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APPLICATION NUMBER:

125499Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA Standalone Biologic
Application Number(s)	BLA-125499
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Division / Office	Division of Neurology Products
Reviewer Name(s)	Lawrence Rodichok, M.D.
Review Completion Date	January 14, 2014
Established Name	PEGylated interferon beta-1a
(Proposed) Trade Name	Plegridy
Therapeutic Class	Interferon
Applicant	Biogen Idec

Formulation(s)	125µg/0.5mL single use pre-filled syringe and prefilled pen 63µg/0.5mL and 94µg/0.5mL pre-filled syringe and prefilled pen (Starter pack)
Dosing Regimen	125µg subcutaneously every 2 weeks
Indication(s)	Multiple Sclerosis
Intended Population(s)	Adults

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Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment.....	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	8
1.4	Recommendations for Postmarket Requirements and Commitments	8
2	INTRODUCTION AND REGULATORY BACKGROUND	8
2.1	Product Information	8
2.2	Tables of Currently Available Treatments for Proposed Indications	9
2.3	Availability of Proposed Active Ingredient in the United States	10
2.4	Important Safety Issues With Consideration to Related Drugs.....	10
2.5	Summary of Presubmission Regulatory Activity Related to Submission	10
2.6	Other Relevant Background Information	10
3	ETHICS AND GOOD CLINICAL PRACTICES.....	10
3.1	Submission Quality and Integrity	10
3.2	Compliance with Good Clinical Practices	10
3.3	Financial Disclosures.....	11
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	12
4.1	Chemistry Manufacturing and Controls	12
4.2	Clinical Microbiology.....	12
4.3	Preclinical Pharmacology/Toxicology	12
4.4	Clinical Pharmacology	12
4.4.1	Mechanism of Action.....	14
4.4.2	Pharmacodynamics.....	14
4.4.3	Pharmacokinetics.....	14
5	SOURCES OF CLINICAL DATA.....	15
5.1	Tables of Studies/Clinical Trials	15
5.2	Review Strategy	17
5.3	Discussion of Individual Studies/Clinical Trials.....	17
5.3.1	Trial 301	17
5.3.2	Trial 302	26
6	REVIEW OF EFFICACY	27
	Efficacy Summary.....	27
6.1	Indication	27
6.1.1	Methods	27
6.1.2	Demographics.....	29
6.1.3	Subject Disposition	37

6.1.4	Analysis of Primary Endpoint(s)	41
6.1.5	Analysis of Secondary Endpoints(s).....	46
6.1.6	Other Endpoints	51
6.1.7	Subpopulations	71
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	82
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	83
6.1.10	Additional Efficacy Issues/Analyses	83
7	REVIEW OF SAFETY	84
8	POSTMARKET EXPERIENCE	84
9	APPENDICES	85
9.1	Literature Review/References	85
9.2	Labeling Recommendations	85
9.3	Advisory Committee Meeting.....	85

Table of Tables

Table 1 : FDA-approved treatments for MS.....	9
Table 2 Association of Financial Interests of Clinical Investigators	11
Table 3 Clinical Pharmacology studies of BIIB017	13
Table 4 PD of Avonex and BIIB017	14
Table 5 PK of Avonex and BIIB017	14
Table 6 Medan (Range) PK parameters based on CPE assay	15
Table 7 Clinical trials of efficacy and safety of BIIB017	16
Table 8 : Excluded Treatments for MS	22
Table 9 Baseline Characteristics of ITT Population Trial.....	30
Table 10 Baseline demographic and disease characteristics by region	31
Table 11 Baseline disease characteristics - ITT	32
Table 12 Baseline MRI characteristics (ITT)	33
Table 13 Previous treatment for MS at baseline (ITT).....	34
Table 14 Weeks of exposure and compliance – year one.....	34
Table 15 Weeks of exposure and compliance year 2 (ITT).....	35
Table 16 Subjects excluded from the PP analysis	36
Table 17 Subjects from USA vs non-USA in Trial 105MS301 - 1 year.....	37
Table 18 Relapses by treatment group year 1 (ITT).....	42
Table 19 Primary efficacy endpoint analysis (ITT)	43
Table 20 Primary efficacy endpoint analysis (PP)	43
Table 21 Primary efficacy analysis with all potential relapses included (ITT).....	44
Table 22 Primary efficacy analysis in subjects who completed vs. withdrawals.....	45
Table 23 Annualized Relapse Rate by analysis population.....	46
Table 24 New or newly enlarging T2 MRI lesions at week 48 (ITT)	46
Table 25 Proportion of subjects with an INEC confirmed relapse at one year.....	47
Table 26 Proportion of subjects with sustained EDSS increase (ITT)	50
Table 27 Proportion of Subjects with INEC relapse over 2 years - ITT	54
Table 28 Annual rate of relapses that required treatment with corticosteroids. Year one. ITT.....	57
Table 29 Proportion of Subjects with relapse requiring treatment with corticosteroids. Year 1. ITT.	58
Table 30 Percent of INEC confirmed relapses treated with corticosteroids - ITT - year 1	58
Table 31 Number of new or newly enlarging T2 lesions at 24 weeks, ITT	59
Table 32 New or newly enlarging T2 MRI lesions year 2 – ITT population dosed in year 2	60
Table 33 Gadolinium enhancing lesions year 1.....	62
Table 34 Gadolinium enhancing lesions over 2 years – ITT population dosed in year 2	62
Table 35 T1 hypointense lesions year 1.....	63
Table 36 T1 hypointense lesions year 2 – ITT population dosed in year 2.....	64
Table 37 Volume of T2 hyperintense lesions year 1	65

Table 38 Volume of T2 hyperintense lesions year 2 – ITT population dosed in year 2 .	65
Table 39 Change in T1 hypointense lesion volume year 1	66
Table 40 Volume of T1 hypointense lesions over 2 years – ITT population dosed in year 2	67
Table 41 Volume of Gd-enhancing lesions year 1	67
Table 42 Volume of Gd-enhancing lesions - year 2	68
Table 43 Brain atrophy year 1	69
Table 44 Brain atrophy year 2	69
Table 45 Annualized Relapse Rate by baseline demographic characteristics	71
Table 46 Annualized Relapse rate at one year by baseline disease characteristic	72
Table 47 Number of new or newly enlarging T2 lesions at 1 year - ITT by demographic subgroup	73
Table 48 Number of New or Newly Enlarging T2 lesions by baseline disease characteristic	74
Table 49 Proportion of Subjects with an INEC confirmed relapse in year one - ITT - by baseline demographics	75
Table 50 Proportion of subjects with an INEC relapse in year 1 - ITT - by baseline disease characteristic.....	77
Table 51 Time to sustained disability by EDSS year 1 by baseline demographics	78
Table 52 Time to Sustained Disability by EDSS year 1 - ITT - by baseline disease characteristics	79
Table 53 Summary of results of primary and secondary endpoint for BIIB017 q4W and q2W	82

Table of Figures

Figure 1 Design of Study 301 Design of Study 301.....	19
Figure 2 Study 302 Assessment Schedule.....	27
Figure 3 Overview of Subject Disposition Year 1 (Sponsor Figure 4, CSR page 124/4864).....	39
Figure 4 Overview of Subject Disposition Year 2	41
Figure 5 Time to first INEC confirmed relapse - ITT	49
Figure 6 Time to Sustained Progression of Disability - Year 1 - ITT.....	51
Figure 7 Summary of Annualized INEC confirmed relapse rate by study year - ITT population dosed in year 2	53
Figure 8 Time to first INEC confirmed relapse over 2 years (ITT dosed in year 2).....	55
Figure 9 Time to Sustained Progression of Disability - ITT - 2 years	56
Figure 10 ARR (INEC confirmed) at year 1 - q2W dose – by demographic subgroup - Forest Plot.....	81
Figure 11 ARR (INEC confirmed) at year 1 - q2W dose - by baseline disease characteristic - Forest plot.....	82

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This review recommends approval of BIIB017 125µg given subcutaneously every 2 weeks for the treatment of adults with relapsing forms of multiple sclerosis.

1.2 Risk Benefit Assessment

A single 1516-patient randomized placebo controlled clinical trial of two doses of peginterferon-β-1a in patients with relapsing forms of multiple sclerosis has demonstrated the effectiveness of 125µg peginterferon-β-1a given subcutaneously every 2 weeks in reducing the annualized rate of MS relapses compared to placebo. Progressive forms of MS were excluded from the trial. The reduction in annualized relapse rate was comparable to that of other interferon products approved for the treatment of relapsing forms of MS, i.e. approximately 30% compared to placebo after one year of treatment. The risks are comparable to those for other interferons. The trial data supports that the benefits of peginterferon-β-1a outweigh the risks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None. Prior experience with the interferon drug products and the findings in the clinical trials of peginterferon-β-1a do not suggest that any additional measures are required to evaluate or mitigate risks after approval.

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

BIIB017 is supplied as a liquid in pre-filled syringes to deliver 0.5 mL of 0.25 mg/mL (125 µg dose) of 20 kDa mPEG-O-2-methylpropionaldehyde-modified

human IFN β -1a in (b) (4) acetic acid/sodium acetate (b) (4) pH 4.8, (b) (4) arginine hydrochloride, and (b) (4) Polysorbate 20.

BIIB017 is also supplied as a liquid in pre-filled syringes for titration dosing to deliver 0.5 mL of 0.13 mg/mL (63 μ g dose) or 0.19 mg/mL (94 μ g dose) of 20 kDa mPEG-O-2- methylpropionaldehyde-modified human IFN β -1a in (b) (4) acetic acid/sodium acetate (b) (4) pH 4.8, (b) (4) arginine hydrochloride, and (b) (4) Polysorbate 20.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 includes the currently available treatments for relapsing forms of multiple sclerosis.

Table 1 : FDA-approved treatments for MS

FDA-Approved Treatments for Multiple Sclerosis					
Approved Drug	Name	Sponsor	Approved	Dose	Frequency
beta interferon 1b	Betaseron	Bayer	1993	0.25 mg --increase by 0.0625 mg every 6 weeks	SQ qod
beta interferon 1a	Avonex	Biogen Idec	1996	30 μ g (increase by 7.5 μ g q 3 weeks)	IM q week
glatiramer acetate	Copaxone	Teva	1996	20 mg/day	SQ qd
mitoxantrone	Novantrone	EMD Serono	2000	12mg/m ² IV over 5 to 15 min	IV q 3 mo
beta interferon 1a	Rebif	EMD Serono Pfizer Inc.	2002	22 μ g or 44 μ g	SQ tiw
natalizumab	Tysabri	Elan	2004	300mg IV over 1 hour	every 4 weeks
beta interferon 1b	Extavia	Novartis	2009 (1993)	0.25 mg (increase by 0.0625 mg 6 weeks)	SQ qod
fingolimod	Gilenya	Novartis	2010	0.5 mg	orally once daily
teriflunomide	Aubagio	Sanofi	2012	7 mg or 14 mg	orally once daily
dimethyl fumarate	Tecfidera	Biogen-Idec	2013	120 mg for 7 days then 240 mg	twice daily

2.3 Availability of Proposed Active Ingredient in the United States

Interferon β -1a is available as Avonex® in the United States. A PEGylated formulation is not currently available in the US.

2.4 Important Safety Issues With Consideration to Related Drugs

As seen in Table 1 there are a number of interferons available for the treatment of multiple sclerosis. The most common adverse reactions have been local injection site reactions and systemic influenza-like symptoms occurring within hours to days following treatment. An increased risk of depression has been reported with the use of interferon- β . Hepatic injury, reduced peripheral blood counts in all cell lines and autoimmune disorders have also been reported.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Biogen Idec submitted an IND to develop a PEGylated interferon- β -1a for MS on April 23, 2007. The first trial was a phase one trial in healthy volunteers.

Following completion of a single dose study (105HV101) and a multiple dose study (105HV102) study in healthy volunteers the sponsor requested a Special Protocol Assessment for a phase 3 pivotal trial. The initial protocol was submitted on 12/23/08. The sponsor submitted a revised protocol that addressed comments in a No Agreement letter of 2/6/09. The Agreement letter was sent on 5/3/10.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

The submission was of acceptable quality.

3.1 Submission Quality and Integrity

This reviewer found the overall quality of the submission to be acceptable. The information required to review efficacy was easily found. The sponsor did respond adequately to requests for additional information.

3.2 Compliance with Good Clinical Practices

The sponsor has provided statements asserting compliance with Good Clinical Practice on the face page of each of the study reports for the trials designated 105RI101, 105HV101, 105HV102, 105HV103, 105MS301, and 105MS302. The 105MS302 study report is an interim report. The others are final.

3.3 Financial Disclosures

For the one trial that formed primary evidence of effectiveness, 105MS301, at 26 sites 32 investigators received a total of \$2,297,785, an average of \$71,800 each. The sponsor notes that the trial was double-blind and that these investigators could not have influenced the outcome of the trial. These payments were payment for consulting, external meetings, honoraria, investigator fees, marketing seminars, and promotion.

The sites involved were (b) (6). The sponsor was not able to obtain financial disclosures from 10 investigators at 7 sites (b) (6) despite efforts to obtain the information.

For the extension trial, 105MS302, significant payments totaling \$152,309 were made to three clinical investigators (average \$50,769) at sites (b) (6) for consulting, clinical trial consulting, centralized physician programs, and external meetings. The sponsor was unable to obtain disclosure forms for 2 investigators at site (b) (6).

In response to requests in the July 15, 2013, filing letter, the sponsor analyzed the association between the relapse rate primary outcome and the financial interests of the clinical investigator. The investigators with a financial interest treated 178 subjects (12%) and those without a financial interest treated 1334 subjects (88% of 1512). The following table summarizes the analysis. The table shows a trend for more favorable outcome in BIIB017-treated subjects at clinical sites where investigators received compensation from Biogen.

Table 2 Association of Financial Interests of Clinical Investigators

Relapse Rate Association with Financial Interests of Clinical Investigators					
Financial Interest	Treatment Arm	Placebo	BIIB017		N
			Every 4 weeks	Every 2 weeks	
With financial interest	N	60	58	60	178
	Adjusted relapse rate (95% CI)	0.612 (0.375,0.999)	0.247 (0.133,0.460)	0.339 (0.197,0.582)	
	Rate ratio (active/placebo) (95% CI)		0.403 (0.203,0.800)	0.553 (0.299,1.021)	
Without financial interest		440	442	452	1334
	Adjusted relapse rate (95% CI)	0.371 (0.301,0.457)	0.287 (0.229,0.359)	0.242 (0.191,0.307)	
	Rate ratio (active/placebo) (95% CI)		0.774 (0.590,1.014)	0.653 (0.494,0.862)	

The sponsor's test for interaction determined the p-value to be 0.3540

In the BLA application using FDA form 3454, Biogen Idec, Inc., certified that they had not entered into any financial arrangement with clinical investigators in which the value of compensation to the investigator could be affected by the outcome of the trials they performed and that, when asked, none of the clinical investigators disclosed a proprietary interest in BIIB, had significant equity in Biogen-Idec, or received any

significant payments from Biogen-Idec for the following trials: 105HV101, 105HV102, 105HV103, 105RI101.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See primary CMC review.

4.2 Clinical Microbiology

See primary microbiology review of this submission by Chi Bo Ph.D.

4.3 Preclinical Pharmacology/Toxicology

See primary Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

Table 3 below lists the five clinical trials that the sponsor performed to evaluate BIIB017, peginterferon- β -1a, for MS. The sponsor randomized the first subject on May 30, 2007, and the last subject on November 23, 2011. PK and PD data were collected for BIIB017 at doses of 63 μ g, 125 μ g, and 188 μ g administered by IM and SC routes. The normal volunteer phase 1 trial data were the basis for the selection of the 125 μ g subcutaneous dose used in the Phase 3 trial.

Dose selection. In brief, the 125 μ g SC dose reached peak serum concentration 1 to 1.5 days after administration (t_{max}). The half-life was 2 to 3 days ($t_{1/2}$). For comparison, the approved Avonex formulation of interferon- β -1a t_{max} is 15 hours and the $t_{1/2}$ is 19 hours.¹

Approved interferon biologics for MS require self-injection 1 to 3.5 times every week. The sponsor estimated the half-life of biological activity for BIIB017 using various pharmacodynamic (PD) biomarkers, primarily neopterin. PD profiles suggest longer duration of biological activity than for currently approved products. Together, the PK and PD data lead the sponsor to choose dosing every 2 weeks [Q2W] or every 4 weeks [Q4W] for BIIB017.

¹ Overview of Clinical Pharmacology, clinical-overview.pdf, page 9/60.

Table 3 Clinical Pharmacology studies of BIIB017

Trial	Objective(s)	Study Design	Treatment	Duration	N	Age
PPD Studies in Healthy Volunteers						
105HV101 May 30, 2007 Sept 30, 2007	Maximum tolerated dose; PK and PD ; Safety and tolerability	Phase 1 Single-dose, blinded, randomized, IM and SC dose escalation	IFN β-1a (Avonex) 30µg IM BIIB017 63, 125, & 188µg both IM and SC	Single-dose	37M/23F; 36M/22F 60 Total	18-45
105HV102 March 1, 2008 May 25, 2008	Optimal dose; safety and tolerability; PK and PD	Phase 1, double-blind, randomized, placebo- controlled, multiple-dose, dose-ranging, parallel-group	BIIB017 at 63, 125, and 188 µg Q2W and Q4W SC	Multiple doses 2 doses for Q4W and 4 doses for Q2W.	36M/33F; 35M/30F 69 Total	18-46
105HV103 June 25, 2012 Oct 25, 2012	PK of BIIB017 delivered by autoinjector (PFP) and a PFS; safety and tolerability	Phase 1, randomized, open-label, 2-sequence, 2-period crossover	BIIB017 125 µg SC	One injection per device with a 3-week washout in between	32M/23F; 14M/10F 55 Total	18-44
PK and PD in Renal Impairment Subjects						
105RI101 May 4, 2010 Aug 3, 2011	PK and PD in renal impairment; safety and tolerability	Phase 1, single-dose, open-label, multicenter, serial group, non-randomized	BIIB017 63 and 125 µg; SC	Single-dose	22M/13F; 22M/13F 35 Total	36-75
PK and PD Studies in MS Subjects						
105MS301 June 5, 2009 Nov 23, 2011	Efficacy and safety; PK and PD in relapsing MS	Phase 3, multicenter, randomized, double blind, parallel-group, placebo controlled	BIIB017 125µg SC at 2 dose frequencies (Q2W and Q4W)	2 years	441M 1071F 1512 Total	18-61

F: female; IM: intramuscular; M: male; MS: multiple sclerosis; PD: pharmacodynamics; PFP: pre-filled pen; PFS: pre-filled syringe; PK: pharmacokinetics;
 Q2W: once every 2 weeks; Q4W: once every 4 weeks; SC: subcutaneous

4.4.1 Mechanism of Action

The mechanism by which the use of interferon- β benefits patients with MS remains unclear. Type 1 IFN receptors are expressed on a wide variety of cells including dendritic cells, T cells, B cells, macrophages, neutrophils, microglia, astrocytes, and neurons. Binding to the receptor may result in the production of proteins with roles in modulating the immunologic response. Some of these effects are anti-inflammatory by a variety of mechanisms.

4.4.2 Pharmacodynamics

The pharmacodynamic effect of interferon- β is typically assessed by measuring neopterin levels following exposure to the drug. The table below compares the PD effect of Avonex® to that following BIIB017 at several doses.

Table 4 PD of Avonex and BIIB017

	Avonex 30 μ g IM QW	BIIB017 63 μ g SC Q2W	BIIB017 125 μ g SC Q2W	BIIB017 125 μ g SC Q4W
Neopterin E_{AUC} per month (h·ng/mL)	2128	1790	2140	1070
Biological activity per dose (MIU)	6	6	12	12
Biological activity per month (MIU)	24	12	24	12

AUC: area under the concentration time curve; MIU: million international units; Q2W: once every 2 weeks; Q4W: once every 4 weeks; SC: subcutaneous.

