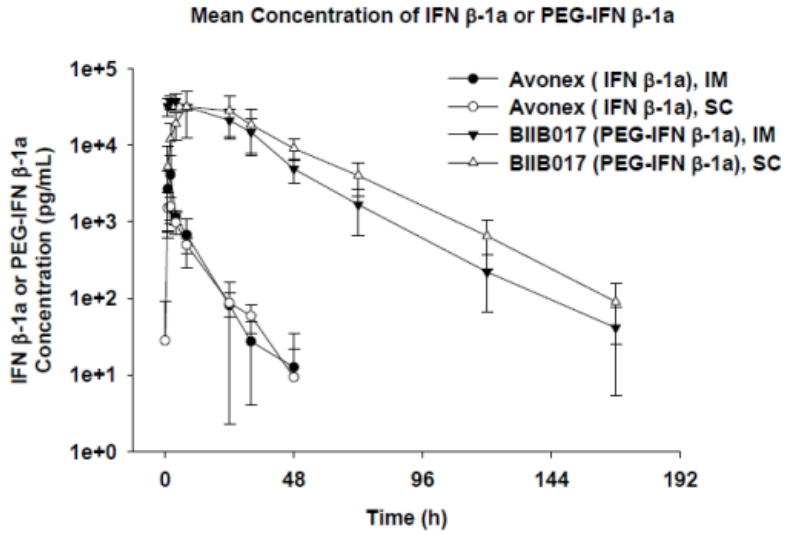
Rhesus toxicology studies show reduced lymphocyte counts, increased temperature, and increased serum neopterin. The investigators established the no observed adverse effects level (NOAEL) as 100μg/kg, approximately 31-fold greater that the maximum recommended human biweekly dose of 125μg.

Biogen decided that standard reproductive and developmental toxicity studies are not feasible because of the abortifacient and teratogenic effects described in the Avonex label for interferon-β-1a. Because of the variability of hormonal and menstrual cyclicity studies conducted for peginterferon, the non-clinical pharmacology recommendation is to use the fertility data from the Avonex label in the Plegridy label.

The non-clinical pharmacokinetic profile in rhesus monkeys is shown in Figure 1, below, copied from page 18 of Dr. Houghtling's review.

Figure 1 Non-Clinical Pharmacokinetics of Peginterferon (BIIB017)

The serum concentration-time profiles of BIIB017 and Avonex® in rhesus monkeys following a single IM or SC dose.



BIIB017 and interferon beta-1a serum concentrations in rhesus monkeys were determined using an ELISA. Data are represented as mean ± S.D. (n=5)

Dr. Houghtling concludes his review with a recommendation that the application is approvable.

In the secondary non-clinical review, Lois M. Freed, Ph.D., prefaced her comments with the qualification that the biological activity of peginterferon is limited in some species and altered by immunological responses in others. Dr. Freed concludes that additional nonclinical studies would not be useful for evaluating differences between interferon-β-1a and peginterferon. "The data provided by the sponsor demonstrate that [peginterferon] exerts effects consistent with its pharmacological activity, and provide sufficient information for labeling."

5. Clinical Pharmacology/Biopharmaceutics

To support the approval of the application, the sponsor conducted four Phase 1 clinical pharmacology studies to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of BIIB017, including three Phase 1 studies in healthy volunteers following single or repeated doses (Studies 105HV101, 105HV102, and 105HV103) and one study in subjects with renal impairment (Study 105RI101[1]). Study 105HV101 also evaluated the intramuscular (IM) route of administration for BIIB017,

[1] The process of covalently conjugating a PEG moiety to a protein can decrease renal clearance and decrease the rate of proteolysis, thus extending the terminal half-life

compared to SC administration. Study 105HV103 was designed to compare the PK profile of BIIB017 delivered by prefilled syringe (PFS) to that of the prefilled pen (PFP or AI). Additional PK characterization was carried out in Phase 3 clinical trial with MS patients (Study 105MS301).

Clinical Pharmacology Studies of Peginterferon				
Trial	**Phase[2]**	**Population**	**Route and Dose**	**Number of Subjects**
105HV101	Phase 1 RB	Healthy Volunteer	30, 63, 125, 188 μg IM and SQ	60
105HV102	Phase 1 R-DB-PC	Healthy Volunteer	63, 125, 188 μg SQ, Prefilled syringe and prefilled pen	69
105HV103	Phase 1 OL-CO	Healthy Volunteer	125 μg SQ	55
105RI101	Phase 1 OL	Subjects with Renal Impairment	63 and 125 μg SQ	35
105MS301	Phase 3 R-DB-PG-PC	Multiple Sclerosis Patients	125 μg SQ q2w and q4w	1512

Important clinical pharmacology findings in these studies are the following:[3]

-Peginterferon at doses from 63 to 188μg SC has a higher exposure and longer half-life than Avonex at the approved 30μg IM dose.
-The 125μg dose administered every 14 days does not accumulate.
-Subjects with all degrees of renal impairment showed relative increases ranging from 26 to 53% in the maximum concentration and overall drug exposure compared to normal volunteers.
-Following SC administration peginterferon was widely distributed in the body (volume of distribution 481 liters)
-The time to maximum concentration was 1 to 1.5 days.
-Clearance occurs through renal elimination, primarily, and protein catabolism, secondarily.
-Pegylation extended the terminal elimination of peginterferon to approximately twice as long as that for non-pegylated interferon-β-1a.
-The terminal half-life in MS patients was approximately 78 hours.
-The emergence of anti-drug antibodies during treatment was low.
-The peginterferon pharmacokinetics did not vary significantly between the autoinjector pen and the pre-filled syringe.

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[2] R=Randomized, B=Single Blind, DB=Double-Blind, PC=Placebo-Controlled, OL=Open-Label, CO=Crossover, PG=Parallel Group

[3] Angela Men and Ta-Chen Wu, Clinical pharmacology review (Reference ID 3441168), page 3.

The clinical pharmacology team concluded that prescribers should be informed of the potential for increased exposure to peginterferon in MS patients with impaired renal function. They found no reason to adjust the dose because of body mass index.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The primary clinical reviewer, Larry Rodichok, MD, recommends approval for Plegridy peginterferon beta-1a. Dr. Tristan Massie, the statistical reviewer, agrees that the results of the applicant's single clinical trial suggest that Plegridy is effective for reducing the relapse rate in subjects with relapsing forms of MS.

