CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125499Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Billy Dunn, MD
Subject	Division Director Summary Review
NDA/BLA # Supplement #	125499
Applicant Name	Biogen Idec, Inc.
Date of Submission	5/16/13
PDUFA Goal Date	8/15/14
Proprietary Name / Established (USAN) Name	Plegridy/peginterferon beta-1a
Dosage Forms / Strength	Injection/125 micrograms
Proposed Indication(s)	Treatment of relapsing forms of multiple sclerosis
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Larry Rodichok, MD
Statistical Review	Tristan Massie, PhD
Pharmacology Toxicology Review	Rick Houghtling, PhD
CMC Review/OBP Review	Ralph Bernstein, PhD; Ennan Guan, PhD; Serge Beaucage, PhD; Tracy Denison, PhD; Bo Chi, PhD; Lakshmi Narasimhan, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Ta-Chen Wu, PhD; Xiaofeng Wang, PhD
OPDP	Aline Moukhtara, RN, MPH
OSI	N/A
CDTL Review	John Marler, MD
OSE/DMEPA	Justine Harris, RN; Liu Liu, PharmD
OSE/DDRE	N/A
OSE/DRISK	George Neyarapally, PharmD
OMP/DMPP	Shawna Hutchins, PharmD
PMHS	Ethan Hausman, MD
SEALD	N/A
Other	Ryan McGowan/Jason To (CDRH Engineering); QuynhNhu Nguyen (CDRH Human Factors); Lori Love, MD, PhD/Stephen Sun, MD (CSS)

OND=Office of New Drugs
OPDP=Office of Prescription Drug Promotion
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CDRH=Center for Devices and Radiologic Health
PMHS=Pediatric and Maternal Health Staff
DDRE=Division of Drug Risk Evaluation
DRISK=Division of Risk Management
OMP=Office of Medical Policy
DMPP=Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling Development
CSS=Controlled Substance Staff

1. Introduction

Avonex (interferon beta-1a) is an approved drug product for the treatment of relapsing forms of multiple sclerosis (MS).

Biogen Idec, Inc., (Biogen) has submitted an application for a new pegylated form of Avonex, peginterferon beta-1a (Plegridy; in this memo may also be described as "pIFN"). The interferon component of this new form is identical to Avonex. Pegylation, by decreasing renal clearance and proteolysis resulting in a longer half-life, allows for less frequent dosing and is therefore more convenient. While Avonex is given once weekly, the sponsor proposes a dosing regimen for Plegridy of one dose every two weeks. This new regimen is supported by the results of one primary randomized, double-blind, placebo-controlled trial in patients with relapsing-remitting MS (RRMS), study 105MS301.

The members of the review team recommend approval and I will briefly discuss their major findings.

2. Background

Avonex was initially approved in 1996. It is one of the primary treatments for MS with extensive clinical use. Its efficacy and safety are well characterized. It is currently indicated for the treatment of relapsing forms of MS. The currently approved dose is a 30 microgram (mcg) intramuscular injection given once per week. A titration to 30 mcg from a series of lower doses in an attempt to minimize side effects is an approved initial dosing regimen.

Biogen submitted study 105MS301 for special protocol assessment and, after revising the protocol following initial review, received a special protocol assessment agreement letter from the Division. A pre-BLA meeting held on March 12, 2013, led to agreement with the sponsor that data from that single study (105MS301) could potentially provide substantial evidence of effectiveness. This decision was based upon our extensive experience with interferons for the treatment of MS and was consistent with the general stance of the Division when discussing the development of new interferons with sponsors. In light of the prior probability of effectiveness based on the consistent effects seen with other interferons, in general, for a new interferon, the Division is prepared to accept the results from a single otherwise adequate study of one year's duration as constituting substantial evidence of effectiveness.

In this application, the sponsor requests approval of both a prefilled syringe and an autoinjector, both of which will deliver the same 125 mcg dose. In contrast to the intramuscular dosing of Avonex, pIFN is given subcutaneously.

3. CMC/Device

I concur with the conclusions reached by the chemistry and device reviewers regarding the acceptability of the manufacturing of the drug product and drug substance and of the prefilled syringe and autoinjector delivery systems. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months at 5 ± 3ºC and (b) (4) months at (b) (4) °C. The manufacturing review team has negotiated with the sponsor postmarketing commitments concerning release and stability specifications, leachables, and sub-visible particulates. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval. I note, with reference to Dr. Lois Freed's comments in her supervisory memo concerning reproductive toxicology and the potential utility of a pregnancy registry, that we plan to impose a postmarketing requirement for a pregnancy registry.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The clinical pharmacology team notes that patients with renal impairment have higher exposures. Although the review team does not feel that formal dose reduction is warranted, patients with renal impairment should be monitored closely for clinical manifestations of higher exposure. There were no significant differences in the primary outcome or pharmacokinetics by gender, age, or weight.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

As discussed by Dr. Massie, Dr. Rodichok, and Dr. Marler, and as noted above, a single trial provides the primary data supporting efficacy and the Division agreed to this approach at the pre-BLA meeting in 2013. Study 105MS301 was a randomized, double-blind, placebo-controlled (for the first year of the trial – placebo patients were re-randomized to one of the pIFN groups after the first year), parallel-group trial of pIFN 125 mcg given either every two weeks or every four weeks in patients with RRMS, with 500 patients receiving placebo, 500 patients receiving pIFN every four weeks, and 512 patients receiving pIFN every two weeks.