Source: Summary of Clinical Pharmacology Table 5.

In general the neopterin peak level occurs approximately 1 to 1.5 days after the BIIB017 peak. Neopterin levels remain elevated 10 days after dosing despite undetectable levels of BIIB017 by 2 weeks after both q2W and q4W dosing. The presence of binding antibodies to BIIB017 does not appear to affect the neopterin response.

4.4.3 Pharmacokinetics

All of the doses of BIIB017 tested resulted in higher exposures compared to 30 μ g of Avonex.

Table 5 PK of Avonex and BIIB017

	Avonex 30 μ g IM QW	BIIB017 63 μ g SC Q2W	BIIB017 125 μ g SC Q2W	BIIB017 125 μ g SC Q4W
AUC cumulative per month (10^3 h·IU/mL)	3.1	5.70	14.3	7.14
AUC single dose (CPE) [10^3 h·IU/mL]	0.77	2.85	7.14	7.14

AUC: area under the concentration time curve; MIU: million international units; Q2W: once every 2 weeks; Q4W: once every 4 weeks; SC: subcutaneous.
Source: Summary of Clinical Pharmacology Table 5.

PK parameters at the proposed clinical dose of 125 µg are shown in the table below.

Table 6 Medan (Range) PK parameters based on CPE assay

PK parameter	IFN β – 1a 30 µg IM	BIIB017 125 µg IM	BIIB017 125 µg SC
AUC _{168h} (X10 ³ h IU/mL)	0.77 (0.05-1.99)	6.69 (2.19-14.6)	7.14 (2.52-21.9)
Cmax (IU/mL)	20.8 (11.5-81.1)	80.7 (18.5-268)	70.1 (28.6-146)
T _{1/2} (h)	24.3 (12.6-1064)	33.3 (27.0-112)	39.2 (28.3-776)
Tmax (h)	12.0 (9.0-48.0)	30.0 (12.0-72.0)	33.0 (30.0-96.0)

Source: Summary of Clinical Pharmacology Table 2

AUC_{168h}: area under the concentration-time curve from time 0 to 168 hours post-dose; Cmax: highest observed serum concentration; IM: intramuscular; t_{1/2}: terminal half-life; Tmax: time to reach Cmax; SC: subcutaneous

The PK parameters for both Avonex® and for BIIB017 appear to be very variable.

The PK of BIIB017 has not been studied in subjects over 65 years old. PK in patients with renal impairment was studied in 105RI101. The results demonstrated an increase in AUC_{336h} up to 53% and increases in C_{max} up to 42% in subjects with varying degrees of renal impairment. Based on a linear regression, the non-renal clearance accounts for 53% (90% confidence interval: [33%, 77%]) of the total BIIB017 clearance. There were not a sufficient number of subjects with renal impairment in 105MS301 to further assess PK in subjects these patients. There was no difference in PK comparing patients with MS to healthy volunteers.

5 Sources of Clinical Data

Documents and datasets were submitted electronically and may be found at the following link. <http://cberedrweb.fda.gov:8080/esp/cberedr.jsp>

5.1 Tables of Studies/Clinical Trials

A single clinical study, 105MS 301, is the basis for this application and is the single adequate and controlled study in which both safety and efficacy were assessed. The primary efficacy endpoint was at 48 weeks after start of treatment after which subjects randomized to placebo were re-randomized to one of the two doses of BIIB017. Subject randomized in the first 48 weeks to one of two doses of BIIB017 remained on the same dose for the second 48 weeks. Subjects remained blinded to dosing interval until completion of 96 weeks of treatment. Subjects could choose to enter a long term safety study, 105MS302 at that point.

Table 7 Clinical trials of efficacy and safety of BIIB017

Trial	Objective(s)	Study Design	Treatment	Duration	N	Age
105MS301 Completed	To evaluate the efficacy, safety, PK and PD in subjects with relapsing forms of MS	Phase 3, Multi-center, randomized, double blind, parallel group, placebo controlled	BIIB017; Year 1: <ul style="list-style-type: none"> Placebo every 2 weeks, or BIIB017 125 mcg SC every 2 weeks, or BIIB017 125 mcg SC every 4 weeks Year 2: <ul style="list-style-type: none"> BIIB017 125 mcg SC every 2 weeks, or BIIB017 125 mcg SC every 4 weeks 	96 weeks	1512	18 to 65
105MS302 Ongoing	Evaluate the long-term safety and efficacy of BIIB017 in subjects with relapsing remitting multiple sclerosis	Phase 3, multicenter, parallel group, dose frequency blinded extension	BIIB017; BIIB017 125 mcg SC every 2 weeks or BIIB017 125 mcg SC every 4 weeks	96 weeks		
105MS302 Sub-study Completed	Evaluate the safety, tolerability, subject ease of use, and satisfaction with the single-use BIIB017 autoinjector (prefilled pen)	See above	Either BIIB017 125 mcg SC every 2 weeks or BIIB017 125 mcg SC every 4 weeks, delivered by a single-use autoinjector device	6 weeks	39 subjects enrolled and dosed; 39 completed treatment; 34 completed follow up	

5.2 Review Strategy

The results of the first 48 weeks of treatment were the primary source of efficacy data. The efficacy data from 48 to 96 weeks were reviewed primarily to support that any efficacy in the first 48 weeks was sustained to 96 weeks. Since fewer than 5% of subjects were from the United States special attention was directed to the applicability of the overall results to the population in the US with multiple sclerosis. The primary safety review was conducted by Dr. Gerald Boehm.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Trial 301

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

5.3.1.1 Study design and definitions

The pivotal trial for this submission is a 1512-subject, 3-arm, one-year, double-blind, randomized, and placebo-controlled clinical trial that was the first year of a two-year trial that compared placebo to two doses of peginterferon: 125µg every 2 weeks or every 4 weeks (see Figure 1). 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. Although subjects were then aware that they were receiving BIIB017 the blind as to dosing frequency was maintained during the second year of the trial.

Subjects in the BIIB017 arms were titrated to the target dose over 4 weeks, 63µg first dose, 94µg second dose and then 125µg every 2 weeks or every 4 weeks thereafter. The matched diluent/placebo ((b) (4) acetic acid/sodium acetate pH 4.8, (b) (4) arginine hydrochloride, and (b) (4) Polysorbate 20) for this study was provided in pre-filled syringes, to deliver 0.5 mL.

Two dosing frequencies (every 2 weeks and every 4 weeks) were selected because: 1) single doses of 125 mcg of BIIB017 SC produced prolonged pharmacological responses when compared with single doses of Avonex 30 mcg IM (Study 105HV101), 2) with repeat dosing there was neither an accumulation of BIIB017 nor a loss of pharmacodynamics (PD) responsiveness to receptor activation (Study 105HV102), and 3) based on the pharmacokinetic (PK) and PD profiles observed in Phase 1 studies, the proposed dosing regimens with BIIB017 were expected to yield similar (125 mcg every 4 weeks) or higher (125 mcg every 2 weeks) exposures, compared to that of Avonex 30µg weekly, which were expected to lead to efficacy at least equal to that of Avonex

while improving both compliance and convenience over other interferons due to a reduced frequency of side-effects (e.g., flu-like symptoms).

Subjects participated in this study for up to approximately 108 weeks (2 years, 3 months), which consisted of a 6 week screening period, a 96 week (2 years) treatment period which included the 4 week titration period, and up to a 12-week safety follow-up period for those subjects who did not enter the extension study under a separate protocol (105MS302). Subjects who stopped study drug prematurely for any reason were asked to remain in the study for 24 weeks of follow-up evaluations.

Eligible subjects who continued in the study until Week 96 were offered the option to enroll in the extension study.

During the trial subjects had an option to change to an approved therapy if:

They had completed 48 weeks of blinded treatment and had experienced two or more relapses confirmed by an Independent Neurological Evaluation Committee (INEC)

Or

They had experienced significant progression of disability as defined by the protocol (at least 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 = 0 that was sustained for 12 weeks).

Figure 1 Design of Study 301 Design of Study 301

Design of Trial 301											
Study Phase	Screening	Randomize	Treatment Period							Post Treatment	
Treatment Arms			BIIB017 125 µg SC Q2W								
			BIIB017 125 µg SC Q4W								
			Matching Placebo					Re-Randomize Placebo Subjects			BIIB017 125 µg SC Q2W
Visit Week	-6	0	12	24	36	48			BIIB017 125 µg SC Q4W		
Clinical Events	✓	✓	✓	✓	✓	✓	60	72	84	96	100
EDSS	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
MRI Scans	✓			✓		✓				✓	

Relapse definition:

Relapses were defined as any new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the *examining neurologist*. The *examining neurologist* must not have been involved with any other aspect of subject care and management and must have been blinded to AEs, concomitant medications, laboratory data, MRI data, and any other data that have the potential of revealing the treatment assignment. The subject was required to have objective signs on the *examining neurologist's* examination confirming that the event was reviewed and confirmed by the *INEC*. New or recurrent neurologic symptoms that evolved gradually over months were considered disability progression, not an acute relapse. New or recurrent neurologic symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

Subjects who experienced new neurologic symptoms were to contact the *treating nurse* or *treating neurologist* as soon as possible within 48 hours of the onset of symptoms. A

Telephone Questionnaire was to be completed to determine the necessity of an Unscheduled Relapse Assessment Visit. If required, the subject would then be evaluated in person by the *treating neurologist* as soon as possible within 72 hours of the onset of the potential relapse.

Additionally, all subjects were then to be evaluated by the *examining neurologist* as soon as possible within 5 days of the onset of the symptoms. The *examining neurologist* would then perform a detailed neurological examination and obtain an EDSS score. New objective findings on neurological examination by the *examining neurologist* were required to determine if a suspected protocol-defined relapse had occurred. The *examining neurologist's* findings were to be provided to the treating neurologist via source documentation so he/she could evaluate treatment options. Subjects were not to begin corticosteroid treatment of the relapse per protocol until the *examining neurologist* had performed his/her exam. If the *examining neurologist* confirmed that there were new objective neurological findings on exam, all information was to be sent to the *INEC* for confirmation of relapse. If the *examining neurologist* did not confirm new objective neurological findings on exam, the information will not be sent to the *INEC*.

Reviewer comment: The treating neurologist made the decision as to whether an event should be evaluated by the examining neurologist. There was a potential for biased referral of events for further evaluation since the treating neurologist was not blinded to clinical data that could tend to unblind the treating neurologist to treatment assignment. The sponsor did conduct an analysis of all potential relapses (confirmed or not) to support the primary analysis of only confirmed relapses. Protocol-defined relapses would be the most reasonable ones to analyze since they at least fulfilled the definition of a relapse whereas "all relapses" could have included events related to fever or events without objective deficit.

Definitions of MS Relapses (full CSR page 93/4864)

All relapses included any event suspected of being a relapse by a subject (i.e., the subject notified the treating neurologist or nurse of new acute relapse symptoms **whether or not** the event met the criteria for protocol-defined or *INEC*-confirmed relapse.

Protocol-defined relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, with onset more than 30 days after the last relapse, and accompanied by new objective neurological findings upon examination by the examining neurologist. Protocol-defined relapses may or may not have been confirmed by *INEC*.

INEC-confirmed relapses were protocol-defined relapses that were evaluated by 3 INEC members and confirmed by a majority vote (2 out of 3 members confirmed the event as an MS relapse). Only INEC-confirmed relapses were included in the primary endpoint analysis.

Note: Relapses not evaluated by the treating neurologist within 72 hours of onset of symptoms or not evaluated by the examining neurologist within 5 days of onset of symptoms were not sent to INEC for confirmation, and could not be INEC confirmed.

Reviewer comment: See Table 18 for the proportions of relapses that were not determined by the investigator to be a protocol defined relapse or determined by the INEC to be a “confirmed” relapse.

Definition of Disability progression:

Progression of disability was defined as at least a 1.0 point increase on the EDSS from a baseline EDSS ≥ 1.0 that was sustained for 12 weeks or a 1.5 point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks. In either case, the subject must then have been informed s/he had experienced a worsening of physical disability. Repeat consent was then required to continue participation in the study. The subject was given the option to continue study treatment, prematurely discontinue study treatment and switch to open-label treatment with an approved open-label MS therapy in accordance with local practices managed by the Investigator and complete a Modified Evaluation Schedule, or prematurely discontinue study treatment, decline open-label treatment and complete a Modified Evaluation Schedule.

5.3.1.2 Key Inclusion and Exclusion Criteria

Inclusion

- Aged 18 to 65 years old inclusive
- Confirmed diagnosis of relapsing Multiple Sclerosis (McDonald criteria)
- EDSS score of 0 – 5.0
- At least 2 relapses in the preceding 3 years one of which must have been within 12 months of randomization (Day 1)

Exclusion

- Primary progressive, secondary progressive or progressive relapsing forms of MS

- Prior treatment with interferon for more than 4 weeks; interferon treatment must have been discontinued 6 months prior to baseline
- History of seizure disorder or unexplained blackouts OR history of a seizure within 3 months prior to Baseline.
- History of suicidal ideation within 3 months prior to Baseline or an episode of severe depression within 3 months prior to Baseline. Severe depression was defined as an episode of depression that required hospitalization, or at the discretion of the Investigator.
- An MS relapse that had occurred within the 50 days prior to randomization and/or the subject had not stabilized from a previous relapse prior to randomization (Day 1).
- Treatment with other agents to treat MS symptoms or underlying disease as specified below:

Table 8 : Excluded Treatments for MS

Agent	Time Required off Agent Prior to Baseline
Total Lymphoid Radiation Cladribine Fingolimod T-cell or T-cell Receptor Vaccine Any therapeutic monoclonal antibody (e.g., rituximab, natalizumab, alemtuzumab)	Prior treatment not allowed
Cytoxan Mitoxantrone	1 year
Interferon	6 months <i>Note: Prior treatment cannot have exceeded 4 weeks</i>
Cyclosporin Plasma Exchange Intravenous Immunoglobulin (IVIg) Azathioprine Mycophenylate Methotrexate	6 months
Systemic Corticosteroids	50 days
Copaxone	4 weeks

- Unable to perform the Timed 25-Foot Walk, Nine-Hole Peg Test (9HPT) with both upper extremities, and PASAT 3.
- Unable to perform visual function tests.

5.3.1.3 Blinding

Separate study personnel were designated to conduct efficacy assessments and to treat subjects in order to protect against perceived unblinding of treatment assignment.

The *treating neurologist* was responsible for assessment of adverse events, reviewed laboratory results from the central laboratory. The *treating nurse* was also aware of adverse events and assisted in treatment of subjects.

The *examining neurologist* determined the EDSS score at scheduled and unscheduled assessments. The examining neurologist was not aware of adverse events and laboratory results.

To ensure treatment blinding, each subject received one injection of BIIB017 or placebo every 2 weeks and the titration procedure was to be handled in the same manner between treatment groups. To ensure treatment blinding, all subjects were re-randomized at Week 48. After re-randomization, subjects knew that they were receiving BIIB017 treatment, but remained blinded to the treatment frequency (every 2 or 4 weeks).

White blood cell count (WBC) data (including the differential) obtained after the Screening visit was not sent to the sites. The WBC and differential were reviewed by an Independent Laboratory Monitor. All other laboratory data will be reviewed by the sites.

For the first 26 weeks of each study treatment year (starting at Baseline and again at Week 48), all subjects were instructed to take either acetaminophen (paracetamol) or ibuprofen prior to each injection and for the 24 hours following each injection at the recommended doses and frequencies per the local labels. If a subject was allergic to or intolerant of acetaminophen or ibuprofen, other non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen or aspirin may be administered at the recommended dose and frequency per the local labels. After 26 weeks within a study treatment year, acetaminophen, ibuprofen or other NSAID treatment could be discontinued at the discretion of the investigator.

5.3.1.4 Discontinuation

Subjects may have had treatment temporarily or permanently discontinued based on the results of the White Blood Cell (WBC) count, Absolute Neutrophil Count (ANC), platelet count, liver function studies.

Subjects were also discontinued for severe depression or suicidal ideation (defined as requiring hospitalization or at the discretion of the investigator)

5.3.1.5 Concomitant therapies

The following were not permitted while receiving investigational treatment:

- Any additional therapy, including investigational treatment, for MS
- Systemic corticosteroids
- Total lymphoid radiation, cladribine, T cell or T cell receptor vaccination, any therapeutic monoclonal antibody, mitoxantrone, cyclosporine, IV immunoglobulin, plasmapheresis or cytapheresis.

Subjects who received any of the above therapies were discontinued from the study.

Symptomatic therapies were permitted although stabilization of the dose(s) early in the study was encouraged.

The only protocol-approved treatment for relapse in this study was either 3 days or 5 days with IVMP, 1000 mg/day. Subjects could refuse relapse treatment. Study treatment dosing is to continue uninterrupted during IVMP treatment.

5.3.1.6 Neuroimaging

All subjects were to have brain MRI scans with and without Gadolinium at Screening, Week 24, Week 48, and Week 96. The baseline MRI was to be obtained no more than 30 days and not less than 5 days prior to first dose. MRI was not to be performed within 30 days of receiving a course of steroids.

5.3.1.7 Primary Outcome

The primary outcome endpoint for 105MS301 was the annualized relapse rate (ARR). The primary analysis is a negative binomial regression for the ARR at one year. The model includes terms for treatment group, age (<40 vs. ≥40), and EDSS (4 or ≥4). Baseline relapse rate was defined as the number of relapses over the 3 years prior to the day of screening, divided by 3.

5.3.1.8 Secondary Outcome measures

- Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 24 and 1 and 2 Years. The number of new or newly enlarging T2 hyperintense lesions will be summarized by treatment group and time point. Comparison between each BIIB017 group and placebo group at Week 24 and 1 year will be made using the negative binomial regression model. The analysis model will include a term for treatment group and for the number of baseline T2 lesions.
- Proportion of Subjects Relapsed at 1 Year. The analysis method for proportion of subjects relapsed at 1 year is a Cox proportional hazards model for time to first relapse. The model includes 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). Baseline relapse rate is defined as the number of relapses over the 3 years prior to study entry. The proportion of relapsed subjects will be estimated using the Kaplan-Meier product limit method based on the time to first relapse survival distribution.
- Disability Progression as Measured by EDSS Score at 1 Year and 2 Year. Time to disability progression over 1 year (comparing each BIIB017 group with placebo) and over 2 year (comparing each BIIB017 group with the 1 yr placebo+1yr BIIB017 group) is analyzed by a Cox proportional hazards model. The model includes a term for treatment group and adjusts for baseline EDSS values, and age (<40 vs. ≥40).

5.3.1.9 Statistical considerations

The pre-specified primary efficacy population is the “Intent to Treat” population defined as all subjects who were randomized and received at least 1 dose of study treatment (BIIB017 or placebo). Subjects were to be analyzed in the groups to which they were randomized.

For the primary efficacy analysis a sequential (closed) procedure was pre-specified as follows: If the first comparison (the every 2 week group versus placebo) is statistically significant ($p \leq 0.05$) then the second comparison (the every 4 week

group versus placebo) will also be made at the 0.05 alpha level. However, if the first comparison is not statistically significant, then the second comparison will not be considered statistically significant.

Secondary endpoints were also prioritized by endpoint and dose group.

The sample size calculation was based on the type I error rate of 0.05 and a dropout rate of 10%. It was assumed that the treatment effect for BIIB017 would be 32% reduction from placebo in the 1-year ARR. In Version 3 of the protocol, a sample size of 420 per treatment group was planned to provide approximately 90%, 87%, and 85% power when the placebo 1-year ARR is 0.6, 0.55, or 0.5, respectively. As permitted by the protocol, the pooled 1-year ARR was monitored and the placebo 1-year ARR was estimated by back-calculating from the pooled ARR and the assumed treatment effect. As a result of this monitoring, the sample size was increased in version 5.1 of the protocol from 420 to 500 subjects per group.

A futility analysis was planned after the first 210 subjects completed the 6 month MRI time point using MRI data. The endpoint was the number of new or newly enlarged T2 lesions on a single MRI scan obtained at the 6 month time point when compared with baseline results.