At a pre-NDA meeting on March 12, 2013, the Division of Neurology Products (DNP) agreed that the one-year results from a **single trial** could serve as substantial evidence of effectiveness.[4] That single 1516-patient trial is denoted 105MS301. Patients participated in the trial for two years, but only the first year of their participation included a placebo control group for comparison to peginterferon. This review refers to the placebo-control phase of 105MS301 as "Year One". This two-part trial design is reflected in the product labeling. The safety sections refer to two years of drug exposure. The clinical efficacy section describes only data from the one year placebo controlled phase for the q2w dose ("Year One").

Year One of trial 105MS301, a 1516-subject,[5] three-arm, 48-week, double-blind, randomized, and placebo-controlled clinical trial, compared placebo to two subcutaneous dose regimens of peginterferon beta-1a: *125μg* ***every 2 weeks*** or *125μg* ***every 4 weeks***. Investigators at 183 sites in 26 countries[6] randomized untreated multiple sclerosis patients with EDSS scores less than 5.0, two relapses in the prior 3 years, and one relapse in the prior year.

Investigators randomized the first patient on June 5, 2009. On December 1, 2010, the applicant performed a successful interim futility analysis based on MRI scans in the first 210 of the Year One trial patients. In addition, following a pre-specified

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[4] FDA: "On face and subject to full review of a complete application, we agree that the 1-year results of 105MS301 appear adequate to contribute to and potentially provide a demonstration of substantial evidence of effectiveness of BIIB017 for the treatment of relapsing MS." (FDA Meeting Minutes)

[5] Four subjects did not take study drug: modified intent-to-treat population has 1512 patients.

[6] Most patients are from Poland (386), Ukraine (189), India (170), Russian Federation (145), and Serbia (134). Other countries enrolled fewer than 100 subjects.

procedure, the applicant increased the sample size from 420 per treatment group to 500 when an interim estimate of the pooled ARR was less than anticipated. The final Part One 500-patient sample size calculation assumed an alpha of 0.05, a dropout rate of 10%, and a 32% treatment effect for the ARR.

Investigators randomized the last patient 2.5 years after the first on November 23, 2011, and locked the Year One dataset on December 7, 2012. Pertinent features of the trial population are that the mean number of relapses in the three years before baseline is 2.5[7] and the mean EDSS score is 2.5. Europeans constitute 78% of the population, North Americans 3.5%, and others 18%.

The **primary outcome** for 105MS301, Year One, is the annualized relapse rate (ARR) of confirmed relapses[8] analyzed using a negative binomial regression model for the ARR at one year with an offset for time in the trial and terms for treatment group, baseline age (<40 vs. ≥40), baseline relapse rate, and baseline EDSS (<4 vs. ≥4 or more).

The applicant's analysis shows statistically significant 27.5% and 35.6% reductions in the ARR compared to placebo for the q4w and q2w doses, respectively, with p-values 0.0114 and 0.0007. The applicant reports 422 INEC-confirmed relapses in Year One: 181, 125, and 116 in the placebo, q4w, and q2w groups. The applicant's raw count of the relapses by patient in the three treatment groups is summarized below in Figure 2, generated from the sponsor's data on page 172 of the 105MS301 study report and summarized below in Table 2.

Table 2 Relapses During Year One in 105MS301 by Treatment Group

Outcome Measure	Placebo	Peginterferon beta-1a 125µg		Total	%
		q4w	q2w		
All Relapses	213	142	132	487	
Protocol-defined Relapses	204	134	126	464	95%

[7] Therefore the crude ARR at baseline was 2.5/3.0 = 0.83.

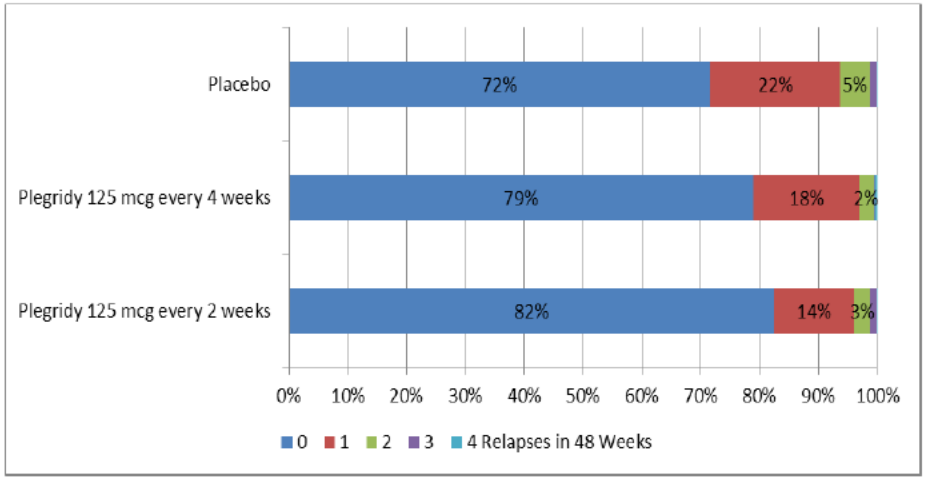
[8] Confirmed relapse events occurred when patients notified the designated treating nurse or neurologist that they had experienced the onset of new neurological symptoms within 72 hours, responses to scripted questions indicated a possible relapse, an examining neurologist found new "objective" findings on neurological examination within 5 days, and an independent neurological events committee confirmed that the event is a relapse event. "Objective" is undefined. The large effort expended to blind the examining neurologist indicates that the EDSS is vulnerable to bias. Blinding the examiner does not counteract bias introduced by patients and treating physicians.

Outcome Measure	Placebo	Peginterferon beta-1a 125µg		Total	%
		q4w	q2w		
Confirmed Relapses[9]	181	125	116	422	87%
Adjusted ARR ** (95% CI)	0.397 (.328 to 0.481)	0.288 (0.234 to 0.355)	0.256 (0.205 to 0.318)		
Unadjusted ARR	0.407	0.288	0.266		
Rate Ratio		0.725	0.644		
Rate Reduction		27.5%	35.6%		
p-value		0.0114	0.0007		

** Protocol-defined primary outcome

For comparison, the ARR was 0.67 for Avonex versus 0.82 for placebo in Study 1 on the Avonex label, an 18% relative reduction in ARR and a 15% absolute reduction.