The primary efficacy endpoint was the annualized relapse rate (ARR) over one year. The ARR was based on confirmed relapses. As noted by Dr. Marler on page 8 of his memo, and as discussed by Dr. Rodichok and Dr. Massie, confirmed relapses "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 (INEC) confirmed that the event is a relapse event." All parties involved were blinded.

Three secondary outcomes were specified, to be assessed in the following order after the primary outcome. Further, each outcome was to be assessed first in the every two week group and then in the every four week group before proceeding to the next outcome. Hierarchical testing would stop at the first analysis that failed.

1. Number of new or newly enlarging T2 hyperintense lesions at 48 weeks.
2. Proportion of subjects relapsed at 48 weeks,
3. Progression of disability as measured by EDSS Score at week 48.

Various exploratory MRI measurements, of the sort we are accustomed to seeing in various MS trials, including those of interferons, were also captured and analyzed in a non-hierarchical fashion.

A detailed discussion of these findings is presented by the review team and is summarized below in these tables from Dr. Massie and Dr. Marler.

The following table from page 15 of Dr. Massie's review describes subject disposition in the study:

Table 2 Study 301 Subject Disposition (from pages 119 and 120 of the sponsor's study report)

	Placebo	BIIB017 125 (mcg) SC		Total
		Every 4 weeks	Every 2 weeks	
Number of subjects randomized	500	501	515	1516
Number of subjects randomized but not dosed	0	1	3	4
Number of subjects dosed	500 (100)	500 (100)	512 (100)	1512 (100)
Number of subjects who completed year 1 study treatment (a)	456 (91)	438 (88)	438 (86)	1332 (88)
Number of subjects who discontinued study treatment in year 1	44 (9)	62 (12)	74 (14)	180 (12)
Adverse event	5 (1)	24 (5)	24 (5)	53 (4)
Protocol defined disability progression	0	0	0	0
Lost to follow-up	3 (<1)	4 (<1)	2 (<1)	9 (<1)
Consent withdrawn	30 (6)	30 (6)	35 (7)	95 (6)
Investigator decision	0	1 (<1)	4 (<1)	5 (<1)
Death	2 (<1)	1 (<1)	1 (<1)	4 (<1)
Other	4 (<1)	2 (<1)	8 (2)	14 (<1)

The following table from pages 8 and 9 of Dr. Marler's review describes the primary outcome:

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

Both pIFN regimens were significant, the every two week option more highly so and with a notably larger treatment effect than the every four week option, though these were not formally compared.

Dr. Marler presents the results of the secondary outcomes in this table from page 10 of his review:

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 Weeks (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

All secondary outcomes were significant in favor of pIFN, with the every two week option being more highly significant and of larger effect on T2 lesions and proportion of relapsed patients, and both pIFN regimens being identical on disability progression.

The exploratory MRI outcomes generally favored pIFN, specifically the every two week option, as seen in this table from page 13 of Dr. Marler's review:

48-Week MRI Outcomes a 48 Weeks **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		

Various sensitivity analyses of these primary and secondary outcomes were consistent and supportive.

While Dr. Massie points out that the US subgroup favored placebo numerically for the relapse outcomes, he also notes that the subgroup was quite small (3% of patients), when Canada was included the effect was diminished, and the MRI data were not consistent with this finding. Overall, he deems it an unreliable finding.

This pattern of clinical and MRI results appears generally consistent with that described in currently approved Avonex labeling.

8. Safety

The sponsor has submitted safety data for 1664 subjects exposed to pIFN. These subjects included healthy volunteers and subjects with renal impairment in Phase 1 trials (196 exposed), and patients with MS in Phase 3 trials (1468 exposed in study 105MS301 [2 year study – first year placebo-controlled, second year all patients on pIFN every 2 or 4 weeks] and its extension, study 105MS302 [ongoing]). ICH guidelines for exposure were met with 1350 MS patients exposed for at least 6 months, 1182 exposed for at least 1 year, and 648 exposed for at least 2 years.