5.3.2 Trial 302

Study 302 is a 2-year extension of study 301 intended to evaluate long-term safety of BIIB017 and to continue assessment of clinical outcome. At the time of database lock and submission the study was ongoing, all subjects continuing the dosing regimen assigned in the 301 trial. This assessment schedule is in Figure 2 below.

Figure 2 Study 302 Assessment Schedule

Design of Trial 302									
Study Phase	Baseline	Treatment Period							
		Treatment Group							
Treatment Group	BIIB017 125 µg SC Q2W								
	BIIB017 125 µg SC Q4W								
Visit Week	0	12	24	36	48	60	72	84	96
Clinical Events	✓	✓	✓		✓		✓		✓
EDSS		✓	✓		✓		✓		✓
MRI Scans	✓				✓				✓

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The proposed indication is for the treatment of patients with relapsing forms of multiple sclerosis.

6.1.1 Methods

6.1.1.1 Interim Analysis

The futility analysis was based on the MRI data from 210 subjects obtained at Week 24. The number of new and newly enlarged T2 hyperintense lesions was analyzed using a negative binomial regression model, which was to include the treatment group and was adjusted for the baseline number of T2 hyperintense lesions. The Sponsor was to consider terminating the futility study if both of the following conditions were met in both BIIB017 dosing groups in terms of

treatment effect, which was calculated as the percentage reduction from placebo group in the mean new and newly enlarged T2 hyperintense lesions:

Observed treatment effect <17%

AND

Upper bound of 95% CI of the treatment effect <45%

Upon completion of the interim futility analysis, the DSMC recommended continuing the study.

6.1.1.2 Database

The analyses described in this report represent the study period from date of first visit up to the time of data cutoff of 24 October 2012, which coincides with the date that all subjects had completed Year 1 of the study or had prematurely withdrawn from the study. Of note, for subjects who had a tentative disability progression at Week 48, data from Week 60 was used to confirm disability progression.

6.1.1.3 Protocol amendments

- Enrollment into Study 105MS301 began under global protocol Version 1, dated 13 March 2009. The global protocol was subsequently amended 4 times: Version 2 (27 October 2009), Version 3 (16 April 2010), and Version 4 (14 March 2011), and Version 5 (27 March 2012). All changes made to the protocols occurred prior to breaking the blind of the study.
- Version 3 added an objective of determining the effect on the number of “new active” MRI lesions. The number of new active lesions was calculated as the sum of the Gadolinium-enhancing lesions and the non-enhancing new or newly enlarging T2 hyperintense lesions.
- Version 3.1 added a sub-study of subjects with frequent MRI and biomarker assessments.
- Version 4 and 4.1 (14 March 2011) increased the sample size from 1260 to approximately 1500 subjects. See section 5.3.1.9 of this review. It also increased the upper age limit to 65 years. At that point approximately 600 subjects had received at least one dose of investigational treatment.
- Version 5 and 5.1 (27 March 2012) removed the MSIS-29 from the hierarchy of secondary endpoints. Also, the analysis for Primary Endpoint, EDSS (≤ 3.5 or 3.5) was changed to (4 and ≥ 4).

6.1.2 Demographics

6.1.2.1 Baseline demographic characteristics

The baseline demographic characteristics of the population composing the placebo-controlled 1-year part of the 105MS301 trial were similar across the three treatment arms (Table 9). 70% of the subjects were from Eastern Europe. 3% were from the United States. Consequently, the composition of the trial population by race was not representative of the US population.

The population was recruited from 183 sites in 26 countries.² The median number of subjects at each site was 6 (2.5 in the 12 US sites; Table 17).

² Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, the Czech Republic, Estonia, France, Georgia, Germany, Greece, India, Latvia, Mexico, the Netherlands, New Zealand, Peru, Poland, Romania, the Russian Federation, Serbia, Spain, the Ukraine, the United Kingdom (UK), and the United States (US). (03-15-report-body.pdf, page 38 of 4864)

Table 9 Baseline Characteristics of ITT Population Trial

Baseline Characteristics ITT Population Trial 105MS301 Part 1				
Baseline Characteristic	Placebo	BIB017 Peginterferon		All
		Every 4 Weeks	Every 2 Weeks	
Age (yrs)	500	500	512	1512
Mean (SD)	36.3(9.7)	36.4 (9.9)	36.9 (9.8)	36.5 (9.8)
< 40, n (%)	310 (62)	304 (61)	320 (63)	934 (62)
>= 40, n (%)	190 (38)	196 (39)	192 (38)	578 (38)
Gender, n	500	500	512	1512
Female, n (%)	358 (72)	352 (70)	361 (71)	1071 (71)
Male, n (%)	142 (28)	148 (30)	151 (29)	441 (29)
Height n	492	493	506	1491
Median (cm)	167.0	167.0	167.0	167.0
Weight n	498	497	511	1506
Median (kg)	66.00	67.00	65.60	66.00
Body mass index n	492	493	506	1491
Mean (kg/m ²)	24.61	24.25	24.59	24.48
Race, n	500	500	512	1512
White, n (%)	412 (82)	409 (82)	416 (81)	1237 (82)
Asian, n (%)	56 (11)	56 (11)	59 (12)	171 (11)
Other, n (%)	29 (6)	32 (6)	33 (6)	94 (6)
Black, n (%)	3 (<1)	1 (<1)	3 (<1)	7 (<1)
Not reported	0 (0)	2 (<1)	1 (<1)	3 (<1)
Geographic areas ^a	500	500	512	1512
India, n (%)	56 (11)	56 (11)	58 (11)	170 (11)
North America, n (%)	17 (3)	16 (3)	19 (4)	52 (3)
West Europe, n (%)	38 (8)	39 (8)	41 (8)	118 (8)
East Europe, n (%)	354 (71)	355 (71)	355 (69)	1064 (70)
Rest of World, n (%)	35 (7)	34 (7)	39 (8)	108 (7)

^a:North America includes Canada, United States. West Europe includes Belgium, France, Germany, Netherlands, Spain, and United Kingdom. East Europe includes Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Poland, Romania, Russia, Serbia, and Ukraine. Rest of World includes Chile, Colombia, Georgia, Mexico, New Zealand and Peru.

Reviewer comment: Only 3% of the population was from North America which includes the US and Canada. In the Response to Filing Letter Requests (Amendment 5) the sponsor provided a rationale for the applicability of the data from the overall study to the U.S. population as follows:

1. The U.S. data was analyzed as part of "Region 1" which included Canada, Belgium, Netherlands, Germany, France and Spain which were considered to have similar health care systems.
2. The protocol was consistent with the practice of medicine in the U.S.
3. The baseline demographic and disease characteristics did not differ significantly in Region 1 from Region 2 (mainly Eastern Europe) or Region 3 (South America, Georgia, India and New Zealand)

4. The results in Region 1 do not differ significantly from those in Regions 2 and 3 or from the overall result

Table 10 shows the baseline demographic and disease characteristic by region.

Table 10 Baseline demographic and disease characteristics by region

	US	Region 1	Region 2	Region 3	Total
No. (% total) of subjects	41	170 (11.2)	1064 (70.4)	278 (18.4)	1512 (100)
Age (years)	39.7	38.5	36.6	35.1	36.5
Female gender, %	73	71	71	68	71
BI EDSS score, mean	2.3	1.97	2.50	2.60	2.46
Prior MS treatment, % yes	41	25	16	18	17
Relapses last 12 months, mean	1.5	1.6	1.5	1.5	1.5
≤2	39 (95)	160 (94.1)	1001 (94.1)	254 (91.4)	1415 (93.6)
3	2 (5)	9 (5.3)	53 (5)	18 (6.5)	80 (5.3)
≥4	0	1 (0)	10 (1)	6 (2.2)	17 (1.1)
Time since first MS symptoms, Mean (years)	7.0	6.5	6.8	5.6	6.6
Median (years)		4.0	4.0	4.0	4.0
Baseline Gd+ MRI lesions Mean (SD)	0.4 (0.9)	1.3 (5.6)	1.5 (4.0)	1.7 (4.5)	1.5 (4.3)

Source: Sponsor Table 1, Amendment 5 (page 6/14); reviewer calculation shaded in grey

Reviewer comment: The baseline demographic and disease characteristics that might influence the primary result do not appear to differ by region. Baseline characteristics that tended to correlate with less benefit included those who had prior treatment for MS, a feature more common in Region 1. Of the 41 subjects from the US, 41% had prior treatment for MS which is higher than for Region 1 overall which itself had a higher proportion with prior treatment. Most other baseline demographic and disease characteristics did not differ greatly for the US population in comparison to Region 1 overall or to the other regions. Although the data is limited I believe that it is reasonable to extrapolate the overall study results to the US population.

6.1.2.2 Baseline disease characteristics

The diagnosis of MS was based on the presence of 2 or more relapses and 2 or more objective lesions in 88% of subjects overall with no significant difference between the three treatment groups. The treatment groups were balanced for baseline functional deficits as measured on the components of the MS Functional Composite (MSFC)

which included the 25 Foot Walk and the 9 Hole Peg Test (Sponsor Table 16 pg. 138/4864), as well as on the Visual Function Test (Sponsor Table 17 – pg. 140/4864)

Table 11 Baseline disease characteristics - ITT

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks	Total
ITT, n	N=500	N=500	N=512	N=1512
Diagnosis based on MacDonald criterion 1 ^a	89	86	88	88
EDSS (mean,SD) (median,range) <4	2.44 (1.18) 2.00 (0, 5.0) 432 (86)	2.48 (1.2) 2.5 (0, 5.0) 413 (83)	2.47 (1.3) 2.5 (0, 5.5) 423 (83)	2.46 (1.2) 2.5 (0, 5.5) 1268 (84)
# relapses previous 3 years (mean, SD) (median, range)	2.6 (1) 2.0 (1-9)	2.5 (0.8) 2.0 (1-7)	2.6 (1) 2.0 (1-12)	2.5 (0.9) 2.0 (1-12)
# relapses past 12 months (mean, SD) (median, range)	1.6 (0.7) 1.0 (1-4)	1.5 (0.6) 1.0 (1-4)	1.6 (0.7) 1.0 (1-5)	1.5 (0.7) 1.0 (1-5)
Months since most recent pre-study relapse (mean, SD) (median, range)	4.8 (2.7) 4.0 (1-13)	5.1 (2.9) 4.0 (1-13)	5.1 (2.95) 4.0 (0-13)	5.0 (2.8) 4.0 (0-13)
Time since first MS symptoms, years (mean, SD), (median, range)	3.5 (4.6) 2.0 (0-40)	3.4 (4.36) 1.0 (0-22)	4.0 (5) 2.0 (0-31)	3.6 (4.7) 2.0 (0-40)
25 foot Walk Test (seconds) Mean (SD)	7.93 (7.8)	7.62 (5.9)	7.60 (5.9)	7.72 (6.6)
9-Hole Peg Test (1/sec) Mean (SD)	0.046 (0.01)	0.047 (0.01)	0.047 (0.01)	0.047 (0.01)
PASAT 3 (# items) Mean (SD)	46.9 (11.7)	46.7 (11.6)	47 (11.6)	46.9 (11.6)

^a :2 or more relapses, 2 or more objective lesions.

Source: Sponsor Tables 12-15, pp 132-136/4864; Sponsor Table 16

Reviewer comment: The baseline disease characteristics did not differ significantly by treatment assignment. The MSFC is another measure of some types of baseline function. There were no differences at baseline for these measures.

The MRI characteristics at baseline are in Table 12 below. Most characteristics are balanced across the three treatment groups. However the BIIB017 group did have more subjects with no Gadolinium (Gd) enhancing lesions, a smaller volume of Gd enhancing lesions, fewer and a smaller volume of T2 and T1 lesions. The imaging results should be adjusted for these differences.

Table 12 Baseline MRI characteristics (ITT)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks	Total
ITT	N=500	N=500	N=512	N=1512
No. of Gd lesions	(n=497)	(n=498)	(n=510)	(n=1505)
0	59%	59%	62%	61%
1-4	29%	31%	28%	29%
Mean (SD)	1.6 (3.8)	1.8 (5.4)	1.2 (3.4)	1.5 (4.3)
Median (Range)	0 (0-38)	0 (0-68)	0 (0-32)	0 (0-68)
Vol. of Gd lesions (cm ³)	(n=497)	(n=498)	(n=510)	(n=1505)
Mean (SD)	0.22 (0.55)	0.25 (0.83)	0.164 (0.49)	0.211 (0.64)
Median (Range)	0 (0-5)	0 (0-10.6)	0 (5.6)	0 (0-10.6)
No. of T2 lesions	(n=497)	(n=499)	(n=511)	(n=1507)
Mean (SD)	50.6 (36)	51.4 (36)	48.7 (37)	50 (36)
Median (Range)	43 (1-212)	45 (0-206)	39 (0-249)	43 (0-249)
Vol. of T2 lesions (cm ³)	(n=497)	(n=499)	(n=511)	(n=1507)
Mean (SD)	10 (12)	11 (13)	9.8 (11.6)	10.4 (12.3)
Median (Range)	5.9 (0.02-99)	6 (0-80)	5.8 (0-109)	6 (0-109)
No. of T1 hypointense lesions	(n=497)	(n=499)	(n=511)	(n=1507)
0	5%	6%	6%	6%
Mean (SD)	28 (29)	30 (31)	28 (28)	29 (29)
Median (Range)	20 (0-212)	19 (0-213)	18 (0-185)	19 (0-213)
Vol. of T1 hypointense lesions (cm ³)	(n=497)	(n=498)	(n=510)	(n=1505)
Mean (SD)	3.1 (4.8)	3.1 (4.8)	3 (4.5)	3.1 (4.7)
Median (Range)	1.1 (0-39)	1.2 (0-40)	(0-39)	1.2 (0-40)

Source: Sponsor Table 18

Reviewer comment: The first secondary endpoint in the hierarchy is the number of new of newly enlarging T2 hyperintense lesions. Therefore the imbalance in Gadolinium enhancing and T2 lesions at baseline favoring the BIIB017 q2W group could influence the imaging results. The analysis if new and new enlarging T2 lesions did include the baseline number of T2 lesions in the model which should have adjusted for the baseline difference.

Medical History

There was no significant imbalance between treatment groups of concomitant medical conditions. The most common were cardiovascular disorders in 53% overall, genitourinary in 23%, musculoskeletal in 21%.

Previous Treatment for MS

Only 17% of subjects had been treated with any therapy for MS (Table 13). The treatment groups were balanced for the use of any previous treatment and for the two

most common therapies, glatiramer acetate and corticosteroids. No subjects had been treated with natalizumab.

Table 13 Previous treatment for MS at baseline (ITT)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks	Total
ITT	N=500	N=500	N=512	N=1512
Any prior treatment	86 (17)	85 (17)	89 (17)	260 (17)
Glatiramer acetate	24 (5)	28 (6)	27 (5)	79 (5)
Corticosteroids	58 (12)	56 (11)	58 (11)	172 (11)

Source: Sponsor table 20 (pg. 153/4864)

6.1.2.4 Exposure/compliance

There was a lower proportion of subjects treated with BIIB017 who completed all 48 weeks of treatment in the double blinded phase. This is largely explained by the discontinuations due to adverse events. The %compliance was high for those continuing in the study (Table 15).

Table 14 Weeks of exposure and compliance – year one

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=500	N=500	N=512
Weeks on study treatment ^a			
Mean (SD)	46.2 (7.7)	44.8 (10.5)	43.9 (11.7)
Median (Range)	48.1 (2-50)	48.1 (2-49)	48.1 (2-49)
<8 weeks, n (%)	5 (1)	17 (3.4)	17 (3.3)
<24 weeks	22 (4.4)	35 (7)	50 (9.8)
<48 weeks	43 (8.6)	62 (12.4)	65 (13)
≥ 48 weeks n, %	457 (91)	438 (88)	435 (85)
Study treatment taken, % ^b			
Mean (SD)	99.6 (1.4)	99.6 (2.2)	99.4 (2.7)
Median (Range)	100 (88-100)	100 (67-100)	100 (60-100)

^a: Weeks on study treatment is calculated as ((date of last dose in year 1 + 14 days) – date of first dose +1)/7.

^b: Calculated as actual number of injections/number of injection the subject was expected to take during year 1.

Percentage values greater than 100% due to rounding are considered 100% for summary purposes.

Source: Sponsor Table 21 (pg. 158/4864)

Reviewer comment: Ultimately 88% and 85% of subjects in the BIIB017 q4W and q2W groups respectively completed 48 weeks of treatment compared to 91% of placebo subjects. The difference is not likely to have a large influence on the analysis of efficacy. The sponsor did perform an analysis of those who completed all 48 weeks of the study (Table 22) which supported the primary analysis.

The proportion of subjects continuing on study drug was lower in the second year compared to the first as seen in **Table 15** below.

Table 15 Weeks of exposure and compliance year 2 (ITT)

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=228	N=228	N=438	N=438
Weeks on study treatment ^a				
Mean (SD)				
Median (Range)	33.1 (16) 38.1 (2-50)	33.7 (16.8) 38.6 (2-50)	33.1 (16.8) 38.3 (2-51)	33.7 (16.5) 38.3 (2-50)
< 8 weeks, n (%)	18 (8)	25 (11)	42 (10)	42 (10)
< 24 weeks, n (%)	65 (29)	69 (30)	138 (32)	129 (29)
<48 weeks, n (%)	138 (61)	128 (56)	242 (55)	246 (56)
≥ 48 weeks (n, %)	90 (20)	100 (44)	196 (45)	192 (44)
Study treatment taken, % ^b				
Mean (SD)	99.6 (1.8)	99.6 (2.4)	99.5 (3.1)	99.7 (2.2)
Median (Range)	100 (86-100)	100 (79-100)	100 (54-100)	100 (67-100)

^a : Weeks on study treatment is calculated as ((date of last dose + 14 days) – (date of first dose in year 2 +1))/7.

^b : Calculated as actual number of injections/number of injection the subject was expected to take during year 2. Percentage values greater than 100% due to rounding are considered 100% for summary purposes.

Source: Sponsor Table 22 (pg. 160/4864)

In year one the percentage of subjects who were on study drug for 48 weeks or more was 91% for placebo, 88% for BIIB017 q4W and 85% for BIIB017 q2W. Exposure therefore was lower in the two active drug groups compared to placebo, especially for the q2W group. In year two the percentages were lower at 39% and 44% for those continuing in to year 2 and randomized to BIIB017 q4W and q2W respectively; 45% for BIIB017 q4W and 44% for BIIB017 q2W. The compliance rate (%) appears to be based on the number of expected injections up to the time of discontinuation.

Reviewer comment: The difference in exposure is most likely due to the increased number of early discontinuations in the active drug groups. This would not affect interpretation of the primary efficacy endpoint since the calculation of the ARR uses the number of days in the study as the denominator. However it does appear that those who discontinue prematurely for treatment-related reasons, e.g. adverse events, may be counted as relapse free for purposes of the primary endpoint.

6.1.2.5 Concomitant medications

The use of concomitant non-steroidal anti-inflammatory drugs was directed by protocol for the first 26 weeks. Paracetamol was used by approximately 90% of subjects each of the three treatment arms. Ibuprofen was used by fewer subjects in the placebo group

(33%) and by a slightly greater percent of subjects in the BIIB017 q4W group (41%) and the BIIB017 q2W group (38%).

Methylprednisolone was the protocol directed intervention for relapses. It was used by 29% of subjects in the placebo group and by fewer in the BIIB017 q4W group (21%) and by the BIIB017 q2W group (17%). In year 2 the use of ibuprofen was similar in all groups at approximately 33%. The overall use of MP in year 2 was lower than in year 1, 16% vs. 22% and it was similar in the two groups previously on placebo, 20% for the BIIB017 q4W group and 18% for the BIIB017 q2W group, but remained lower in those who in year one had been on BIIB017 q4W (17%) or BIIB017 q2W (11%).