Figure 2 Percent of Patients with 0, 1, 2, 3, or 4 Relapses[10]



The protocol and statistical analysis plan (SAP) specify the order for analyzing the results for the three **secondary outcomes:**

1. Number of new or newly enlarging T2 hyperintense lesions at 48 weeks.

[9] from page 172 of the sponsor's study report 03-15-report-body.pdf

[10] Data from Table 28, Page 175 of applicant's study report for 105MS301.

2. Proportion of subjects relapsed at 48 weeks,
3. Progression of disability as measured by EDSS Score at week 48.

The analysis of secondary outcomes maintains statistical significance for a p-value of 0.05 despite multiple tests by pre-specifying a hierarchy of outcomes then testing each outcome in hierarchical order for the two-week dose and then the four-week dose. Formal testing in the hierarchy stops at the first analysis that fails to demonstrate a statistically significant difference in favor of treatment. As it turns out, all the secondary analyses show a statistically significant benefit with both treatment regimens. See Table 3, below.

Table 3 Applicant's Analysis of Secondary Outcomes for Year One of 105MS301 Trial

Secondary Outcomes	Placebo	Peginterferon 125µg	
		q4w	q2w
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%
p-value		0.0008	0.0001
Proportion Relapsed at 48 Months (Year 1)	0.291	0.222	0.187
Reduction in Risk of Relapse		26%	39%
p-value		0.0200	0.0003
Disability Progression by EDSS at 48 Weeks – Number of Subjects	50	31	31
Percent of subjects	10%	6%	6%
Risk Reduction		38%	38%
p-value		0.0380	0.0383

The SAP specifies use of a Cox proportional hazards model to estimate the *proportion of subjects relapsed at 48 weeks* using the time to first relapse for each patient. The model has a term for treatment and adjusts for the baseline relapse rate, age (<40 vs. ≥40), presence of Gd enhancing lesions at baseline, and EDSS (4 or ≥4). The SAP defines baseline relapse rate to be the number of relapses over the 3 years prior to trial entry. Figure 3 is the Kaplan-Meier plot of the time to first relapse.[11] Note that the

[11] Copied from Dr. Massie's statistical review of statistics and also found on page 183/4864 of CSR.

y-axis only goes from 0 to 40%; i.e., the graph emphasizes the relative difference and deemphasizes the fact that even in the placebo group 72% of the patients were relapse-free for the entire year.

Figure 3 Kaplan-Meier Plot Showing Time to First INEC-confirmed Relapse

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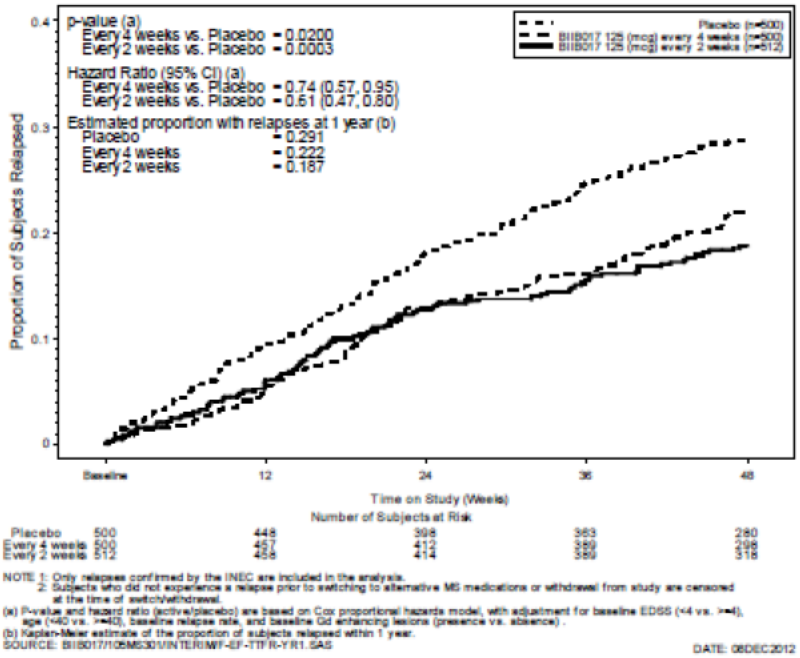


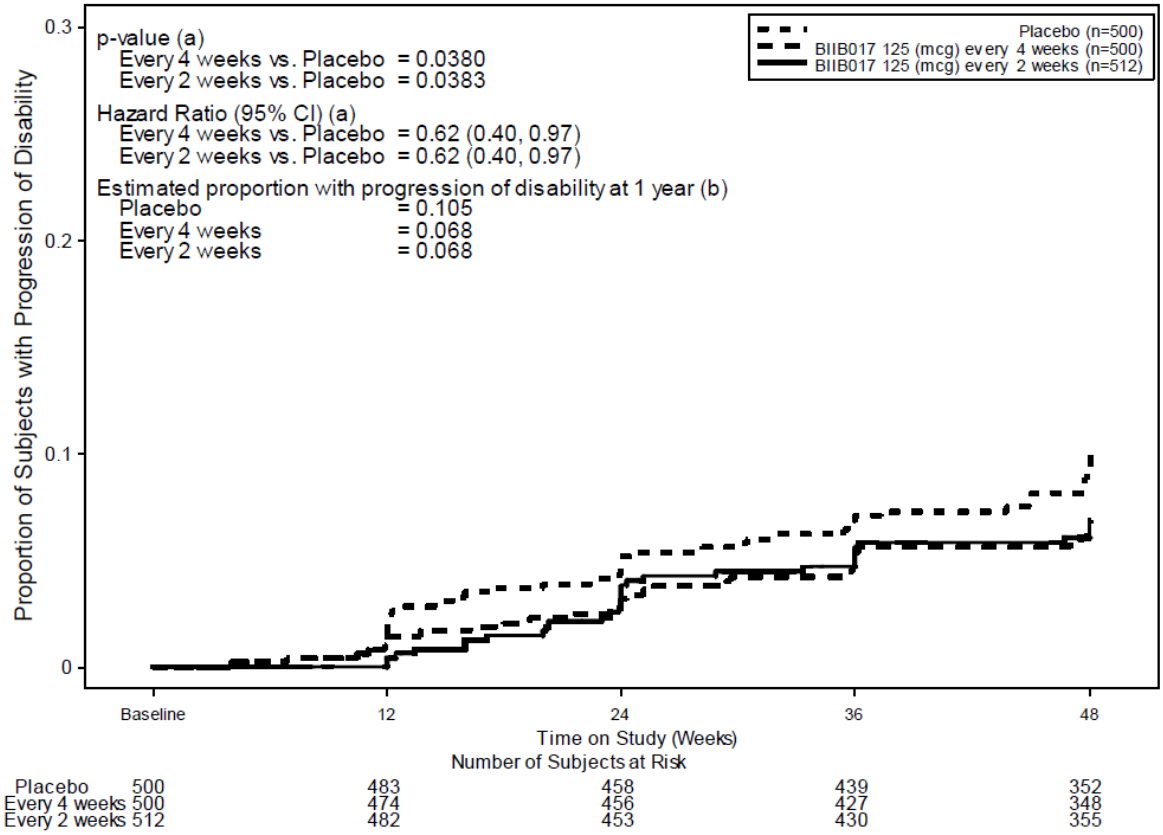
The *risk of progression of disability confirmed over 12 weeks* during the 48 weeks of Year One is 38% less than placebo with both peginterferon beta-1a every 2 and every 4 weeks (p=0.0380 for both). 10.5% of placebo patients and 6.8% of the subjects in both peginterferon groups experienced disability progression.