Deaths

There were a total of 8 deaths in pIFN exposed patients throughout the development program. In the first year of study 105MS301 (the placebo-controlled phase) there were 2 deaths (0.2%) in pIFN patients and 2 deaths (0.4%) in placebo patients. This is the most reliable group for comparison and the mortality rate is larger in the placebo group. Dr. Boehm reviewed the deaths in detail on pages 19-23 of his review and concludes that the data overall do not indicate an increased mortality risk with pIFN. I agree.

Serious Adverse Events (SAEs)

Dr. Boehm concludes that there did not appear to be evidence of an increased risk of SAEs with pIFN from the placebo-controlled phase of trial 105MS301 and that the SAEs reported in the BLA appeared consistent with the safety profile of approved interferons. The following table from page 24 of Dr. Boehm's review indicates this lack of risk:

SAEs reported by at least 2 pIFN patients and more frequently compared to placebo during trial 105MS301, year 1

	Placebo	BIIB017 125 mcg SC		
		Q 4 weeks	Q 2 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)

There were few discontinuations due to AEs in the placebo-controlled phase of trial 105MS301, though there was an excess (5% vs 1%) in the pIFN group. This excess was generally due to flu-like symptoms (FLS) and injection site reactions (ISR) and is consistent with prior experience with interferons.

AEs of Special Interest and Common AEs

Dr. Boehm provides a thorough discussion of AEs of special interest and common AEs in his review and Dr. Marler summarizes these findings on pages 17-22 of his memo. Both found no issues of concern that were unexpected or would challenge approval and noted that these AEs were consistent with those of the approved interferons. I will briefly mention several of interest:

Flu-like symptoms – occurred in approximately 50% of pIFN patients using a rigorous definition (approximately 80% of pIFN patients using a broad capture of multiple individual symptoms). There was no significant change over the year of placebo-controlled treatment. This compares with approximately 50-60% of patients treated with the approved interferons Avonex and Rebif.

Injection site reactions – 66% of the every two week patients experienced ISRs (60% of every four week patients). This risk was highest during the first 12 week (60%) and there was a mild reduction to 40-50% over the remainder of the year. This is higher than Avonex (3%) but lower than Rebif (90%).

Infections – no increased risk was seen.

Hepatic toxicity – there was a slightly higher risk of aminotransferase elevations 3x ULN compared to placebo (4-7% vs. 3%), there were 2 unexplained "Hy's Law" cases (aminotransferase elevations 3x ULN associated with total bilirubin >2x ULN) with one of them resulting in acute hepatic failure that may have been due to corticosteroids rather than pIFN (both cases recovered), and there were no deaths due to hepatic failure and no liver transplants. This is a known issue with interferons and the approved interferons for MS include information about this risk in labeling, to include autoimmune hepatitis, hepatic failure resulting in transplant, and increased risk of aminotransferase elevations.

In summary, the safety profile of the currently approved formulation of Avonex (and the other approved interferons) is well established and described in labeling. Dr. Boehm and Dr. Marler present a thorough discussion of safety analyses related to the current submission. After careful consideration, there are no safety issues that appear unique to this formulation. Overall, there are no new safety findings of significant concern. A REMS is not required for this application.

9. Advisory Committee Meeting

This application was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with relapsing forms of multiple sclerosis and because the clinical trial design is similar to that of trials of previously approved drugs for the treatment of relapsing MS.

10. Pediatrics

This application was discussed at a PeRC/PREA Subcommittee meeting on February 26, 2014. The Division presented a request for partial waiver for patients 0 to 9 years and deferral for patients 10 to 17 years of age. PeRC agreed with the Division.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

13. Decision/Action/Risk Benefit Assessment

I agree with the review team that this application should be approved.

The applicant has provided substantial evidence of effectiveness from Study 105MS301, as supported both by the known benefits and effects of approved Avonex and in the context of the consistent benefits and effects seen with various interferons for MS, for Plegridy (whether administered by prefilled syringe or autoinjector) in a dose of 125 mcg every two weeks as a treatment for relapsing forms of multiple sclerosis. There are no safety concerns that preclude approval. Given the general consistency of clinical results between this new peginterferon and various approved interferons, the risk benefit assessment for these various products may fairly be viewed as similar, recognizing the inherent challenges associated with cross-study comparisons. Due to this general consistency, it is reasonable for Plegridy to inherit various cautions that are included in the approved interferon labels.

A study in pediatric MS patients aged 10 to 17 years and a pregnancy registry are both needed and will be conducted as postmarketing requirements.

Several postmarketing commitments have been negotiated with the sponsor to ensure continued manufacturing quality.

Specific postmarketing risk management activities are not needed.

We have agreed with the sponsor on product labeling that describes the effectiveness and safety of Plegridy 125 micrograms every two weeks for the treatment of relapsing forms of multiple sclerosis.

For these reasons, I recommend approval of this BLA, to include the agreed-upon product labeling.

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

/s/

WILLIAM H Dunn
08/13/2014