Reviewer comment: The less frequent use of MP by the two active treatment groups in year 1 is consistent with the reduced ARR in these groups. The overall reduction in year two is consistent with the overall reduction on ARR when all subjects were on effective treatment. The even lower use in those who had been on effective treatment in year one is most likely a chance observation.

Table 25 of the CSR lists subjects who changed to an approved therapy during year 1. The table lists 16 such subjects, 7 in the placebo group, 3 in the BIIB017 q4W group and 6 in the BIIB017 q2W group.

Reviewer comment: Based on the listing of subjects who discontinued in Appendix 16.2.1, the above numbers of subjects do not appear to include those who discontinued due to a relapse and presumably changed to alternate treatments after the relapse.

6.1.2.6 Protocol violations and deviations

Forty-seven (47) subjects are identified with protocol violations/deviations that led to exclusion from the per protocol (PP) analysis. The use of alternative treatments for MS accounted for 18 of these and inadequate compliance with study treatment accounted for 17 (defined as missing 2 consecutive doses or a total of 4 doses). Thirteen (13) subjects were excluded due to failure to meet inclusion or exclusion criteria that had the potential to affect patient safety or data integrity.

Table 16 Subjects excluded from the PP analysis

	Placebo in year one			BIIB017 in year one	
	Placebo	PBO to BIIB017 q4W	PBO to BIIB017 q2W	BIIB017 q4W	BIIB017 q2W
Total excluded from year one analysis	18			15	18
Number excluded from PP analysis	7	7	4	15	18
Use of alternate	7			3	8

	Placebo in year one			BIIB017 in year one	
	Placebo	PBO to BIIB017 q4W	PBO to BIIB017 q2W	BIIB017 q4W	BIIB017 q2W
treatment ^a					
Compliance ^b		3	2	8	3
Inclusion/exclusion		4	2	3	4
"Not in ITT population"				1	3

^a:Subject took any Alternative MS Medication during 1st year

^b:Missed more than 2 consecutive dose or more than 4 total doses during first year

Reviewer comment: The subjects listed in Appendix 16.2.3 as excluded from the PP analysis are those in the table above. There are 51 unique subjects listed. The number of subjects not included in the PP analysis is relatively small.

6.1.3 Subject Disposition

A total of 1516 subjects were randomized at 183 investigational sites in 26 countries. The highest enrolling countries were Poland (386 subjects), the Ukraine (189 subjects), India (170 subjects), the Russian Federation (145 subjects), and Serbia (134 subjects); all other countries each enrolled fewer than 100 subjects. Only 41 subjects were randomized at 12 sites in the US (Table 17)

Table 17 Subjects from USA vs non-USA in Trial 105MS301 - 1 year

US and Foreign Sites Randomized Subjects in Year One of 105MS301 Trial				
Location	Sites (%)	Subjects (%)	Subjects Per Site	
			Mean	Median
Non-US	171 (93%)	1475 (97%)	8.7	6
US	12 (7%)	41 (3%)	3.4	2.5
Total	183	1516 (100.00%)	8.3	6

Reviewer comment: See discussion above regarding the applicability of the overall study result to the US population.

Study Populations:

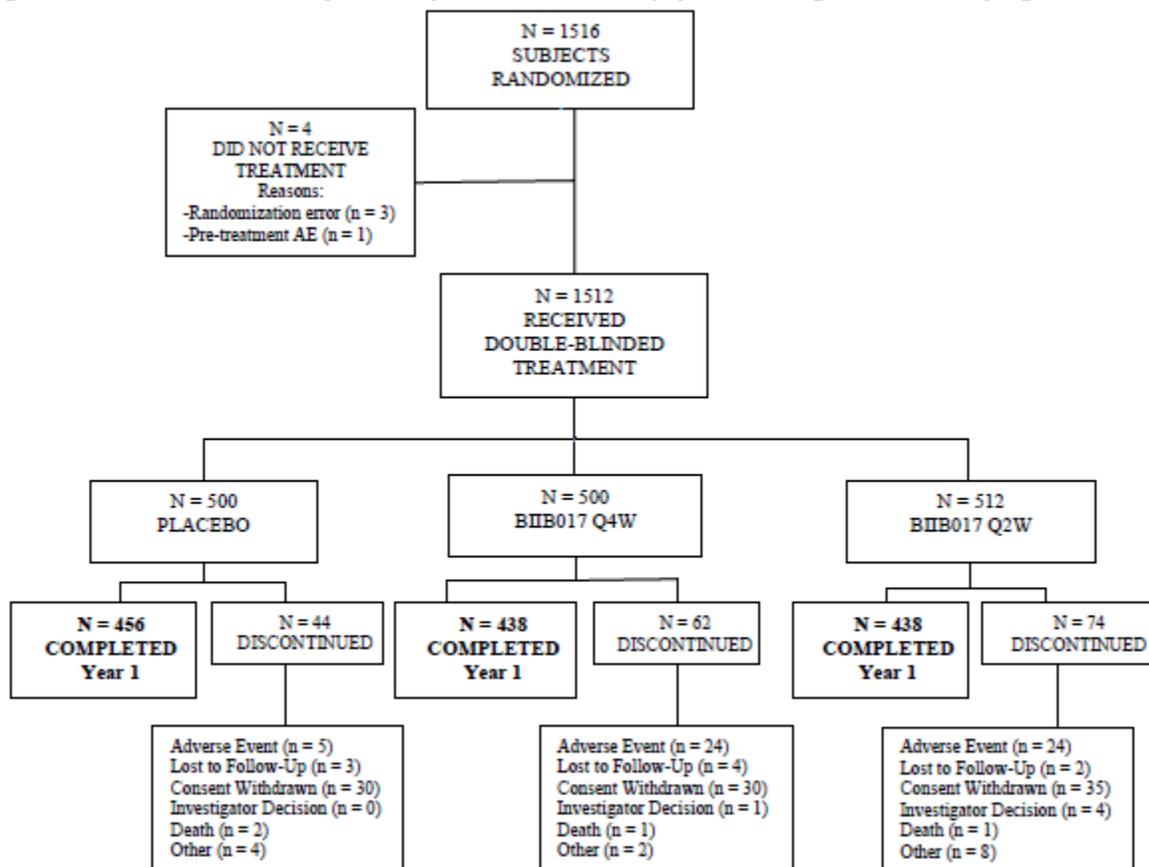
The 1512 subjects who received at least 1 dose of study treatment comprised the ITT and safety populations. The 4 randomized subjects who did not receive a dose of investigational treatment and not included in the ITT or safety populations included three (3) subjects who did not receive a dose of investigational treatment because of a randomization error and one subject because of adverse event.

The per-protocol population, defined as all subjects in the ITT population who did not have any major protocol deviations, included 1465 subjects (97%) overall with 482, 486, and 497 subjects in the placebo, BIIB017 every 4 weeks, and BIIB017 every 2 weeks groups, respectively.

Disposition Year 1 (Figure 3 below)

With one exception, subjects who withdrew from study treatment within the first year also withdrew from the study. The percentage of subjects who discontinued study treatment or withdrew in Year 1 was lower in the placebo group compared with the BIIB017 treatment groups: 9% for placebo, 12% for BIIB017 every 4 weeks, and 14% for BIIB017 every 2 weeks. The difference in discontinuation rates between treatment groups was largely due to the difference in AEs leading to discontinuation or withdrawal (5% in each BIIB017 treatment group, 1% in the placebo group). For the BIIB017 treatment groups, withdrawals occurred more frequently during the first 12 weeks of treatment than in any other 12-week period during Year 1 (Sponsor Table 76 – page 420/4864).

Figure 3 Overview of Subject Disposition Year 1 (Sponsor Figure 4, CSR page 124/4864)



N, n = number of subjects; Q2W = every 2 weeks; Q4W = every 4 weeks
 Source: Sponsor Table 9, pp 119-120 Study report

Reviewer comment: More subjects discontinued in the two active treatment groups. Those due to adverse events could be considered treatment failures. In addition, of those who withdrew consent some were related to the occurrence of relapses and/or a perceived lack of effectiveness. These also could be considered treatment failures. In the placebo group 4 subjects withdrew consent due to the occurrence of relapses or due to perceived ineffective treatment and one “other” discontinuation was related to an allergic reaction to methylprednisolone used to treat a relapse. In the BIIB017 q4W group there was one discontinuation due to adverse effects of treatment, one lost to follow-up related to a relapse, 4 withdrawal of consent due to relapse/ineffective treatment and one withdrawal of consent due to adverse effects of treatment. In the q2W group 3 discontinuations were due to adverse effects of treatment, 3 due to relapse/ineffective treatment, one Investigator decision for “safety” reasons. However since in most cases the reason

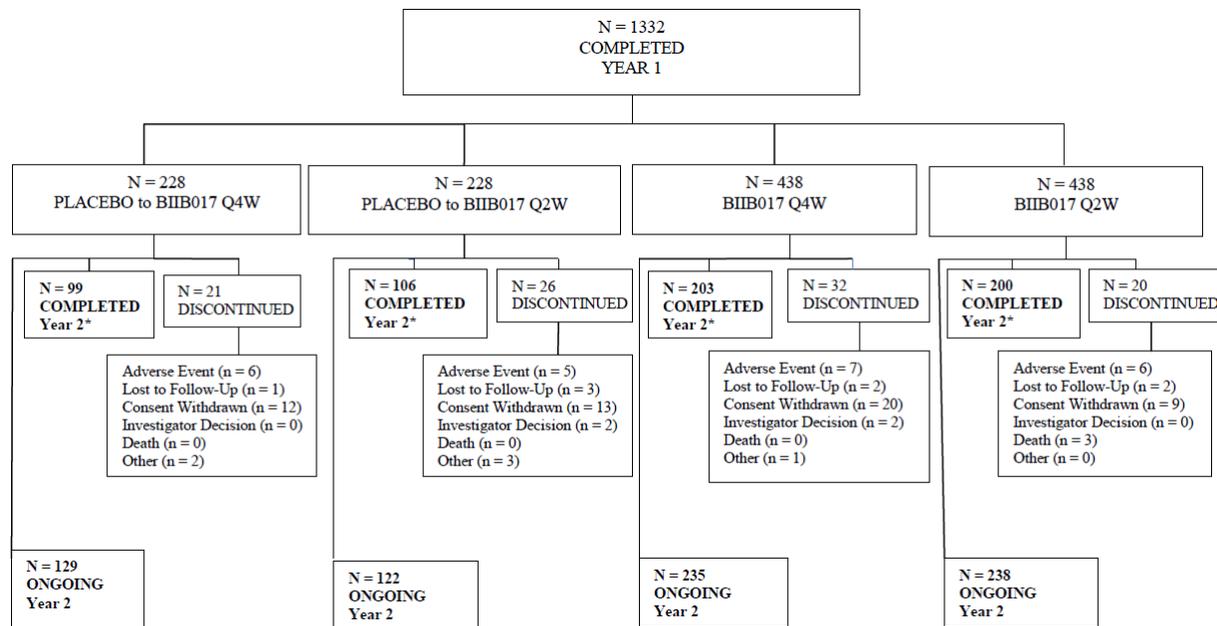
for withdrawal of consent is not well documented. In the analyses of the ITT population all of these subjects would be included up to the time of withdrawal but censored after that. The impact of the discontinuations on the results is not clear. However, the sponsor has partially addressed this issue in section 11.2.1.1 of the CSR (see Table 22) in which those who withdrew early are analyzed separately. The ARR was higher in those who withdrew early from the groups treated with BIIB017 compared to those who completed suggesting that early withdrawal did not enhance the benefit seen in these groups.

Year 2 (Figure 4 below)

Of the 1512 subjects who received treatment, 1332 (88%) completed Year 1 treatment. Of the 1332 subjects who received treatment in Year 2, 608 subjects (46%) had completed the 2-year treatment period (completed the study), and 625 subjects (47%) were continuing Year 2 treatment and assessments at the data cutoff date (24 October 2012).

Reviewer comment: Data from year two is incomplete. The proportion of subjects discontinuing appears to be higher than in year 1 but this may be due to the tendency for withdrawals to occur early in the subjects newly randomized to BIIB017.

Figure 4 Overview of Subject Disposition Year 2



*Completed Year 2 as of the data cutoff date, 24 October 2012; the study is ongoing.
 N, n = number of subjects; Q2W = every 2 weeks; Q4W = every 4 weeks
 Source: (Sponsor Figure 4) and Sponsor Table 10

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Overall result

The Annualized Relapse Rate (ARR) was analyzed using the pre-specified method, i.e. using a negative binomial regression adjusted for baseline EDSS category (<4 vs. ≥4), baseline age category (<40 vs. ≥40) and baseline relapse rate. The analysis did not include relapses that occurred after a subject switched to an alternative approved therapy (see 6.1.2.5 above - there were 16 such subjects, 7 in the placebo group, 3 in the BIIB017 q4W group and 6 in the BIIB017 q2W group). For the primary analysis only relapses confirmed by the INEC were included. There were 487 possible relapses reported of which 464 were assessed as “protocol-defined” and 422 were confirmed by the INEC. These categories of relapse are listed by treatment group in Table 18.

Table 18 Relapses by treatment group year 1 (ITT)

	Placebo	BIIB017 Q4W	BIIB017 Q2W	Total
All relapses	213	142	132	487
Protocol-defined relapses	204	134	126	464
INEC-confirmed relapses	181	125	116	422
Percent <u>not</u> protocol-defined (n)	4.2% (9)	5.6% (8)	4.6% (6)	4.7% (23)
Percent of all relapses <u>not</u> confirmed by INEC (n)	15.0% (32)	12.0% (17)	12.1% (16)	13.3% (65)
Percent of all protocol defined relapses <u>not</u> confirmed by INEC (n)	11.3% (23)	6.7% (9)	7.9% (10)	9.1% (42)

Areas shaded in grey: Reviewer calculation.
Source: Sponsor Table 27.

Reviewer comment: There appears to be a significant difference in the number of relapses, either overall or “protocol-defined”, that were confirmed by the INEC when comparing the placebo group to the two active treatment groups. It is unclear if this could be due to an unidentified bias, e.g. by the investigator in referring relapses to the INEC. Table 21 below includes all relapses without regard for INEC adjudication. The primary result remains significant and therefore this did not appear to significantly influence the primary result.

The ARR at one year was reduced by 27.5% in the BIIB017 q4W group (p=0.014) and by 35.6% in the BIIB017 q2W group (p=0.0007) compared to placebo (Table 19). Relapses that were not confirmed by the INEC are not included in this analysis. Relapses that occurred after a subject changed to an approved therapy for MS are also excluded. The analysis was conducted according to the pre-specified method including use of a negative binomial distribution for the regression analysis. The analysis is adjusted for baseline age group (less than 40 years old vs. 40 or more), the baseline relapse rate and baseline EDSS which were all well balanced at baseline (Table 9, Table 11).

Table 19 Primary efficacy endpoint analysis (ITT)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT population N	N=500	N=500	N=512
Number of INEC confirmed relapses n, (%)			
0	358 (72)	395 (79)	422 (82)
1	110 (22)	90 (18)	71 (14)
2	26 (5)	12 (2)	13 (3)
≥3	6 (3)	3 (2)	6 (5)
Total relapses	181	125	116
Subject-years	445	434	435
Unadjusted ARR ^a	0.407	0.288	0.266
Adjusted ARR (95% CI) ^b	0.397 (0.328, 0.481)	0.288 (0.234, 0.355)	0.256 (0.206, 0.318)
Rate ratio (Active/placebo) 95% CI ^b		0.725 (0.565, 0.930)	0.644 (0.500, 0.831)
p-value compared to placebo		0.014	0.007

NOTE 1: Only relapses confirmed by INEC are included in the analysis.

2: Data after subjects switched to alternative MS medications are excluded.

^a: The annualized relapse rate is calculated as the total number of relapses occurred during year 1 for all subjects, divided by the total number of subject-years followed in year 1.

^b: Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. ≥4), baseline relapse rate, age (<40 vs. ≥40).

^c: The number of relapses for each subject divided by the number of years followed in year 1 for that subject. Summary statistics across all subjects are presented.

Source: Sponsor Table 28

Reviewer comment: Given that there may have been a disproportionately higher number of potential relapses not confirmed by the INEC for the placebo group, the analyses based on all or all protocol-defined relapses become important sensitivity analyses. See Table 21 for the analysis that includes all potential relapses. The result supports the primary result. A relatively high proportion of subjects remained relapse free in all groups at one year, approximately 80 percent in the two BIIB017 groups and approximately 70% in the placebo group.

Table 20 Primary efficacy endpoint analysis (PP)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Per protocol population N	N=482	N=486	N=477
Number of INEC confirmed relapses n, (%)			
0	345 (72)	383 (79)	411 (83)
1	106 (22)	99 (18)	68 (14)
2	25 (5)	12 (2)	13 (3)
≥3	6 (3)	3 (2)	5 (5)
Total relapses	175	123	110
Subject-years	431	425	427
Unadjusted ARR ^a	0.406	0.290	0.258
Adjusted ARR	0.397	0.291	0.248

(95% CI) ^b	(0.327, 0.482)	(0.237, 0.359)	(0.199, 0.310)
Rate ratio (Active/placebo)		0.734	0.625
95% CI ^b		(0.570, 0.944)	(0.482, 0.809)
p-value compared to placebo		0.0158	0.0004

NOTE 1: Only relapses confirmed by INEC are included in the analysis.

2: Data after subjects switched to alternative MS medications are excluded.

^a: The annualized relapse rate is calculated as the total number of relapses occurred during year 1 for all subjects, divided by the total number of subject-years followed in year 1.

^b: Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. >=4), baseline relapse rate, age (<40 vs. >=40).

^c: The number of relapses for each subject divided by the number of years followed in year 1 for that subject.

Summary statistics across all subjects are presented.

Source: Sponsor Table 94

Reviewer comment: Relatively few subjects were excluded from the PP analysis, 18 from the placebo group, 15 from the BIIB017 q4W and 18 from the BIIB017 q2W groups (Table 16). The analysis is consistent with the primary analysis.

Table 21 Primary efficacy analysis with all potential relapses included (ITT)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=500	N=500	N=512
Number of relapses n, (%)			
0	335 (67)	384 (77)	412 (80)
1	126 (25)	97 (19)	78 (15)
2	32 (6)	15 (3)	14 (3)
≥3	7 (3)	4 (3)	8 (6)
Total relapses	213	142	132
Subject-years	445	434	436
Unadjusted ARR ^a	0.478	0.327	0.303
Adjusted ARR (95% CI) ^b	0.469 (0.392, 0.560)	0.328 (0.270, 0.398)	0.293 (0.239, 0.359)
Rate ratio (Active/placebo)		0.700	0.625
95% CI ^b		(0.554, 0.883)	(0.493, 0.792)
p-value compared to placebo		0.0026	<0.0001

NOTE 1: All relapses reported on the unscheduled relapse assessment visit are included in the analysis..

2: Data after subjects switched to alternative MS medications are excluded.

^a: The annualized relapse rate is calculated as the total number of relapses occurred during year 1 for all subjects, divided by the total number of subject-years followed in year 1.

^b: Based on negative binomial regression, with adjustment for baseline EDSS (<4 vs. >=4), baseline relapse rate, age (<40 vs. >=40).

Source: Sponsor Table 96

Reviewer comment: This sensitivity analysis addresses the concern that the INED may have been biased somehow in the confirmation of relapses. The result is not changed significantly.

Additional sensitivity analyses were conducted:

- 1) INEC confirmed relapses using a Poisson regression model (Sponsor Table 95)
- 2) Protocol defined relapses in the ITT population (Sponsor Table 97)

3) INEC confirmed relapses with the result adjusted for the presence or absence of gadolinium enhancing lesions on MRI at baseline

All continued to show a statistically significant difference between both active treatment groups and placebo.

Reviewer comment: The pre-specified primary endpoint using the pre-specified analysis was met and is supported by multiple sensitivity analyses.