In his review, Dr. Massie explains that the data for determining the onset of progression of disability are EDSS scores at baseline 12, 24, 36 and 48 week visits as well as unscheduled EDSS examinations. An examining neurologist who did not treat the patient determined these scores. Disability progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. Progression is defined as an increase above the baseline EDSS by at least 1.5 or 1.0 point depending on whether the baseline is 0 or 1, respectively. Tentative EDSS progression begins at the time of a scheduled or unscheduled study visit. Continued progression at the next study visit 74 days from the initial tentative onset confirms the occurrence of a 12-week progression of disability event. No data is imputed.

The SAP specifies use of a Cox proportional hazards model to estimate the time to onset of sustained disability progression, adjusting for the baseline EDSS score as a

continuous variable, and age (<40 versus ≥40 years). The model did not adjust for the baseline relapse rate. Figure 4 shows the corresponding Kaplan-Meier plot.[12]

Figure 4 Time to Start of 12 Week Sustained Disability Progression



NOTE: Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.
(a) P-value and hazard ratio (active/placebo) are based on a Cox proportional hazards model, with adjustment for baseline EDSS and age (<40 vs. >=40).
(b) Kaplan-Meier estimate of the proportion of subjects with progression within 1 year.

The protocol schedule calls for MRI scans with and without gadolinium (Gd) contrast at screening, week 24, week 48, and week 96 visits. Qualified MRI readers at a reading center reviewed all scans. The SAP specifies imputation rules for missing MRI data. If the Week 48 MRI data is missing, the analysis uses data carried forward from Week 24. If there is no Week 24 MRI scan data to carry forward for a patient, the analysis uses the mean from the Week 48 scans of patients in the same treatment group. Dr. Massie did an analysis without imputation and saw little difference. He concluded that the imputation had little effect on the MRI results.

[12] CSR page 186/4864.

Table 4, below, summarizes the tertiary MRI outcomes. For the high dose (q2w), all the measurements show a very significant difference at 48 weeks except the magnetic transfer ratio (MTR) and "brain atrophy." The relationship to clinical outcomes is one of correlation and not surrogacy. MRI outcomes may be measuring collateral or off-target effects of the medication. The most that can be said is that these results do not cast doubt on the beneficial effect seen in the primary clinical outcomes.

Table 4 MRI Outcomes at 48 Weeks by Treatment Group

48-Week MRI Outcomes a 48 Weeks[13] Mean Median p-value			
MRI Outcome	**Placebo**	**q4w**	**q2w**
Subjects	500	500	512
Scans (%)	476 (95%)	462 (92%)	457 (89%)
New Active Lesions	7.0 3.0	5.5 2.0 0.0006	2.6 1.0 <0.0001
Gd-Enhancing Lesions	1.4 0	0.9 0 .0738	0.2 0 <.0001
New T1 Hypointense	3.8 1	3.1 1 0.0815	1.8 0 <0.0001
T2 Hyperintense Lesion Volume Change from Baseline	0.7746 0.2955	0.0565 0.0150 <0.0001	-0.2584 -0.1410 <0.0001
T1 Hypointense Lesion Volume Change from Baseline	0.5428 0.2130	0.5713 0.1680 <0.0001	0.3150 0.0840 <0.0001
Volume of Gd-Enhancing Lesions Change from Baseline	0.0594 0.00	-0.1277 0.00 <0.0001	-0.1279 0.00 <0.0001
Brain Atrophy and MTR	No Changes Seen Between Groups		

For the higher q2w dose, the MRI, secondary, and primary endpoints are all consistently positive except for brain atrophy and magnetization transfer ratio. Exploratory clinical outcomes including the SDMT, the PASAT3, the MSFC, the 25-

[13] Summarized by CTDL from CSR pages 215-235/4864 and Larry Rodichok, MD, Clinical Review, pages 59ff.

Foot Walk showed no findings with low p-values. Patient reported outcomes, the EQ-5D, and the MSIS-29, showed no significant differences over 48 weeks.

Trial quality rests primarily on the double-blind design.

8. Safety

Gerald Boehm, MD, reviewed this submission and found no serious issues related to safety that might prevent approval. The review identifies no significant adverse events not anticipated with approved forms of interferon or any event attributed to pegylation. Likewise, the safety review team finds it reasonable to expect adverse events associated with approved interferons to also occur in MS patients taking peginterferon even if there was no safety signal during the pre-approval clinical development period.

Exposure

The applicant performed 6 trials during the development of peginterferon. They enrolled 1735 individuals and exposed 1664 of them to peginterferon. See Table 5, below.

Table 5 Number of Participants in All Trials of Clinical Development Program for Peginterferon

Trial	Design	Subjects
105HV101	IM and SQ Single Dose Safety and Tolerability	60 volunteers
105HV102	SQ Multiple Dose Safety and Tolerability	69 volunteers
105HV103	Device Safety and Tolerability	55 volunteers
105RI101	Renal Impairment	35 volunteers
105MS301 and 302	Efficacy	1516 MS patients
Total		**1735** subjects

In their submission Biogen-Idec reports that they exposed 1664 of the 1735 trial enrollees to one or more doses of peginterferon in the 6 trials. Of these 167 did not have multiple sclerosis: 138 were healthy volunteers, 29 had renal impairment. Trials 301 and 302 provide a total of 1203 patient-years of exposure to the q2w dose. Of the 1664, 1468 (88%) are from the 301 and 302 trials.