Subjects withdrew for various reasons that were generally evenly distributed between the placebo and active treatment groups with the exception of withdrawals due to adverse events. The rates of withdrawal were 8.8%, 12.4% and 14.3% for the placebo, BIIB017 q4W and BIIB017 q2W groups respectively. For those who withdrew by the end of year one the confidence interval for the rate ratio crosses 1.0 for both the BIIB017 q4W group and for the BIIB017 q2W group. For those who completed the first year the confidence interval for the rate ratio remains below 1.0 for both the BIIB017 q4W group (0.581, 0.974) and for the BIIB017 q2W group (0.461, 0.793).

Table 22 Primary efficacy analysis in subjects who completed vs. withdrawals

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=500	N=500	N=512
Subjects who withdrew	44	62	73
Adjusted relapse rate	0.648	0.323	0.530
95% CI ^a	0.336, 1.247	0.153, 0.681	0.291, 0.967
Rate ratio		0.498	0.819
95% CI		(0.207, 1.199)	(0.385, 1.739)
Subjects who completed	456	438	439
Adjusted relapse rate	0.380	0.286	0.230
95% CI	0.312, 0.464)	(0.231, 0.354)	(0.182, 0.290)
Rate ratio		0.752	0.605
95% CI		(0.581, 0.974)	(0.461, 0.793)

NOTE: Data after subjects switched to alternative MS medications are excluded.

(a) Assessing the difference between the treatment groups, based on negative binomial regression, adjusted for baseline EDSS (<4 vs. >=4), baseline relapse rate, age (<40 vs. >=40).

Source: Sponsor Table 99.

Reviewer comment: Withdrawals were more frequent and tended to occur earlier in the active treatment groups. The effect of including these subjects up to the time of withdrawal on the calculation of the ARR is unclear. Their relapse rate as a group is higher suggesting that the rate is affected by those who withdrew after one or more exacerbations. On the other hand those who withdrew due to an adverse event may have contributed time on study without adequate time to observe an exacerbation, especially the early withdrawals due to adverse events in

the active treatment groups. An analysis limited to completers still shows a significant benefit in both active treatment groups compared to placebo.

The table below lists the range of relapses rates found in the trial.

Table 23 Annualized Relapse Rate by analysis population

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=500	N=500	N=512
Primary analysis	0.397	0.288	0.256
Per protocol	0.397	0.291	0.248
All relapses	0.469	0.328	0.293
Completers	0.380	0.286	0.230
Withdrawals	0.648	0.323	0.530
Year 2			
BIIB017 in Year 1		0.282	0.197
Placebo in year 1		0.270	0.291
Year 1+2		0.287	0.210

Reviewer comment: The annualized relapse rate varies from approximately 0.25 to nearly 0.4 for the ITT population and limited to INEC confirmed relapses. As expected the ARR is higher when all relapses are included regardless of whether determined to meet the protocol definition or confirmed by the INEC. The annualized relapse rate is expected to be high in those who did not complete the study since most would have failed to complete due to relapses.

To assess whether the occurrence of adverse effects of therapy may have biased subjects in reporting symptoms, an analysis of those with and without flu-like symptoms with injections and of those with and without local injection site reactions was conducted. There is no apparent influence of either the occurrence of flu-like symptoms or local reactions on the reduction in ARR with BIIB017 treatment. In general, subjects who had an AE of flu-like symptoms had a higher ARR compared to those without (Sponsor Table 100).

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Number of New or Newly Enlarging T2 Hyperintense Lesions at Year 1

Treatment with BIIB017 every 4 weeks and BIIB017 every 2 weeks reduced the number of new or newly enlarging T2 hyperintense lesions that developed over the first year by 28% (p=0.0008) and 67% (p<0.0001), respectively, compared with placebo.

Table 24 New or newly enlarging T2 MRI lesions at week 48 (ITT)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
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	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Baseline to week 48 new lesions	n=476	n=462	n=457
0 lesions - n, (%)	91 (19)	115 (25)	187 (41)
≥4 lesions – n, %	280 (59)	218 (47)	127 (28)
Mean (SD)	13.3 (19.5)	9.2 (15.8)	4.1 (8.6)
Median (25 th – 75 th percentile)	6.0 (1-17)	3.0 (1-11)	1.0 (0-4)
Adjusted mean ^a	10.9	7.9	3.6
Lesion mean ratio (95% CI)		0.72 (0.6, 0.87)	0.33 (0.27, 0.40)
p-value		0.0008	<0.0001

Note: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are imputed based on previous visit data assuming the constant rate of lesion development or group mean at same visit. Number of subjects with imputed data for each group are 2, 1, 1 for week 24, and 18, 23, 18 for week 48.

^a: Adjusted mean, lesion mean ratio (95% CI) and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for baseline number of T2 lesions.

Source: Sponsor Table 29.

Similar results were seen for the Per Protocol population and using observed data only or using alternate imputation methods.

Reviewer comment: The result for T2 lesions at 48 weeks is consistent with the primary endpoint analysis. Based on a rate ratio of 0.72 for BIIB017 q4W vs. 0.33 for BIIB017 q2W, treatment with BIIB017 q2W may be superior to BIIB017 q4W for this endpoint. The number of subjects with no new T2 lesions at one year, 41% vs. 25% also suggests that the BIIB017 q2W may be superior to BIIB017 q4W.

6.1.5.2 Proportion of Subjects relapsed at one Year

As compared with placebo, the risk of relapse over 1 year was significantly reduced by 26% (p = 0.0200) following treatment with BIIB017 every 4 weeks and 39% (p = 0.0003) following treatment with BIIB017 every 2 weeks. This result was derived using the Cox proportional hazards model adjusting for baseline EDSS, age group, baseline relapse rate and the presence or absence of Gd-enhancing lesions at baseline.

Table 25 Proportion of subjects with an INEC confirmed relapse at one year

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=500	N=500	N=512
Number of subjects relapsed	142 (28)	105 (21)	90 (18)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Estimated proportion relapsed at 48 weeks ^a	0.291	0.222	0.187
Hazard ratio (active/placebo) ^b		0.74	0.61
95% CI		(0.57, 0.95)	(0.47, 0.80)
P-value		0.02	0.0003

NOTE 1: Only relapses confirmed by INEC are included in the analysis.

2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrew from study are censored at the time of switch/withdrawal.

a : Based on Kaplan-Meier product limit method.

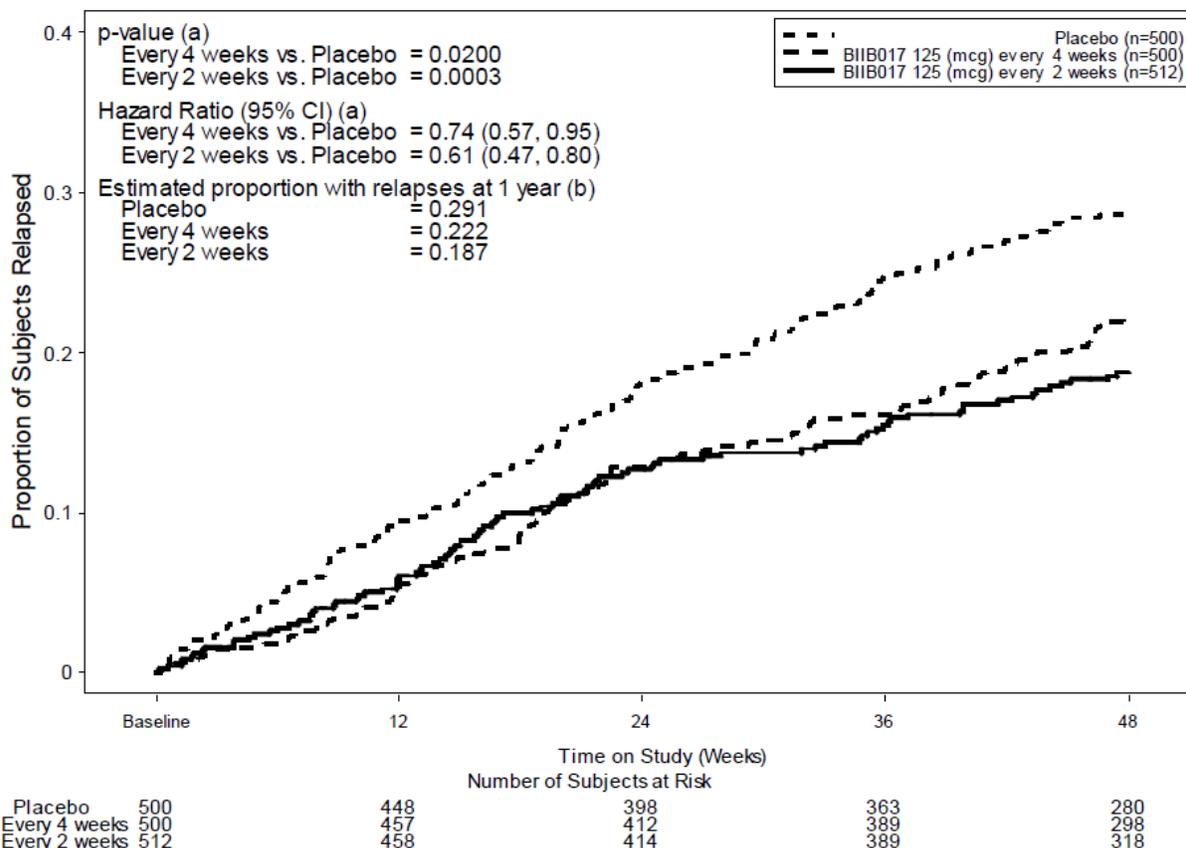
b : Based on Cox proportion hazards model, adjusted for baseline EDSS (<4 vs. >=4), age (<40 vs. >=40), baseline relapse rate, and baseline Gd enhancing lesions (presence vs. absence).

Source: Sponsor Table 30

Similar reductions in the risk of relapse were seen for the PP population. If all relapses are included (Sponsor Table 106) there was an approximately 32% reduction compared to placebo for the BIIB017 q4W group (p=0.0018) and a 43% reduction for the BIIB017 q2W group (p<0.0001).

The time to first relapse is assessed in the Kaplan-Meier graph below.

Figure 5 Time to first INEC confirmed relapse - ITT



NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
 2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored at the time of switch/withdrawal.
 (a) P-value and hazard ratio (active/placebo) are based on Cox proportional hazards model, with adjustment for or baseline EDSS (<4 v s. >=4).
 (b) Kaplan-Meier estimate of the proportion of subjects relapsed within 1 year.
 Source: Sponsor Figure 7

Reviewer comment: This endpoint is a subject level result which supports the clinical relevance of the overall reduction in ARR for the population as a whole. Sensitivity analyses including an analysis of all relapses are consistent with the ITT analysis. Visual inspection of the Kaplan-Meier plot shows an early separation of the time to first relapse between the BIIB017 groups and placebo with a continued divergence over the first year.

6.1.5.3 Disability Progression by EDSS at one year

As compared to placebo, the risk of progression of disability (12-week confirmation) over 1 year was reduced by 38% (p = 0.0380) following treatment with BIIB017 every 4 weeks and 38% (p = 0.0383) following treatment with BIIB017 every

2 weeks.

Table 26 Proportion of subjects with sustained EDSS increase (ITT)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=500	N=500	N=512
Number of subjects progressed (%)	50 (10)	31 (6)	31 (6)
Estimated proportion progressed at 48 weeks ^a	0.105	0.068	0.068
Hazard ratio (active/placebo) ^b		0.62	0.62
95% CI		(0.40, 0.97)	(0.40, 0.97)
p-value		0.0380	0.0383

NOTE 1: 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.

2: Subjects are censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression.

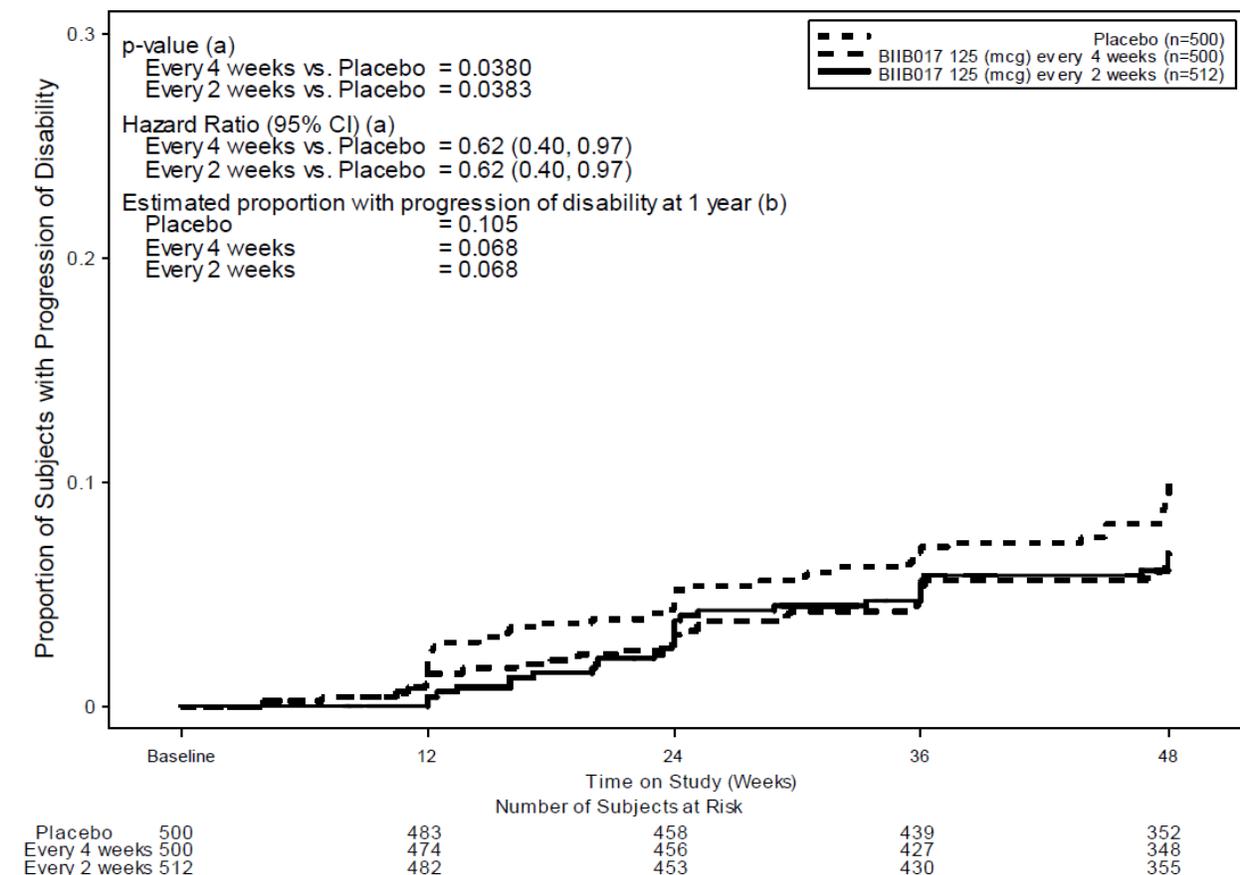
^a : Estimated time to progression and proportion of patients with progression based on the Kaplan-Meier product limit method.

^b :Based on Cox Proportional Hazards model, adjusted for baseline EDSS and age (<40 vs. ≥ 40).

Source: Sponsor Table 31

Very similar results were seen with the PP population. If the tentative EDSS progression prior to withdrawal was assumed to be sustained (i.e. without confirmation over the next 90 days on alternate therapy) then the reductions in risk are 39% and 29% for the BIIB017 q4W and q2W groups respectively. This further supports the result of the primary analysis.

Figure 6 Time to Sustained Progression of Disability - Year 1 - ITT



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 v s. ≥ 40).

(b) Kaplan-Meier estimate of the proportion of subjects with progression within 1 year.

Source: Sponsor Figure 8.

Reviewer comment: There does not appear to be a difference between the two BIIB017 doses on the reduction in the proportion of subjects with sustained disability based on the EDSS. Visual inspection of the Kaplan-Meier plot does not show a difference between the two doses for the time to progression.

6.1.6 Other Endpoints

Although 456 subjects in the placebo arm were re-randomized to either BIIB017 q4W or BIIB017 q2W for year two, and 438 subjects in both the BIIB017 arms continued in to year 2, at the time of database lock there were only 96 and 106 subjects who completed to week 96 in the placebo to BIIB017 q4W and BIIB017 q2W groups respectively. For those randomized to BIIB017 in year one, 203 and 200 subjects completed week 96 in the BIIB017 q4W and BIIB017 q2W groups respectively.

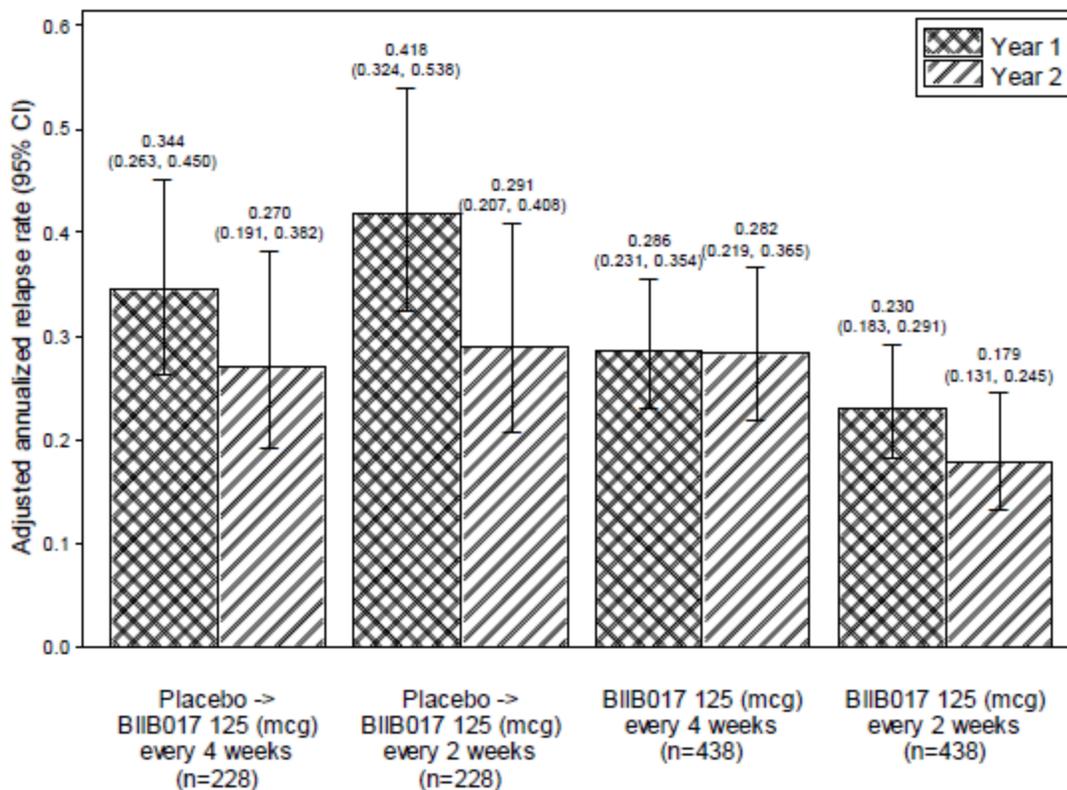
Reviewer comment: The analyses of year two data are limited by incomplete treatment groups. Since not all events necessarily occur uniformly over time the results of these analyses may not be representative of the result when all subjects have completed year 2.

6.1.6.1 Annualized relapse rate over 2 years

6.1.6.1.1 Annualized relapse rate in year 2 compared to year one for those randomized to BII017 in year one

The annualized relapse rate for the two years combined was 0.287 (95% CI: 0.238, 0.345) for the BII017 q4W group and 0.210 (95% CI: 0.171, 0.257) for the BII017 q2W group. For the q4W group the rate did not appear to change from year one to two but it did decline further in year 2 compared to year one for the q2W group.

Figure 7 Summary of Annualized INEC confirmed relapse rate by study year - ITT population dosed in year 2



NOTE 1: Only relapses confirmed by INEC are included in the analysis.
 2: Data after subjects switched to alternative MS medications during the period are excluded.
 3: Adjusted annualized relapse rate and 95% CI are based on negative binomial regression (if the model cannot be converged, Poisson regression is used instead), adjusted for baseline EDSS (<4 vs. >=4), baseline relapse rate and age (<40 vs. >=40).
 Source: Sponsor Figure 9, based on Sponsor Tables 32

Reviewer comment: The ARR's for year one differ somewhat from the primary analysis in that only subjects dosed in year two are included. For those treated with BIIB017 in year 1 the ARR remained stable in year 2 for those treated with BIIB017 q4W in year one and was lower in year 2 for those treated with BIIB017 q2W in year 1. Those treated with placebo in year 1 showed a reduction in the ARR in year 2 for both BIIB017 groups to an ARR comparable to that of the active treatment groups at the end of year 1 (See Table 23 above).

6.1.6.1.2 Proportion of Subjects relapsed over 2 years

The proportion of subjects with a relapse over two years was lower in those treated with BIIB017 for both years compared to those treated with placebo in year one. This was true for INEC confirmed relapses and for all relapses. Compared to subjects who were treated with placebo in year one and either dose of BIIB017 in year two, treatment with BIIB017 q4W over two years was associated with a 22% reduction in the risk of a relapse (nominal p-value 0.0286) and a 36% reduction for the BIIB017 q2W group.

Table 27 Proportion of Subjects with INEC relapse over 2 years - ITT

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=228	N=228	N=438	N=438
Number of subjects relapsed (%)	78 (34)	87 (38)	133 (30)	107 (24)
Estimated proportion relapsed at 48 weeks	0.263	0.294	0.217	0.176
Estimated proportion relapsed at 96 weeks	0.383	0.408	0.340	0.270
Proportion relapsed at 96 weeks – proportion at 48 weeks	0.120	0.114	0.123	0.094

NOTE 1: Only relapses confirmed by INEC are included in the analysis.

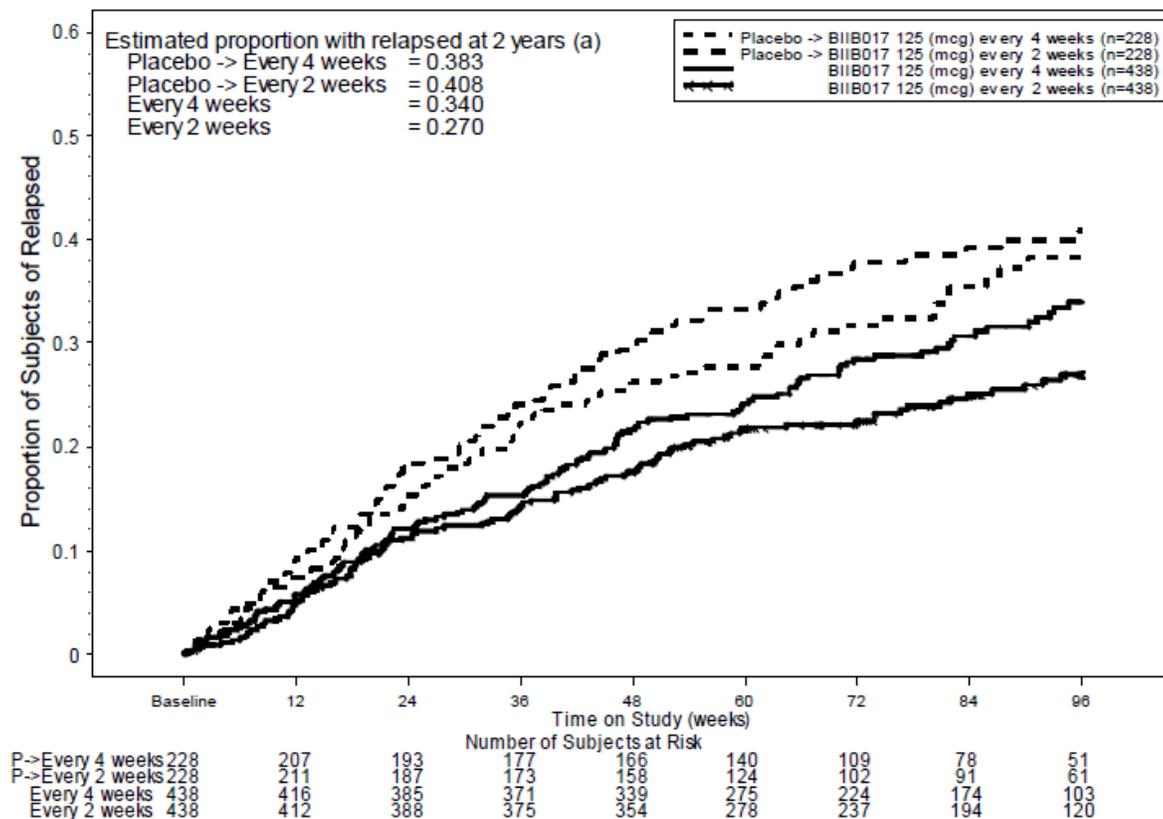
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrew from study are censored at the time of switch/withdrawal.

Source: Sponsor Table 115.

Reviewer comment: The above analysis is based on the full ITT but with incomplete data on a significant proportion of these populations. As with the ARR it appears that the proportion of subjects relapsed in year 2 is approximately the same for both groups randomized from placebo to BIIB017 in year two and for the group treated with BIIB017 q4W in both years. There is a further decline in the proportion for the BIIB017 q2W group in year 2 compared to year one. As more subjects complete year 2 the results could change.

The time to first INEC relapse is depicted in the Kaplan-Meier graph below.

Figure 8 Time to first INEC confirmed relapse over 2 years (ITT dosed in year 2)



NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
 2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored at the time of switch/withdrawal
 (a) Kaplan-Meier estimate of the proportion of subjects relapsed within 2 years.

Reviewer comment: There may be a continuing separation of the BIIB017 q2W group from the q4W group over time based on the above Kaplan-Meier curve. This may further support the superiority of the q2W dosing. This should be reviewed when the dataset for 2 year results is complete.

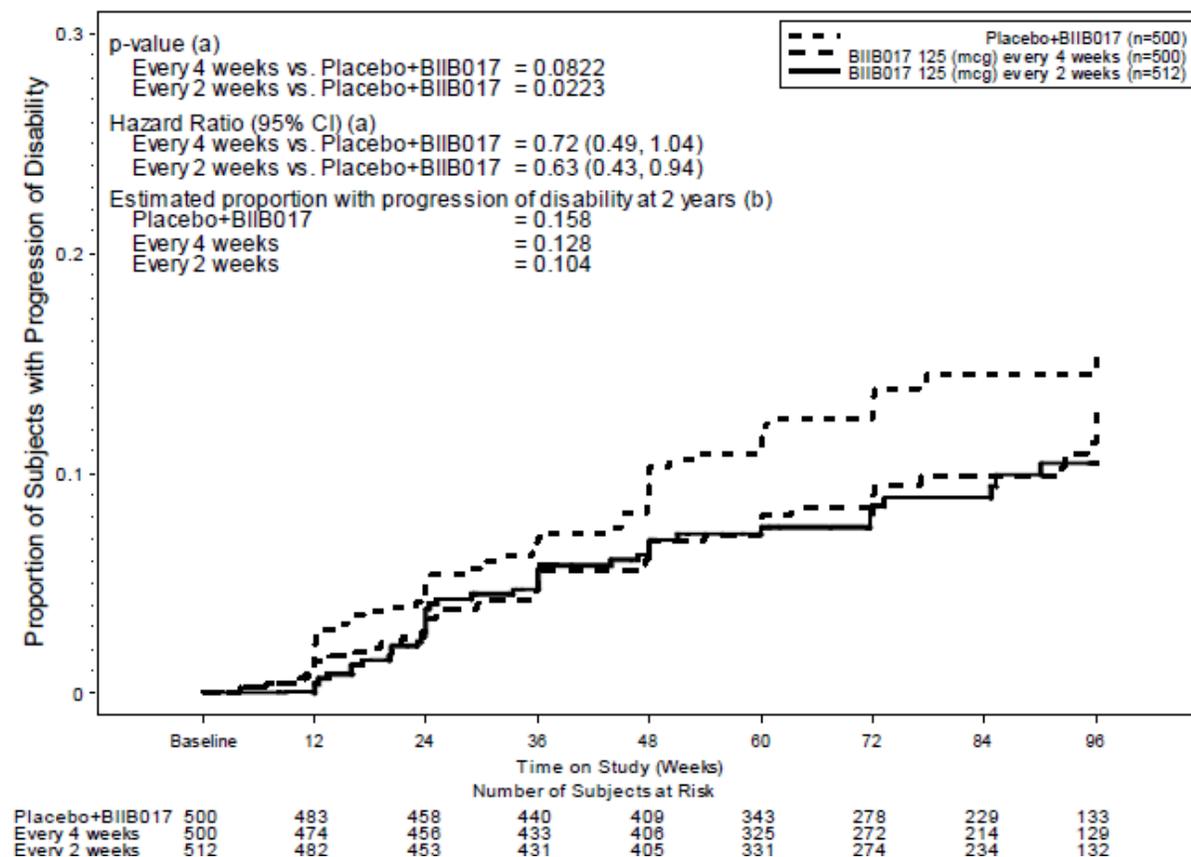
6.1.6.1.3 Disability Progression by EDSS Over 2 years

The Kaplan-Meier estimate of the proportion of subjects in the full ITT population with progression of disability by EDSS as defined in the protocol³ at 2 years after the start of treatment was 28% lower (0.158 vs. 0.128; nominal p-value 0.0822) for those who were

³ Disability progression was defined as either a 1.0 or greater increase on the EDSS for those with a baseline EDSS of 1.0 or more – or a 1.5 or greater increase for those with a baseline EDSS of 0. The increase had to be confirmed at a visit at least 74 days after the increase was first observed.

treated with BIIB017 q4W for two years and 37% lower (0.158 vs. 0.104; nominal p-value 0.0223) for those treated with BIIB017 q2W for years compared to those treated with placebo in the first year and BIIB017 in the second year. The 10th percentile time to progression was also longer for those treated with BIIB017 for 2 years.

Figure 9 Time to Sustained Progression of Disability - ITT - 2 years



NOTE 1: 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

2: Subjects in placebo+BIIB017 group received placebo in year 1, and either BIIB017 125 (mcg) every 4 weeks or every 2 weeks in year 2 if they continued study treatment in year 2.

(a) P-value and hazard ratio (active/placebo) are based on a Cox proportional hazards model, with adjustment for baseline EDSS and age (<40 v s. ≥ 40).

(b) Kaplan-Meier estimate of the proportion of subjects with progression within 1 year.

Source: Sponsor Figure 11

Reviewer comment: As noted above, interpretation of the results is somewhat limited since at the time of database lock only approximately half of the subjects had completed year two and the remainder was continuing. Only approximately 130 subjects in each of the three groups were considered "at risk" at week 96. There

is no apparent separation of the two BIIB017 doses over two years for this endpoint.

6.1.6.1.4 Number of Relapses Requiring IV Steroid therapy

The annualized rate for relapses confirmed by the INEC and that required the use of corticosteroids was lower in those treated with BIIB017 q4W and BIIB017 q2W compared to placebo.

Table 28 Annual rate of relapses that required treatment with corticosteroids. Year one. ITT

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT, N	N=500	N=500	N=512
Number with relapse requiring IV steroids; n, (%)			
0	375 (75)	403 (81)	432 (84)
1	97 (19)	83 (17)	64 (13)
2	22 (4)	11 (2)	10 (2)
>2	6 (1)	3 (<1)	6 (1)
Total relapses requiring IV steroids	160	116	103
Individual subject ARR ^c Mean (SD)	0.378 (0.82)	0.309 (0.98)	0.267 (0.83)
Unadjusted ARR ^a	0.359	0.267	0.236
ARR ^b 95% CI	0.359 (0.3, 0.43)	0.267 (0.22, 0.33)	0.236 (0.19, 0.3)
Rate ratio (active/placebo) 95% CI		0.744 (0.56, 0.986)	0.658 (0.49, 0.88)
p-value		0.0395	0.0049

NOTE 1: Only relapses confirmed by INEC are included in the analysis.

2: Data after subjects switched to alternative MS medications are excluded.

^a: The annualized relapse rate is calculated as the total number of relapses requiring IV steroid during year 1 for all subjects, divided by the total number of subject-years followed in year 1.

^b: Based on Poisson regression, the model includes a term for treatment group only.

^c: The number of relapses for each subject divided by the number of years followed in year 1 for that subject.

Summary statistics across all subjects are presented.

Source: Sponsor Table 33.

Reviewer comment: Relapses that required treatment with corticosteroids might be considered more severe relapses. The rate ratio or percent reduction with BIIB017 treatment are comparable to those seen when all INEC relapses are included.

Table 29 Proportion of Subjects with relapse requiring treatment with corticosteroids. Year 1. ITT.

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT, N	N=500	N=500	N=512
Number with relapse requiring steroids (%)	125 (25)	97 (19)	80 (16)
Estimated proportion at 48 weeks ^a	0.257	0.205	0.167
Hazard ratio ^b		0.76	0.61
95% CI		(0.58, 0.99)	(0.46, 0.81)
p-value (compared to placebo) ^b		0.0391	0.0007

NOTE 1: Only relapses confirmed by INEC are included in the analysis.

2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrew from study are censored at the time of switch/withdrawal.

3: Numbers in parentheses are percentages.

^a: Based on Kaplan-Meier product limit method.

^b: Based on Cox proportion hazards model, the model included a term of treatment group only.

Source: Sponsor Table 122.

Reviewer comment: At a subject level the hazard ratio is comparable to the reduction seen for the ARR, supporting the relevance of the primary analysis to an individual patient.

Table 30 Percent of INEC confirmed relapses treated with corticosteroids - ITT - year 1

	Placebo	BIIB017 Q4W	BIIB017 Q2W	Total
INEC-confirmed relapses	181	125	116	422
Year 1 INEC Relapses treated with corticosteroids (% of INEC confirmed relapses)	160 (88.4)	116 (92.8)	103 (88.8)	379 (90)

Shaded area – reviewer calculation.

Reviewer comment: Of all INEC confirmed relapses that did occur, there was no difference in the number that required treatment with corticosteroids (reviewer calculation based on Sponsor Table 33 and Sponsor Table 7). The reduction in relapses requiring corticosteroids is at the subject level, i.e. a subject on placebo was more likely to have a relapse requiring corticosteroids compared to those on BIIB017.

6.1.6.1.5 Disability Progression by MSFC at Year One

The components of the MSFC include the 9 Hole Peg Test, Timed 25 foot walk (T25FW) and the PASAT 3 tests. The MSFC composite z-score is calculated by creating z-scores for each component of the MSFC, and averaging them to create an overall composite score. A positive change in the composite z-score indicates improvement, and a negative change indicates worsening. At one year the mean change from baseline in the composite z-score was -0.023 (SD 0.66) for the placebo group compared to -0.042 (SD 0.57) for the BIIB017 q4W group (p=0.1894) and compared to 0.041 (SD 0.39) for the BIIB017 q2W group (p=0.22).

6.1.6.1.6 Tertiary MRI endpoints

6.1.6.1.6.1 New or newly enlarging T2 hyperintense lesions

The number of new or newly enlarging T2 MRI lesions was reduced in both BIIB017 groups compared to placebo of the first year of blinded treatment. See Table 24 for week 48 results. At the earlier time point of 24 weeks the mean number of new or newly enlarging T2 lesions was reduced in those treated with either dose of BIIB017. The number of subjects with no new lesions was increased.

Table 31 Number of new or newly enlarging T2 lesions at 24 weeks, ITT

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT, N	N=500	N=500	N=512
New lesions from BL to week 24 (%)			
0	125(26)	158 (34)	212 (46)
1 - 3	129 (27)	150 (32)	156 (34)
≥4	222 (47)	154 (33)	89 (19)
n	476	462	457
Mean (SD)	6.9 (11)	5.4 (10)	2.6 (5)
Adjusted mean ^a	5.8	4.6	2.2
Lesion mean ratio		0.80	0.39

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
95% CI		(0.66, 0.97)	(0.32, 0.47)
		0.0225	<0.0001

NOTE 1: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are imputed based on previous visit data assuming the constant rate of lesion development or group mean at same visit.

Number of subjects with imputed data for each group is 2, 1, 1 for week 24, and 18, 23, 18 for week 48.

^a: Adjusted mean, lesion mean ratio (95% CI) and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for baseline number of T2 lesions.

Source: Sponsor Table 29

Over the first two years of treatment the conversion of the placebo group to active treatment with BIIB017 was associated with an increase in the number of subjects with no new lesions, a decrease in those with 4 or more lesions and a reduction in the mean number of new lesions. These benefits were most noticeable for the BIIB017 q2W group. For those treated with BIIB017 in year one, the benefit appeared to be maintained in year two.

Table 32 New or newly enlarging T2 MRI lesions year 2 -- ITT population dosed in year 2

	Placebo to BIIB017 q4W	Placebo to BIIB017 q2W	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT dosed in year 2	228	228	438	438
New lesions from week 48 to week 96				
n at 96 weeks	96	102	195	188
0	19 (20)	47 (46)	65 (33)	115 (61)
% from 0 to 48 weeks	(18)	(21)	(24)	(40)
1-3	32 (33)	26 (25)	60 (31)	42 (22)
% from 0 to 48 weeks	(21)	(24)	(29)	(32)
≥4	45 (47)	29 (28)	70 (36)	31 (16)
% from 0 to 48 weeks	(61)	(55)	(47)	(28)
Mean – week 48 to 96	7.3 (11)	3.4 (5.7)	6.3 (11.6)	2.0 (4.4)

	Placebo to BIIB017 q4W	Placebo to BIIB017 q2W	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Mean week 0 to 48	13.9 (19)	12.5 (20)	9.4 (16)	4.1 (9)
New lesions from week 0 to week 96				
0 (%)	12 (13)	16 (16)	36 (18)	71 (38)
1-3 (%)	12 (13)	25 (25)	41 (21)	57 (30)
≥4 (%)	72 (75)	61 (60)	118 (61)	60 (32)
Mean (SD)	20.9 (26)	17.9 (29)	13.8 (23)	5.3 (9.5)

NOTE 1 : Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are included and imputed using LOCF with the constant rate.

Source: Sponsor Table 155

Reviewer comment: The q2W dose appears to be superior to the q4W dose for the placebo group randomized to active treatment in year 2. The benefit of q2W dosing may also be superior to q4W dosing in year 2 for those treated with BIIB017 in year 1. The dataset for year 2 is not complete and therefore this result could change.

6.1.6.1.6.2 New Active lesions

In the first year treatment with BIIB017 q4W was associated with a 35% reduction in “new active lesions” on MRI compared to placebo ($p < 0.0001$) and a 67% reduction in the BIIB017 q2W group ($p < 0.0001$). At 48 weeks the mean number of new active lesions during this period was 13.4 in the placebo group compared to 9.5 in the BIIB017 q4W group (ratio 0.65) and compared to 4.1 in the BIIB017 q2W group (ratio 0.33). As for new T2 lesions, the benefit was maintained in year two for those treated with BIIB017 in year one. For those who received placebo in year one, reductions were seen in year two that were comparable to those seen for T2 lesions.

Reviewer comment: Note that “new active lesions” are defined as “the sum of non-enhancing new or newly enlarging T2 lesions plus Gadolinium enhancing lesions”. This was an exploratory endpoint that simply combines new or newly enlarging T2 lesions with gadolinium enhancing lesions which are assessed in the next section.

6.1.6.1.6.3 Gadolinium-enhancing lesions

The number of subjects with no Gd-enhancing lesions was higher and the mean number of Gd-enhancing lesions was reduced at both 24 and 48 weeks in the BIIB017 treated groups. The difference from placebo was statistically significant for the BIIB017 q2W group only.