Part Two of the 301 trial and the entire 302 trial contribute to the safety data but are not considered in the efficacy review because there is no placebo group. After 48 weeks, patients taking placebo in Year One of the 301 trial were re-randomized to blinded treatment with either q4w or q2w dosing with peginterferon. At week 96, the end of the 301 trial, subjects could enroll in the 302 trial and continue the same blinded treatment they were taking in Part Two of the 301 trial. Table 4, adapted from the table on page 15 of 82 in Dr. Boehm's review, summarizes exposure to

peginterferon in Year One of 301, Part Two of 301, and 302. The data in the table is from the applicant's 120 day Safety Update.

Table 6 Summary of duration of exposure to peginterferon in 301 and 302 trials

Duration of exposure	Number of Patients		
	q4w	q2w	Total
At least 1 dose	728	740	1468
>=24 weeks	680	670	1350
>=48 week (End of Year One, 301)s	594	588	1182
>=96 weeks (End of Part Two, 301)	314	334	648
>=144 weeks	76	71	147
Total person years	**1183.2**	**1202.6**	**2385.7**

Deaths

Dr. Boehm concluded that the safety data did not suggest an increased mortality risk in subjects exposed to peginterferon. For a detailed description of each reported death see page 19 and following of Dr. Boehm's review.

At the time of the 120-day report, there were 8 known deaths. In total, 6 subjects who took peginterferon died during the 6 trials, all of them during 105MS301: There were 4 deaths in Year One, 2 of 500 (0.4%) in the placebo and 2 of 1012 (0.2%) in the peginterferon groups, and 4 deaths in Part Two (all subjects on peginterferon).

The deaths in subjects who took peginterferon are attributed to sepsis (2), unknown cause (2), oral cancer, and motor vehicle accident.

After they submitted the 120-day report, Biogen-Idec reported 2 additional deaths in subjects exposed to peginterferon: one death due to sepsis from either bedsores or a urinary tract infection, another due to severe MS and recurrent pneumonia following treatment for meningitis.

In her secondary review Dr. Yasuda agrees with Dr. Boehm the safety data did not suggest that peginterferon caused an increase in mortality risk because there were few events and no cluster of unusual causes.

Serious adverse events

In his review, Dr. Boehm concludes that, except for MS relapse, serious adverse events (SAEs) occurred infrequently during the 6 trials submitted with the BLA. Treatment with peginterferon did not increase the risk of SAEs in the placebo-controlled Year One of the 301 trial. In all trials, the individual types of SAEs reported in the BLA appear consistent with the safety profile of approved interferon beta-1a products.

Table 7, immediately below, summarizes common SAEs possibly related to treatment with peginterferon in the placebo-controlled portion of the 301 trial.

Table 7 SAEs more frequent than in peginterferon than placebo group and occurring in 2 or more peginterferon patients in Year One of the 105MS301 trial.

SAE % (n)	Placebo	BIIB017 125 mcg SC		
		q2w	q4 weeks	Total
	N=500	N=500	N=512	N=1012
Any SAE	15% (76)	14% (71)	11% (55)	12% (126)
Dengue fever	0	<1% (1)	<1% (1)	<1% (2)
Multiple sclerosis	0	<1% (1)	<1% (1)	<1% (2)
Paraparesis	0	<1% (1)	<1% (1)	<1% (2)
Intervertebral disc disorder	0	<1% (1)	<1% (1)	<1% (2)

Discontinuations due to adverse events (AEs)

Adverse events led to discontinuation of the study treatment more often in the placebo than the peginterferon group. Overall, 92 of 1468 patients (6%) in the 301 and 302 trials discontinued peginterferon because of adverse events. Two subjects in the early phase trials discontinued participation because of adverse events.[14] One had an elevated AST level, another developed lymphopenia during the trial.

Table 8 Table of 75 More Frequent and Potentially Important AEs Leading to Discontinuation in Phase 3 Trials

AEs Leading to Discontinuation in 301 and 302 Trials	N
influenza like illness	21
pyrexia	8
injection site erythema	7
ALT increased	6
multiple sclerosis relapse	5
depression	4
suicidal ideation	4
fatigue	3
headache	3
injection site pain	3
angioedema	2
thrombocytopenia	2
transaminases increased	2
acute hepatic failure	1
anaphylactic reaction	1
drug induced liver injury	1
hemoglobin decreased	1
hepatitis toxic	1
All	**75**

[14] Safety Review. Gerald Boehm, MD, page 25

Significant Adverse Events

The BLA contained additional analyses for adverse events known to be of concern for the interferon class:

flu-like symptoms
injection site reactions
infections
cardiovascular disorders
hepatic disorders
autoimmune disorders
hypersensitivity events
malignancies
seizures
depression or suicide.

Experience with each of these "significant" adverse events is summarized in the paragraphs that follow in this section.

None of the *flu-like symptoms* were serious.

Over 60% of peginterferon-treated subjects reported *injection site reactions* (ISRs), mostly erythema, pain, and pruritus. Two patients reported serious ISRs. One patient developed pain, erythema, and pruritus in an area 20 by 10 centimeters on the thigh. The other developed gangrenous cellulitis and required hospitalization for treatment with IV antibiotics. There is no apparent relation of the incidence of ISRs to the presence of antibodies to PEG. The incidence of ISRs is comparable to that with Rebif and Avonex.

In his review, Dr. Boehm concludes that peginterferon did not increase the risk of *infections*, including opportunistic infections, compared to placebo. The 39% rate of infection in the placebo group actually exceeded the 37% rate in the peginterferon group. Only urinary tract infection, oral herpes, and cystitis occurred more frequently in patients taking peginterferon than taking placebo.

Dr. Boehm also reports that there is no apparent increase in *cardiovascular* disorders or autoimmune disorders due to peginterferon. On the other hand, there is insufficient evidence that the possible association of these risks with interferon beta-1a for other approved products does not also apply to peginterferon.

Approved beta interferon MS drugs carry a risk of h*epatic disorders* including severe hepatic injury. Safety data in the BLA suggest peginterferon carries similar risks. If patients took peginterferon they had a greater risk of aminotransferase elevations more than 3x the upper limit of normal (ULN) compared to placebo patients. In the

301 trial report there are summaries of two "Hy's Law" cases[15] in patients who took peginterferon, but no deaths due to liver failure and no liver transplants. The risks for aminotransferase elevations and hepatic injury mirror the hepatic disorders that accompany other beta interferons approved for MS.

In the 301 trial, 4 patients experienced serious hepatic adverse events and 6 discontinued the study drug because of hepatic adverse events.

Table 9 shows the abnormal liver function test results for ALT, AST, and total bilirubin. In general elevations of all degrees for ALT, AST, and bilirubin occurred twice as often in the peginterferon group compared to the placebo group.

Table 9 Abnormal ALT, AST, and TBili Outlier Results in 301 Trial - Year One

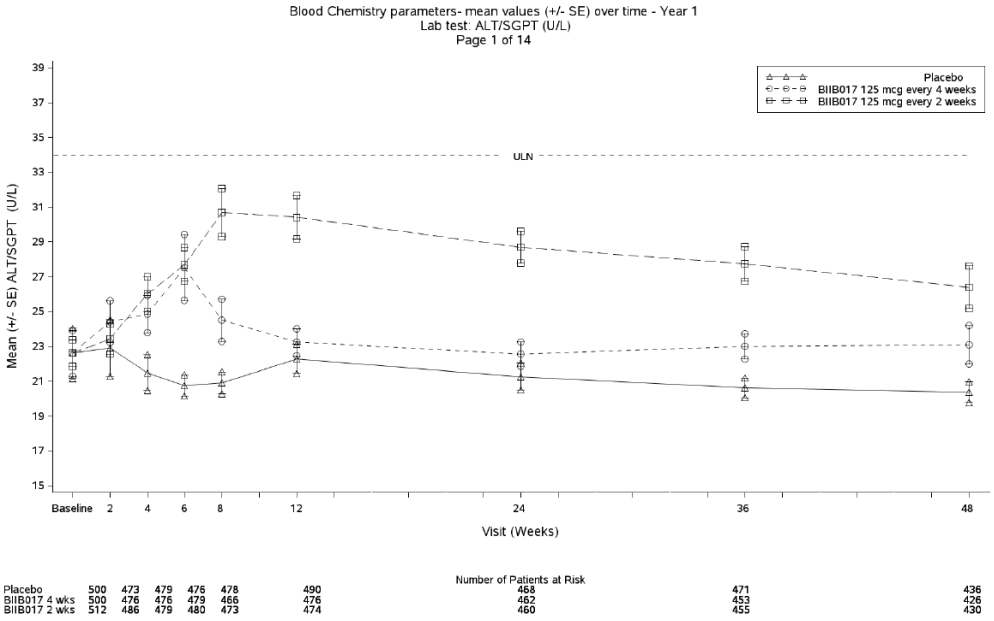
Test and range	Treatment			
	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	Both
	N=500	N=500	N=512	N=1012
ALT				
>ULN	26% (129)	35% (173)	50% (251)	42% (424)
>=3xULN	3% (14)	4% (18)	7% (36)	5% (54)
>5xULN	1% (5)	2% (9)	2% (12)	2% (21)
>10xULN	<1% (2)	<1% (3)	<1% (3)	<1% (6)
>20xULN	0	<1% (1)	0	<1% (1)
AST				
>ULN	15% (73)	19% (92)	33% (166)	26% (258)
>=3xULN	1% (7)	2% (11)	2% (12)	2% (23)
>5xULN	<1% (3)	<1% (4)	<1% (3)	<1% (7)
>10xULN	0	<1% (3)	0	<1% (3)
>20xULN	0	<1% (1)	0	<1% (1)
Total bilirubin				
>ULN	7% (36)	9% (46)	8% (39)	8% (85)
>1.5xULN	3% (13)	2% (10)	3% (14)	2% (24)
>2xULN	<1% (2)	<1% (4)	<1% (2)	<1% (6)

Dr. Boehm included figure 3 (it is captioned below as Figure 5 in this review) from the applicant's submission to display the time course of the mean AST/SGPT ratio with peginterferon in the placebo-controlled portion of the 301 trial.

[15] aminotransferase elevations above 3 x ULN and total bilirubin more than > 2 x ULN

Figure 5 Means Values for Ratio of ALT to SGPT over 48 Weeks in 301 Trial

Figure 3: Blood Chemistry Parameters - Mean Values (±SE) Over Time – Year 1



Dr. Boehm's safety review concludes that the risks for aminotransferase elevations and hepatic injury with peginterferon are comparable to the risks with other beta interferons approved for MS. Data submitted cannot rule out small increases in risk for hepatic injury peginterferon compared to other beta interferons. He concludes that the peginterferon label should include a Warnings and Precaution statement describing the liver injury risk. I agree.

There were 6 *malignancies* in the peginterferon groups of the 301 and 302 trials. Dr. Boehm comments that this number is too low to make comparisons to standardized rates. He makes no conclusions about the association of peginterferon with the incidence of cancer.

There are slightly more reports of *seizures* in the q2w peginterferon group compared to the q4w and placebo groups. Again, Dr. Boehm comments that the numbers are too small to draw any meaningful conclusions. Likewise, he sees no reason that the precautionary statement in the labels of other interferons would not apply to peginterferon.

Biogen found no strong evidence that there is an increased risk of *depression or suicide* with peginterferon compared to placebo. There were no completed suicides and no reports of suicide attempts in any patients in the 6 trials reported in the BLA. The 120-day Safety Update showed that the incidence of suicide related AEs was 11% and

10% in the peginterferon q4w and q2w groups, respectively. Dr. Boehm included Table 10, below, in his review. Serious depression occurred in 1 patient in the q4w and 2 patients in the q2w group. Depression and suicidal ideation led to withdrawal of 4 patients in the q4w group and 3 patients in the q2w group. Depression and suicide related AEs were similar in placebo and peginterferon groups.