Table 33 Gadolinium enhancing lesions year 1

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Week 24			
n	477	463	457
Number of subjects with no Gd enhancing lesions (%)	273 (57)	314 (68)	388 (85)
Mean (SD)	1.6 (3.8)	1.2 (4.2)	0.3 (1.1)
% reduction compared to placebo ^a		25%	81%
p-value ^b		0.0988	<0.0001
Week 48			
n			
Number of subjects with no Gd enhancing lesions (%)	302 (63)	335 (72)	406 (89)
Mean (SD)	1.4 (3.7)	0.9 (3.3)	0.2 (0.96)
% reduction compared to placebo ^a		36%	86%
p- value ^b		0.0738	<0.0001

NOTE 1: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using LOCF or group mean at same visit. Number of subjects with imputed data for each group are 1, 1, 1 for week 24, and 19, 25, 18 for week 48.

^a : Calculated as the (placebo mean - active mean)/placebo mean*100.

^b : P-value for comparison between the active and placebo groups, based on multiple logit regression, adjusted for baseline number of Gd-enhancing lesion.

Source: Sponsor Table 37

Reviewer comment: Since there was an imbalance in the number of Gd-enhancing lesions at baseline (a mean of 1.6, 1.8 and 1.2 for the placebo, BIIB017 q4W and BIIB017 q2W groups respectively) the % reduction may not be reliable. However the p-value is derived using baseline adjustment and suggests a significant difference for the q2W group but not the q4W group.

Table 34 Gadolinium enhancing lesions over 2 years – ITT population dosed in year 2

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=228	N=228	N=438	N=438

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Number with no new lesions (%)				
Week 24	127 (56)	136 (60)	299 (68)	370 (85)
Week 48	144 (63)	148 (65)	319 (73)	388 (89)
Week 96	70 (73)	90 (88)	149 (76)	169 (90)
Mean (SD)				
Week 24	1.7 (3.6)	1.5 (4)	1.2 (3.8)	0.3 (1.1)
Week 48	1.5 (3.6)	1.4 (3.8)	0.8 (2.8)	0.2 (1)
Week 96	0.6 (1.2)	0.2 (0.9)	0.8 (2.7)	0.3 (1.2)

NOTE 1: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are included and imputed using LOCF.

Source: Sponsor Table 160

Reviewer comment: As with the other MRI endpoints, the benefit appears to be sustained in those treated with BIIB017 in year one. Those who were treated with placebo in year one appear to have had an increased proportion with no Gd enhancing lesion and a reduction in the mean number of lesions after treatment with BIIB017 in year 2. Data for year 2 are incomplete however.

6.1.6.1.6.4 Number of new T1 hypointense lesions

The number of subjects with no new T1 hypointense lesions was higher and the mean number of lesions was lower at 48 weeks in those treated with BIIB017 q2W but the reduction for this endpoint in the BIIB017 q4W group was not statistically significant.

Table 35 T1 hypointense lesions year 1

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
n	476	462	457
Number with no new lesions (%)			
Week 24	247 (52)	247 (53)	296 (65)
Week 48	190 (40)	198 (43)	266 (58)
Mean number of new lesions (SD)			

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Week 24	2.1 (4)	2.0 (4.3)	1.2 (3.2)
Week 48	3.8 (6.8)	3.1 (6.3)	1.8 (4.4)
% reduction compared to placebo ^a (p-value ^b)			
Week 24		5% (0.234)	43% (<0.0001)
Week 48		18% (0.082)	53% (<0.0001)

NOTE 1: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are imputed based on previous visit data assuming the constant rate of lesion development or group mean at same visit. Number of subjects with imputed data for each group are 2, 2, 2 for week 24, and 18, 24, 18 for week 48.

^a: Calculated as the (placebo mean - active mean)/placebo mean*100.

^b: P-value for comparison between the active and placebo groups, based on multiple logit regression, adjusted for baseline number of T1 lesion.

Source: Sponsor table 38

Table 36 T1 hypointense lesions year 2 – ITT population dosed in year 2

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT	N=228	N=228	N=438	N=438
Number with no new lesions (%)				
BL to Week 24	113 (50)	123 (54)	231 (53)	286 (65)
BL to Week 48	86 (38)	93 (41)	183 (42)	256 (59)
BL to Week 96	42/96 (44)	59/102 (58)	111/195 (57)	150/188 (80)
Mean (SD)				
Week 24	2.3 (4.2)	1.8 (3.7)	2.0 (4.4)	1.2 (3.3)
Week 48	4.0 (7.3)	3.6 (6.1)	3.2 (6.4)	4.4 (0)
Week 96	2.0 (3.8)	1.6 (3.4)	1.8 (5)	0.7 (2.2)

NOTE 1: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are included and imputed using LOCF with the constant rate.

Source: Sponsor Table 162

Reviewer comment: As with other MRI endpoints, the benefit of BIIB017 treatment is most consistent for the BIIB017 q2W group. These T1 hypointense lesions or “black holes” are generally considered to represent irreversible tissue damage and are thus an important MRI endpoint.

6.1.6.1.6.5 Volume of T2 hyperintense lesions

As with other measures of T2 lesions, both BIIB017 treated groups showed a reduction in the volume of T2 lesions at 24 and 48 weeks.

Table 37 Volume of T2 hyperintense lesions year 1

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Baseline, n	497	499	511
Mean (SD)	10.1 (12)	11.3 (13.2)	9.8 (11.6)
Week 24, n	476	462	457
Change: BL to Week 24	0.34 (1.7)	0.14 (2.2)	-0.22 (1.4)
p-value ^a		0.0006	<0.0001
Week 48, n	476	462	457
Change: BL to Week 48	0.77 (2.5)	0.05 (2.0)	-0.26
p-value ^a		<0.0001	<0.0001

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using the mean of the data for each treatment group/visit.

^a : P-value for comparison between the active and placebo groups, based on analysis of covariance (ANCOVA) on ranked data, adjusted for baseline T2 lesion volume.

Source: Sponsor Table 39

Table 38 Volume of T2 hyperintense lesions year 2 – ITT population dosed in year 2

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT dosed in year 2, N	228	228	438	438
Baseline n	226	228	438	438
Mean (SD)	10.7 (13.4)	9.7 (10.3)	11.6 (13.6)	10 (12.1)
Week 24, n	228	228	438	437
Change BL to Week 24	0.42 (1.8)	0.31 (1.6)	0.15 (2.2)	-0.22 (1.5)

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Week 48, n	228	228	438	437
Change BL to Week 48	0.92 (3.1)	0.62 (1.9)	0.05 (2.1)	-0.26 (1.7)
Week 96, n	96	102	195	188
Change BL to Week 96	0.83 (2.3)	0.24 (2.1)	0.38 (2.8)	-0.26 (1.8)

NOTE: Data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are included and imputed using the mean of the data for each treatment group/visit.

Source: Sponsor Table 163

Reviewer comment: The volume appears to be lower in the BIIB017 q2W group at baseline. The analysis does adjust for the baseline difference. The analysis at one year supports that the benefit is not just that the number of T2 lesions is reduced but that the volume is reduced as well. The data from year two are incomplete and difficult to interpret since it appears that there is a reduction in the volume change between week 48 and 96 for the groups treated with placebo in year one, an increase in the BIIB017 q4W group and essentially no change in the BIIB017 q2W group.

6.1.6.1.6.6 Volume of T1 hypointense lesions

The mean volume of T1 hypointense lesions increased for all groups over year one in all groups. However the increase in volume was smaller in the BIIB017 every 2 weeks group as compared to placebo at Week 24 and 1 year. The increases in the BIIB017 every 4 weeks and placebo groups were similar at both time points.

Table 39 Change in T1 hypointense lesion volume year 1

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Baseline, n	497	498	510
Mean vol (cm ³) (SD)	3.08 (4.8)	3.11 (4.8)	3 (4.5)
Week 24, n	476	462	457
Change: BL to Week 24	0.29 (0.86)	0.31 (5.3)	0.17 (0.81)
p-value ^a		0.219	0.0002
Week 48, n	476	462	457
Change: BL to Week 48	0.54 (1.1)	0.57 (1.7)	0.32 (0.96)
p-value ^a		0.1795	<0.0001

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using the mean of the data for each treatment group/visit.

(a) P-value for comparison between the active and placebo groups, based on analysis of covariance (ANCOVA) on ranked data, adjusted for baseline T1 volume.

Source: Sponsor Table 40

Table 40 Volume of T1 hypointense lesions over 2 years – ITT population dosed in year 2

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT dosed in year 2, N	228	228	438	438
Baseline n	226	228	436	437
Mean (SD)	3.3 (5.7)	2.9 (3.9)	3.2 (4.9)	3.0 (4.6)
Week 24, n	228	228	438	437
Change BL to Week 24	0.32 (0.8)	0.24 (0.95)	0.31 (1.2)	0.17 (0.82)
Week 48, n	228	228	438	437
Change BL to Week 48	0.61 (1.2)	0.49 (1.1)	0.58 (1.8)	0.31 (0.98)
Week 96, n	96	102	195	188
Change BL to Week 96	1.0 (1.8)	1.1 (1.8)	1.2 (2.9)	0.58 (1.3)

NOTE: Data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are included and imputed using the mean of the data for each treatment group/visit.

Source: Sponsor Table 164

Reviewer comment: Over the full two years all groups had an increase in the volume of T1 hypointense lesions (“black holes”). The increase was smaller in the BIIB017 q2W group. The result correlates with the analysis of the number of hypointense T1 lesions. Although the year 2 data are incomplete this may again support that the q2W dose is superior to the q4W dose.

6.1.6.1.6.7 Volume of Gd-Enhancing Lesions

Treatment with BIIB017 every 4 weeks and every 2 weeks both produced reductions in Gd-enhancing lesion volume as compared to placebo at 24 weeks and 1 year compared to baseline.

Table 41 Volume of Gd-enhancing lesions year 1

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Baseline, n	497	498	510

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Mean vol (cm ³) (SD)	0.22 (0.55)	0.25 (0.83)	0.16 (0.49)
Week 24, n	476	462	457
Change: BL to Week 24 p-value ^a	0.002 (0.64)	-0.07 (0.55) 0.0269	-0.11 (0.45) <0.0001
Week 48, n	476	462	457
Change: BL to Week 48 p-value ^a	0.06 (1.3)	-0.13 (0.76) <0.0001	-0.13 (0.45) <0.0001

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using the mean of the data for each treatment group/visit.

^a : P-value for comparison between the active and placebo groups, based on analysis of covariance (ANCOVA) on ranked data, adjusted for baseline Gd volume.

Source: Sponsor Table 41

Reviewer comment: For the first 48 weeks the volume of gadolinium enhancing lesions did not change in the placebo group but was less in both BIIB017 groups, correlating with the reduction in the number of these lesions. The reduction in volume is more prominent than the reduction in number for the BIIB017 q4W group.

Table 42 Volume of Gd-enhancing lesions - year 2

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT dosed in year 2, N	228	228	438	438
Baseline n	226	228	436	437
Mean (SD)	0.23 (0.55)	0.18 (0.53)	0.26 (0.82)	0.16 (0.45)
Week 24, n	228	228	438	437
Change BL to Week 24	0.00 (0.65)	0.02 (0.64)	-0.07 (0.56)	-0.11 (0.46)
Week 48, n	228	228	438	437
Change BL to Week 48	0.11 (1.7)	0.01 (0.57)	-0.13 (0.78)	-0.13 (0.46)
Week 96, n	96	102	195	188
Change BL to Week 96	-0.17 (0.66)	-0.21 (0.67)	-0.19 (0.95)	-0.15 (0.49)

NOTE: Data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications up to week 48 are included and imputed using the mean of the data for each treatment group/visit.

Source: Sponsor Table 165

Reviewer comment: In year 2 when all groups were being treated with BIIB017 there was a reduction in the volume of Gd-enhancing lesions for all groups. The

reductions was somewhat more prominent for those newly converted to BIIB017 treatment.

6.1.6.1.6.8 Brain Atrophy

Table 43 Brain atrophy year 1

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Week 24, n	476	462	457
% Change: BL to Week 24 p-value ^a	-0.31 (0.56)	-0.34 (0.57) 0.3561	-0.40 (0.56) 0.0170
Week 48, n	476	462	457
% Change: BL to Week 48 p-value ^a	-0.62 (0.90)	-0.67 (0.83) 0.375	-0.72 (0.75) 0.084
% Change: Week 24 to 48 p-value ^a	-0.32 (0.54)	-0.33 (0.55) 0.700	-0.33 (0.49) 0.929

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using LOCF with constant rate.

^a: P-value for comparison between the active and placebo groups, based on analysis of covariance (ANCOVA), adjusted for baseline (for change from baseline) or week 24 (for change from week 24) normal brain volume.

Source: Sponsor Table 166

Table 44 Brain atrophy year 2

	Placebo to BIIB017 125µg q4 weeks	Placebo to BIIB017 125µg q4 weeks	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT dosed in year 2, N	228	228	438	438
Week 24, n	228	228	438	437
% Change BL to Week 24	-0.31 (0.65)	-0.30 (0.50)	-0.34 (0.57)	-0.40 (0.56)
Week 48, n	228	228	438	437
% Change BL to Week 48	-0.66 (1.0)	-0.57 (0.74)	-0.67 (0.82)	-0.73 (0.74)
% Change Week 24 to 48	-0.35 (0.58)	-0.27 (0.50)	-0.33 (0.55)	-0.33 (0.48)
Week 96, n	89	98	183	176
% Change BL to Week 96	-1.2 (0.92)	-1.5 (1.2)	-1.4 (1.3)	-1.1 (0.90)

Reviewer comment: the percent atrophy over time appears to be approximately the same for all groups to one year. After two years there may be less atrophy in the BIIB017 q2W group. This is probably not significant but should be assessed when all subjects have completed year 2. The significance of any changes should be

viewed in comparison to the atrophy expected over 1 and 2 years in otherwise healthy people.

6.1.6.2 Patient Reported Outcomes

6.1.6.2.1 MSIS-29

The MSIS-29 measures 20 physical items and 9 psychological items that examine the physical and psychological impact of MS from a subject's perspective. A positive change on this scale represents worsening from baseline and a negative change represents improvement from baseline. The treatment effect on the change from baseline to Week 48 in the MSIS-29 physical score was analyzed using an analysis of covariance (ANCOVA) model adjusting for the baseline score. There was no significant change in physical or psychological scores in the first or second year of treatment compared to the baseline scores.

6.1.6.2.2 SF-12

The SF-12 is a generic quality of life instrument consisting of 12 items that measure functional health and well-being from the patient's point of view. The 8 domains of the SF-12 are grouped into 2 summary scores: the physical and mental component scale (PCS and MCS). Higher scores indicate better physical and mental function. Changes from baseline were compared between treatment groups using an ANCOVA model with a term for treatment group, adjusted for baseline SF-12 component or domain score. Data after subjects switched to an approved alternative MS medication were excluded.

No significant changes were seen in any treatment group for year one or two compared to baseline.

6.1.6.2.3 EQ-5D

The EQ-5D™ is a subject-rated instrument that includes the EQ-5D descriptive system and the EQ-VAS. The EQ-5D descriptive system provides a profile of the subject's health state in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), while the EQ-VAS records the respondent's self-rated health on a scale of 0 (Worst imaginable health state) to 100 (Best imaginable health state). Data after subjects switched to an approved alternative MS medication were excluded from the analysis.

Little change was seen for either the EQ-5D or the EQ-VAS for any treatment group in year one or two compared to baseline.

Reviewer comment: The patient reported outcome scales do not show a significant change over the study.

6.1.7 Subpopulations

Table 45 Annualized Relapse Rate by baseline demographic characteristics

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Gender			
Male, n	142	148	151
ARR (95% CI) ^a	0.36 (0.25, 0.52)	0.19 (0.12, 0.30)	0.21 (0.13, 0.32)
Rate ratio		0.53 (0.32, 0.88)	0.57 (0.35, 0.94)
Female, n	358	352	361
ARR (95% CI) ^a	0.41 (0.33, 0.51)	0.33 (0.26, 0.41)	0.27 (0.21, 0.35)
Rate ratio		0.80 (0.60, 1.1)	0.66 (0.49, 0.89)
Baseline age			
<40 years, n	310	304	320
ARR (95% CI) ^a	0.49 (0.38, 0.62)	0.39 (0.31, 0.50)	0.34 (0.27, 0.45)
Rate ratio		0.81 (0.60, 1.1)	0.71 (0.53, 0.95)
≥40 years	190	196	192
ARR (95% CI) ^a	0.35 (0.25, 0.48)	0.19 (0.13, 0.29)	0.18 (0.12, 0.27)
Rate ratio		0.56 (0.35, 0.90)	0.52 (0.32, 0.84)
Geographic region^b			
Region 1, n	55	55	60
ARR (95% CI) ^a	0.64 (0.40, 1.0)	0.44 (0.28, 0.71)	0.53 (0.33, 0.85)
Rate ratio		0.70 (0.38, 1.3)	0.83 (0.47, 1.5)
Region 2	354	355	355
ARR (95% CI) ^a	0.39 (0.30, 0.49)	0.27 (0.21, 0.35)	0.25 (0.19, 0.32)
Rate ratio		0.69 (0.51, 0.94)	0.64 (0.47, 0.87)
Region 3	91	90	97
ARR (95% CI) ^a	0.32 (0.21, 0.50)	0.28 (0.17, 0.45)	0.17 (0.10, 0.30)
Rate ratio		0.87 (0.50, 1.5)	0.53 (0.28, 1.0)

NOTE: Data after subjects switched to alternative MS medications are excluded.

^a: Assessing the difference between the treatment groups, based on negative binomial regression, adjusted for baseline EDSS (<4 vs. ≥4), baseline relapse rate, age (<40 vs. ≥40), except for the subgroup factor of interest.

^b: Region 1 includes Canada, United States, Belgium, France, Germany, Netherlands, Spain, and United Kingdom. Region 2 includes Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Poland, Romania, Russia, Serbia, and Ukraine. Region 3 includes Chile, Colombia, Georgia, India, Mexico, New Zealand and Peru.

Source: Sponsor Table 178

Reviewer comment: The reduction in ARR appears to be significant for both males and females for the BIIB017 q2W group but may not be significant for females in the q4W group. Age group does not appear to have a major effect on ARR. Region 1 which included the US had a higher ARR during the trial (but not prior to entry – see Table 10). The point estimate for the rate ratio is also somewhat higher, i.e. less of a reduction in the ARR in Region 1 compared to Regions 2 and 3. The number of subjects in the US is too small to assess the ARR in the US compared to outside the US. Given the comparability of baseline characteristics in US subjects to those in Region 1 and of Region 1 to Regions 2 and 3 as well as the established efficacy of Avonex® it is reasonable to conclude that the overall benefit on ARR is applicable to US subjects.

Table 46 Annualized Relapse rate at one year by baseline disease characteristic

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Number of relapses in the 3 years prior to entry			
≤2 relapses, n	315	328	313
ARR (95% CI) ^a	0.33 (0.29, 0.50)	0.27 (0.20, 0.36)	0.22 (0.16, 0.30)
Rate ratio		0.71 (0.51, 0.99)	0.58 (0.41, 0.83)
3 relapses, n	119	129	147
ARR (95% CI) ^a	0.43 (0.30, 0.61)	0.24 (0.16, 0.36)	0.24 (0.16, 0.36)
Rate ratio		0.56 (0.34, 0.91)	0.56 (0.35, 0.90)
≥4 Relapses, n	66	43	52
ARR (95% CI) ^a	0.66 (0.44, 0.99)	0.70 (0.44, 1.1)	0.67 (0.42, 1.1)
Rate ratio		1.1 (0.59, 1.9)	1.0 (0.58, 1.8)
Prior treatment for MS			
No, n	414	415	423
ARR (95% CI) ^a	0.39 (0.31, 0.48)	0.31 (0.25, 0.39)	0.25 (0.19, 0.31)
Rate ratio		0.81 (0.61, 1.1)	0.63 (0.47, 0.85)
Yes, n	86	85	89
ARR (95% CI) ^a	0.42 (0.27, 0.63)	0.20 (0.12, 0.34)	0.29 (0.19, 0.46)
Rate ratio		0.48 (0.27, 0.87)	0.70 (0.43, 1.2)

NOTE: Data after subjects switched to alternative MS medications are excluded.