Table 10 Incidence of Depression and Suicide-Related AEs in Placebo-Controlled Portion of 301 Trial

Incidence of Depression and Suicide-Related AEs Placebo-Controlled Year One 48-Minth 105MS301 Trial[16]				
AE	Treatment Group			
	Placebo	Peginterferon		
		q4w	q2w	Total
	N=500	N=500	N=512	N=1012
Depression	4% (20)	5% (25)	4% (21)	5% (46)
Depressed mood	3% (14)	2% (12)	1% (7)	2% (19)
Affect lability	<1% (2)	0	<1% (5)	<1% (5)
Mood altered	<1% (1)	<1% (1)	<1% (4)	<1% (5)
Suicidal ideation	<1% (1)	<1% (2)	<1% (2)	<1% (4)
Mood swings	<1% (1)	<1% (1)	<1% (1)	<1% (2)
Dysphoria	0	<1% (1)	0	<1% (1)
Initial insomnia	0	0	<1% (1)	<1% (1)
Major depression	<1% (1)	0	<1% (1)	<1% (1)
Depressive symptom	<1% (1)	0	0	0
Memory impairment	<1% (1)	<1% (4)	<1% (4)	<1% (8)
Disturbance in attention	<1% (2)	<1% (2)	0	<1% (2)
Crying	<1% (1)	0	0	0

Common adverse events

Table 11 lists the most common adverse events in the 48-month long placebo-controlled part of trial 301 (Year One).

Table 11 AEs at least twice as common in peginterferon group than in placebo group and occurring in more than 2% of subjects in any treatment group of Year One of Trial 301.

AE	Placebo	BIIB017		
		q4w	q2w	Total
	N=500	N=500	N=512	N=1012
Injection site erythema	7% (33)	56% (282)	62% (315)	59% (597)
Influenza like illness	13% (63)	47% (234)	47% (239)	47% (473)
Pyrexia	15% (76)	44% (218)	45% (228)	44% (446)
Myalgia	6% (30)	19% (97)	19% (97)	19% (194)
Chills	5% (23)	18% (92)	17% (88)	18% (180)

[16] Safety Review, page 55, and CSR, Table 64

AE	Placebo	BIIB017		
		q4w	q2w	Total
	N=500	N=500	N=512	N=1012
Injection site pain	3% (15)	13% (67)	15% (77)	14% (144)
Injection site pruritus	1% (6)	11% (56)	13% (68)	12% (124)
Body temperature increased	3% (14)	7% (33)	6% (31)	6% (64)
Vomiting	2% (11)	7% (37)	5% (26)	6% (63)
Pain	3% (16)	6% (29)	5% (25)	5% (54)
ALT increased	3% (13)	4% (19)	6% (29)	5% (48)
Hyperthermia	1% (6)	5% (26)	4% (21)	5% (47)
AST increased	2% (8)	3% (13)	4% (18)	3% (31)
Pruritus	1% (6)	2% (12)	4% (19)	3% (31)
GGT increased	1% (7)	3% (14)	3% (15)	3% (29)
Injection site warmth	0	2% (11)	3% (16)	3% (27)
Oral herpes	1% (7)	3% (14)	2% (12)	3% (26)
Injection site hematoma	1% (7)	2% (8)	3% (15)	2% (23)
Somnolence	1% (5)	3% (13)	2% (10)	2% (23)
Malaise	1% (5)	3% (13)	1% (7)	2% (20)
Tremor	1% (6)	2% (10)	2% (9)	2% (19)
Blood glucose increased	<1% (4)	2% (8)	2% (10)	2% (18)
Feeling cold	<1% (2)	2% (9)	2% (9)	2% (18)
Injection site swelling	<1% (1)	2% (9)	2% (9)	2% (18)
Alopecia	1% (6)	2% (9)	2% (8)	2% (17)
Lymphadenopathy	0	2% (12)	<1% (5)	2% (17)
Bone pain	<1% (1)	1% (5)	2% (11)	2% (16)
Balance disorder	1% (7)	1% (6)	2% (9)	1% (15)
Cystitis	<1% (2)	1% (6)	2% (9)	1% (15)
Visual impairment	1% (5)	1% (6)	2% (9)	1% (15)
Hemoglobin decreased	<1% (3)	<1% (4)	2% (10)	1% (14)

Laboratory tests

There is evidence from the 301 trial that peginterferon reduces *blood cell counts* for neutrophils, lymphocytes, erythrocytes, and platelets. In his review, Dr. Boehm concludes that "peginterferon-treated patients had higher risks for potentially clinically significant low lymphocyte, neutrophil, and erythrocyte counts. One patient had an SAE related to a low platelet count and another discontinued the trial because of a non-serious low platelet count.

Blood chemistry tests and TSH levels were not different in the placebo and peginterferon groups.

Urinalysis tests did not differ significantly between placebo and peginterferon groups.

Vital Signs and Electrocardiograms (ECGs)

There were no significant differences between treatment groups for any of the vital signs. ECGs showed no meaningful group differences for ECG parameters.

Immunogenicity

As noted above in the section on clinical pharmacology, the emergence of anti-drug antibodies during treatment was low. The sponsor measured persistent and neutralizing as well as all binding antibodies in the phase 3 trials. For consistency with the approved labels with other interferons, I recommend that only the percent of patients developing neutralizing antibodies be reported in the peginterferon label (less than one percent). The clinical significance of antibodies to the PEG moeity is unknown. Therefore, I recommend that only the incidence (7%) be reported in the label.

Special safety concerns

There are no special safety concerns that relate to approvability. There are adverse events of special interest (see Significant AE section above), but careful evaluation showed no need for concern.

Discussion of secondaryary reviewer's comments and conclusions

Sally Jo Yasuda, Pharm.D., wrote the secondary safety review. She agreed with Dr. Boehm that there are no safety issues that preclude approval. She finds that the adverse events associated with peginterferon are generally consistent with those of other beta interferons approved for MS. She agrees with Dr. Boehm's recommendation that all post-marketing reports include discussions of hepatic toxicity, hematological toxicity, autoimmune disorders, depression and suicide, infections, and cardiac toxicity.

9. Advisory Committee Meeting

There was no advisory committee meeting for this submission.

10. Pediatrics

The Division of Neurological Products (DNP) consulted the Pediatric and Maternal Health Staff (PMHS) to review the submission, review paperwork required by the Pediatric Review Committee, and assist with pediatric issues. Ethan Hausman, MD, from PMHS attended team meetings, reviewed the synopsis of the intended pediatric plan, and made recommendations.

The PeRC Pediatric Research Equity Act (PREA) Subcommittee discussed the need for pediatric studies of peginterferon on February 26, 2014. The Division proposed a waiver for patients 0 to 9 years of age and deferral for patients 10 to 17 years of age. The Subcommittee agreed with a partial waiver in patients ages birth to less than 10

years because studies would be impossible or highly impracticable and recommended the earliest possible start date for the studies in children 10 and older.

The Division has established a timeline for performance of the studies that is consistent with the goal dates required for completion of pediatric studies for other recently approved MS products. Proposed pediatric study requirements are shown below.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

(b) (4)

Timeline
a. Protocol submission: May 16, 2015
b. Study Completion: May 16, 2018
c. Study Submission: August 16, 2019

11. Other Relevant Regulatory Issues

None.

12. Labeling

The sponsor submitted proposed labeling. The review team agreed in principle to include all the warnings and contraindications in the labels for other β interferon products for MS. For that reason, throughout the label, each warning or contraindication heading is followed first by a summary of experience for all interferon β products and then, second, a description of the peginterferon-specific clinical trial experience from the two year experience from the 105MS301 randomized trial.

Sue Liu, PharmD, Irene Z. Chan, PharmD, and Carol Holquist, PharmD, reviewed the proprietary names "Plegridy" and "Plegridy Pen". They determined that the names are acceptable.

Shawna Hutchins, RN, Aline Moukhtara RN, LaShawn Griffiths, RN, Melissa Hulett, RN, and Mathilda Fienkeng, PharmD, reviewed the proposed Medication Guide. They concluded that, with the recommended changes, that Medication Guide was acceptable.

The package insert and carton and container labeling is pending.

13. CDTL Recommendations/Risk Benefit Assessment

In agreement with the entire review team, I recommend approval for peginterferon 125µg SQ once every 14 days for the treatment of relapsing forms of multiple sclerosis.

There is strong evidence of effectiveness and safety from a single adequate and well-controlled clinical trial that confirms relative benefit of the 14-day 125µg subcutaneous dosing regimen compared to placebo. The trial results show evidence of effectiveness on the primary outcome, relapse rate, as well as all the pre-specified secondary outcomes including MRI and disability progression. In addition, the efficacy and adverse event profile of peginterferon are similar to those of the approved beta interferons. The results of the trial itself are highly consistent among the different pre-specified outcomes and with other trials of interferon beta drugs approved to treat multiple sclerosis. For beta interferons to treat relapsing multiple sclerosis, DNP will generally accept positive results from a single adequate and well-controlled trial because of the extensive post-marketing experience with these drugs since the first was approved in 1993 and because of the confidence that has developed in the clinical trial methodology.

Of the two doses, q2w dosing is consistently more effective across all pre-specified outcomes than q4w dosing. There does not appear to be a significant safety advantage to the lower (less frequent) q4w dosage regimen.

The overall the quality of the trial data appears good. Even though common adverse events such as flu symptoms and injection site reactions may have informed patients about treatment assignment, the adverse effects were reported in both the placebo and active treatment arms of the efficacy trial. There was no apparent significant bias in the drop-out rates or protocol compliance. There was significant financial compensation from the sponsor for many US investigators but the same investigators randomized fewer than 12% of patients in the trial. Dr. Rodichok concludes in his review that it is doubtful that compensation had a significant impact on the overall trial results.

In regard to assessment of the balance between risk and benefit, the 105MS301 Year One trial results suggest that the risk-benefit ratio of peginterferon is very similar to the risk/benefit ratio for the other approved beta interferons. Pegylation does not appear to alter the adverse effects or the effectiveness of the interferon component.

I also recommend post-marketing requirements for a pediatric development program in patients 10-17 years of age and a pregnancy registry. In addition, CMC will impose several post-marketing requirements to assure manufacturing quality.

Additional Table Generated by CDTL

105MS301 Trial Execution and Completion

Milestones				
Trial 105MS301 Milestone	Date of Milestone	Time From Randomization of First Subject		
		Days	Months	Years
301 protocol approval version 1	03/13/2009	-84	-2.8	-0.23
301 Year 1 first patient randomized	06/05/2009	0	0.0	0.00
301 DSMC meeting and teleconference 1	07/22/2009	47	1.6	0.13
301 protocol amendment version 2	10/27/2009	144	4.8	0.39
301 protocol amendment version 3	04/16/2010	315	10.5	0.86
301 protocol amendment version 3.1	04/16/2010	315	10.5	0.86
301 Year 2 first patient randomized	05/07/2010	336	11.2	0.92
301 DSMC meeting and teleconference 2	06/30/2010	390	13.0	1.07
301 statistical analysis plan approval	09/21/2010	473	15.8	1.30
301 futility analysis data lock	10/29/2010	511	17.0	1.40
301 DSMC meeting and teleconference 3	12/01/2010	544	18.1	1.49
301 futility analysis	12/01/2010	544	18.1	1.49
301 protocol amendment version 4	03/14/2011	647	21.6	1.77
301 protocol amendment version 4.1	03/14/2011	647	21.6	1.77
301 first patient completes follow-up	04/11/2011	675	22.5	1.85
301 DSMC meeting and teleconference 4	05/25/2011	719	24.0	1.97
301 Year 1 last patient randomized	11/23/2011	901	30.0	2.47
301 DSMC meeting and teleconference 5	11/30/2011	908	30.3	2.49
301 protocol amendment version 5	03/27/2012	1026	34.2	2.81
301 protocol amendment version 5.1	03/27/2012	1026	34.2	2.81
301 changes to statistical analysis plan	05/01/2012	1061	35.4	2.90
301 DSMC meeting and teleconference 6	06/15/2012	1106	36.9	3.03
301 Year 2 last patient randomized	10/24/2012	1237	41.2	3.39
301 one year analysis data lock	12/07/2012	1281	42.7	3.51
301 one year analysis	12/16/2012	1290	43.0	3.53

Part Two, starting at week 48, had no placebo group. Of the 1512 subjects in Year One, 1332 enrolled in Part Two. Investigators re-randomized Year One patients on placebo to either peginterferon every two or every four weeks at the 48-week follow-up visit. Subjects not on placebo in Year One continued the same treatment in Part 2. At the time the applicant submitted this NDA, the last patient to enter Part Two of 105MS301 had not completed the trial.

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/s/

JOHN R MARLER
08/13/2014