^a : Assessing the difference between the treatment groups, based on negative binomial regression, adjusted for baseline EDSS (<4 vs. ≥4), baseline relapse rate, age (<40 vs. ≥40), except for the subgroup factor of interest
 Source: Sponsor Table 179

Most subjects had two or fewer relapses prior to treatment and relatively few had 4 or more. The ARR during the trial was higher in the latter group compared to those with fewer relapses prior and the ARR during the trial did not appear to be affected by treatment in this group with the highest number of relapses in the 3 years prior to study

treatment. There were approximately an equal number of subjects with a median time of 4 months or less since the most recent pre-study relapse compared to a median time of more than 4 months. This baseline disease characteristic did not appear to influence the ARR during the trial or the effect of treatment with BIIB017. The McDonald criteria used to support a diagnosis of MS did not appear to affect the benefit of BIIB017 treatment. The baseline ARR was numerically higher those with a diagnosis based on criteria 2, 3 and 4 and the rate ratio was lower for this group. MRI baseline T2 lesion volume and the presence of absence of gadolinium-enhancing lesions did not affect the response to treatment.

Reviewer comment: The ARR appears to be reduced at one year after treatment with either dose of BIIB017 for those with 3 or fewer relapses in the three years prior to treatment but it appears to be unchanged by either dose for those with 4 or more. This analysis may be affected by the relatively small number of subjects in the group with 4 or more relapses. Those who had been treated previously for MS (and presumably did not do well) did not appear to respond differently to BIIB017. Similarly baseline EDSS and time since the most recent relapse did not appear to affect the response to BIIB017.

Table 47 Number of new or newly enlarging T2 lesions at 1 year - ITT by demographic subgroup

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Gender			
Male, n	138	141	136
Mean (SD)	10.9 (17.5)	9.2 (15.4)	4.6 (8.8)
% reduction vs PBO 95% CI ^a		11.9 (-26.4, 38.6)	59.9 (42.0, 72.3)
Female, n	338	321	321
Mean (SD)	14.2 (20.2)	9.3 (16.1)	0.27 (0.21, 0.35)
% reduction vs PBO 95% CI ^a		33.6 (17.3, 46.7)	69.3 (61.5, 75.5)
Baseline age			
<40 years, n	299	286	288
Mean (SD)	15.7 (20.8)	11.8 (17.8)	5.0 (8.8)
% reduction vs PBO 95% CI ^a		21.6 (3.0, 36.6)	65.4 (57.1, 72.1)
≥40 years	190	196	192
Mean (SD)	9.1 (16.4)	5.0 (10.8)	2.5 (7.9)
% reduction vs PBO		44.3	72.3

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
95% CI ^a		(21.0, 60.7)	(60.2, 80.7)
Geographic region^b			
Region 1^b, n	52	52	55
Mean (SD)	10.2 (12.9)	6.2 (13.4)	3.0 (7.4)
% reduction vs PBO 95% CI ^a		41.1 (-5.5, 67.2)	61.8 (31.2, 78.7)
Region 2^b, n	337	328	316
Mean (SD)	14.3 (20.9)	9.3 (16.2)	4.2 (8.1)
% reduction vs PBO 95% CI ^a		32.6 (16.0, 46.0)	69.3 (61.5, 75.6)
Region 3^b, n	87	82	86
Mean (SD)	11.1 (17.0)	10.9 (15.6)	4.4 (10.5)
% reduction vs PBO 95% CI ^a		-6.4 (-66.8, 32.2)	57.5 (32.9, 73.0)

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using LOCF with the constant rate.

^a: % reduction and 95% CI for comparison between the active and placebo groups, based on negative binomial regression, adjusted for baseline number of T2 lesions.

^b: Region 1 includes Canada, United States, Belgium, France, Germany, Netherlands, Spain, and United Kingdom. Region 2 includes Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Poland, Romania, Russia, Serbia, and Ukraine. Region 3 includes Chile, Colombia, Georgia, India, Mexico, New Zealand and Peru.

Source: Sponsor Table 180

Reviewer comment: Unlike the ARR at one year, there does not appear to be a male vs. female difference in the reduction in new or newly enlarging T2 lesions. Similar to the ARR there was no effect of age group on this endpoint. Unlike the ARR, there is no change in the point estimate for percent reduction on this endpoint by region although the result for the BIIB017 q4W group in Region 3 is most likely spurious.

Table 48 Number of New or Newly Enlarging T2 lesions by baseline disease characteristic

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Number of relapses in the 3 years prior to entry			
≤2 relapses, n	303	301	285
Mean (SD)	12.8 (19.4)	8.8 (16.1)	4.1 (8.8)
% reduction vs PBO 95% CI ^a		28.2 (8.9, 43.4)	65.8 (56.3, 73.3)

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
3 relapses, n	112	121	126
Mean (SD)	12.8 (20.1)	9.1 (12.7)	3.6 (7.5)
% reduction vs PBO 95% CI ^a		28.6 (-4.8, 51.3)	70.5 (56.6, 73.3)
≥4 Relapses, n	61	40	46
Mean (SD)	16.2 (19.0)	13.2 (21.2)	5.3 (9.8)
% reduction vs PBO 95% CI ^a		14.9 (-42.0, 49.0)	63.5 (39.7, 77.9)
Prior treatment for MS			
No, n	393	389	381
Mean (SD)	12.7 (18.9)	9.4 (16.2)	4.1 (8.8)
% reduction vs PBO 95% CI ^a		23.2 (5.6, 37.5)	65.1 (56.9, 71.8)
Yes, n	83	73	76
Mean (SD)	15.8 (21.9)	8.4 (13.7)	3.8 (7.4)
% reduction vs PBO 95% CI ^a		48.7 (18.7, 67.6)	75.3 (60.6, 84.5)

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are included and imputed using LOCF with the constant rate.

^a :% reduction and 95% CI for comparison between the active and placebo groups, based on negative binomial regression, adjusted for baseline number of T2 lesions.

Source: Sponsor Table 181

Reviewer comment: The number of relapses in the 3 years prior to start of investigational treatment did not have a clear influence the reduction in the number of new or newly enhancing T2 lesions at one year after treatment seen with either dose of BIIB017. Similarly the time since the most recent relapse and the McDonald criteria supporting the diagnosis of MS did not affect the response to treatment with BIIB017. Those who had been treated previously for MS did not appear to respond differently to BIIB017. Similarly baseline EDSS and time since the most recent relapse did not appear to affect the response to BIIB017.

Table 49 Proportion of Subjects with an INEC confirmed relapse in year one - ITT - by baseline demographics

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Gender			
Male, n	142	148	151
Proportion relapsed ^a	0.29	0.15	0.19
Hazard Ratio ^b		0.46	0.57

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
95% CI		(0.28, 0.78)	(0.35, 0.94)
Female, n	358	352	361
Proportion relapsed ^a	0.29	0.25	0.19
Hazard Ratio ^b		0.86	0.63
95% CI		(0.64, 1.2)	(0.46, 0.87)
Baseline age			
<40 years, n	310	304	320
Proportion relapsed ^a	0.31	0.26	0.22
Hazard Ratio ^b		0.80	0.68
95% CI		(0.59, 1.1)	(0.49, 0.93)
≥40 years	190	196	192
Mean (SD)	0.25	0.16	0.13
% reduction vs PBO		0.61	0.48
95% CI ^a		(0.38, 0.97)	(0.29, 0.79)
Geographic region^b			
Region 1^c, n	55	55	60
Proportion relapsed ^a	0.33	0.28	0.32
Hazard Ratio ^b		0.93	1.20
95% CI		(0.46, 1.9)	(0.61, 2.34)
Region 2^c, n	354	355	355
Proportion relapsed ^a	0.29	0.21	0.17
Hazard Ratio ^b		0.70	0.54
95% CI		(0.51, 0.95)	(0.39, 0.75)
Region 3^c, n	91	90	97
Proportion relapsed ^a	0.28	0.23	0.16
Hazard Ratio ^b		0.79	0.58
95% CI		(0.43, 1.5)	(0.30, 1.1)

NOTE: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrew from study are censored at the time of switch/withdrawal.

(a) Based on Kaplan-Meier product limit method.

(b) Based on Cox proportion hazards model, adjusted for baseline EDSS (<4 vs. ≥4), age (<40 vs. ≥40), baseline relapse rate, and baseline Gd enhancing lesions (presence vs. absence), except for the subgroup factor of interest.

^c: Region 1 includes Canada, United States, Belgium, France, Germany, Netherlands, Spain, and United Kingdom.

Region 2 includes Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Poland, Romania, Russia, Serbia, and Ukraine. Region 3 includes Chile, Colombia, Georgia, India, Mexico, New Zealand and Peru.

Source: Sponsor Table 182

Reviewer comment: There does not appear to be a major effect of gender or age (less than 40 vs. 40 or more) on the effect of treatment with BIIB017 on the proportion of subjects with a relapse by one year. The reduction may be greater at the subject level for males compared to females but both results are significant.

For the BIIB017 q2W group the confidence interval of the hazard ratio does cross 1.0 at the second and fourth weight quartile but the number of subjects in each quartile are relatively small. For the second quartile the point estimate supports a benefit but in the highest quartile (weight >78kg) the point estimate is high at 0.91 with an upper CI limit of 1.53.

By region the proportion relapsed is similar for each region in the placebo group, unlike the ARR which was higher for Region 1 compared to Regions 2 and 3. In region 1 including the US and northern Europe, as with the ARR, the point estimate for the hazard ratio is high at 1.20 for the q2W group with an upper CI limit of 2.34. Therefore even at the subject level the reduction in relapses is not apparent for Region 1 which includes the US. Based on the lack of evidence that subjects in Region 1 differ significantly from the overall population and given the small number of subjects in this region and the established efficacy of Avonex® it is reasonable to conclude that the overall benefit of BIIB017 q2W is applicable to the US population.

Table 50 Proportion of subjects with an INEC relapse in year 1 - ITT - by baseline disease characteristic

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Number of relapses in the 3 years prior to entry			
≤2 relapses, n	315	328	313
Est. proportion relapsed ^a	0.26	0.19	0.15
Hazard ratio ^b 95% CI ^b		0.70 (0.50, 0.97)	0.55 (0.38, 0.79)
3 relapses, n	119	129	147
Est. proportion relapsed ^a	0.32	0.21	0.20
Hazard ratio ^b 95% CI ^b		0.60 (0.36, 0.99)	0.63 (0.38, 1.04)
≥4 Relapses, n	66	43	52
Est. proportion relapsed ^a	0.39	0.46	0.37
Hazard ratio ^b 95% CI ^b		1.24 (0.68, 2.28)	0.97 (0.53, 1.79)
Prior treatment for MS			
No, n	414	415	423
Est. proportion relapsed ^a	0.27	0.23	0.17
Hazard ratio ^b		0.86	0.63

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
95% CI ^d		(0.65, 1.14)	(0.47, 0.86)
Yes, n	68	87	89
Est. proportion relapsed ^a	0.41	0.18	0.26
Hazard ratio ^b		0.40	0.55
95% CI ^b		(0.21, 0.77)	(0.32, 0.95)

NOTE: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrew from study are censored at the time of switch/withdrawal.

(a) Based on Kaplan-Meier product limit method.

(b) Based on Cox proportion hazards model, adjusted for baseline EDSS (<4 vs. ≥4), age (<40 vs. ≥40), baseline relapse rate, and baseline Gd enhancing lesions (presence vs. absence), except for the subgroup factor of interest.

Source: Sponsor Table 183

Reviewer comment: The number of relapses prior to study treatment and whether the subject had been treated for MS previously did not appear to affect the response to treatment with BIIB017.

Table 51 Time to sustained disability by EDSS year 1 by baseline demographics

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Gender			
Male, n	142	148	151
Proportion progressed ^a	0.09	0.06	0.05
Hazard Ratio ^b		0.58	0.54
95% CI		(0.24, 1.41)	(0.21, 1.36)
Female, n	358	352	361
Proportion progressed ^a	0.11	0.07	0.07
Hazard Ratio ^b		0.62	0.63
95% CI		(0.37, 1.04)	(0.38, 1.06)
Baseline age			
<40 years, n	310	304	320
Proportion progressed ^a	0.07	0.06	0.07
Hazard Ratio ^b		0.75	0.90
95% CI		(0.40, 1.43)	(0.48, 1.66)
≥40 years	190	196	192
Proportion progressed ^a	0.16	0.09	0.07
Hazard Ratio ^b		0.52	0.43
95% CI		(0.28, 0.98)	(0.22, 0.84)
Geographic region^b			
Region 1^c, n	55	55	60
Proportion progressed ^a	0.19	0.08	0.22

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Hazard Ratio ^b 95% CI		0.35 (0.11, 1.11)	0.89 (0.39, 2.07)
Region 2^c, n	354	355	355
Proportion progressed ^a	0.09	0.06	0.04
Hazard Ratio ^b 95% CI		0.65 (0.37, 1.17)	0.49 (0.26, 0.93)
Region 3^c, n	91	90	97
Proportion progressed ^a	0.12	0.10	0.07
Hazard Ratio ^b 95% CI		0.84 (0.33, 2.13)	0.60 (0.22, 1.65)

NOTE 1: 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.

2: Subjects are censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression.

^a:Based on Kaplan-Meier product limit method.

^b:Hazard ratio assessing the difference between the treatment groups, based on Cox proportional hazards model, adjusted for baseline EDSS, and age (<40 vs. ≥ 40), except for the subgroup factor of interest.

^c:Region 1 includes Canada, United States, Belgium, France, Germany, Netherlands, Spain, and United Kingdom. Region 2 includes Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Poland, Romania, Russia, Serbia, and Ukraine. Region 3 includes Chile, Colombia, Georgia, India, Mexico, New Zealand and Peru.

Source: Sponsor Table 184

Reviewer comment: Gender and age did not have a major effect on the proportion progressed by EDSS at one year. As with other clinical endpoints the benefit of treatment for this endpoint is not clear for regions 1 and 3.

Table 52 Time to Sustained Disability by EDSS year 1 - ITT - by baseline disease characteristics

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
ITT n (%)	N=500	N=500	N=512
Number of relapses in the 3 years prior to entry			
≤ 2 relapses, n	315	328	313
Est. proportion progressed ^a	0.10	0.05	0.05
Hazard ratio ^b 95% CI ^b		0.49 (0.26, 0.91)	0.48 (0.25, 0.91)
3 relapses, n	119	129	147
Est. proportion progressed ^a	0.10	0.10	0.05
Hazard ratio ^b 95% CI ^b		0.97 (0.43, 2.16)	0.52 (0.20, 1.33)
≥ 4 Relapses, n	66	43	52
Est. proportion progressed ^a	0.13	0.11	0.22

	Placebo	BIIB017 125µg q4 weeks	BIIB017 125µg q2 weeks
Hazard ratio ^b 95% CI ^b		0.71 (0.21, 2.36)	1.75 (0.69, 4.44)
Prior treatment for MS			
No, n	414	415	423
Est. proportion progressed ^a	0.11	0.07	0.06
Hazard ratio ^b 95% CI ^b		0.58 (0.36, 0.95)	0.49 (0.30, 0.82)
Yes, n	86	85	89
Est. proportion progressed ^a	0.08	0.07	0.12
Hazard ratio ^b 95% CI ^b		0.96 (0.29, 3.19)	1.75 (0.62, 4.94)
Baseline EDSS			
<4, n	432	413	423
Est. proportion progressed ^a	0.10	0.06	0.07
Hazard ratio ^b 95% CI ^b		0.55 (0.33, 0.92)	0.65 (0.40, 1.06)
≥4, n	68	87	89
Est. proportion progressed ^a	0.15	0.12	0.07
Hazard ratio ^b 95% CI ^b		0.82 (0.33, 2.08)	0.44 (0.15, 1.30)

NOTE 1: 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.

2: Subjects are censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression.

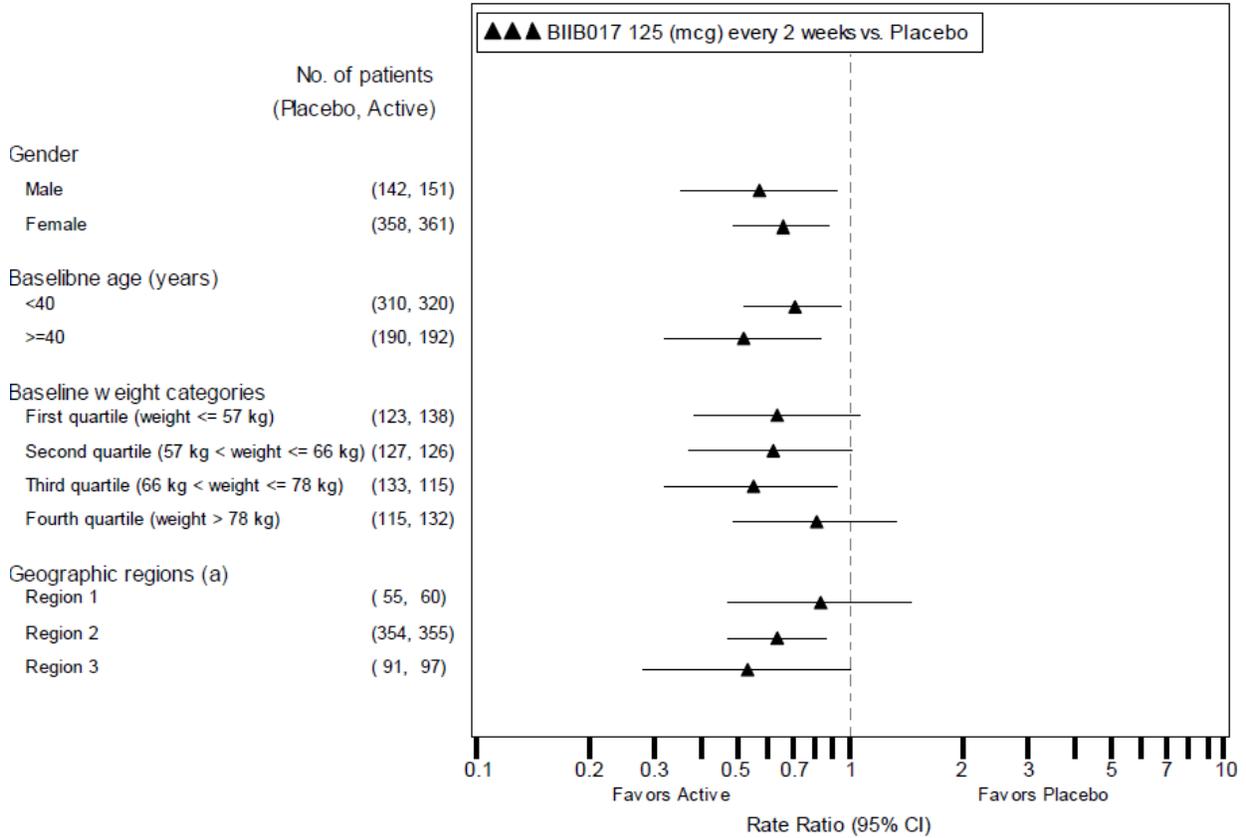
^a: Based on Kaplan-Meier product limit method.

^b: Hazard ratio assessing the difference between the treatment groups, based on Cox proportional hazards model, adjusted for baseline EDSS, and age (<40 vs. ≥ 40), except for the subgroup factor of interest.

Source: Sponsor Table 185

Reviewer comment: As with several other clinical endpoints, subjects with the higher categories of relapses prior to study treatment and those who were treated previously for MS tended to progress more often. Interpretation of the results for those with a baseline EDSS of 4 or more is limited by small number of subjects but the differences do not appear to be a major concern. The 2 Forest plots below summarize the subgroup analyses for the q2W dose.

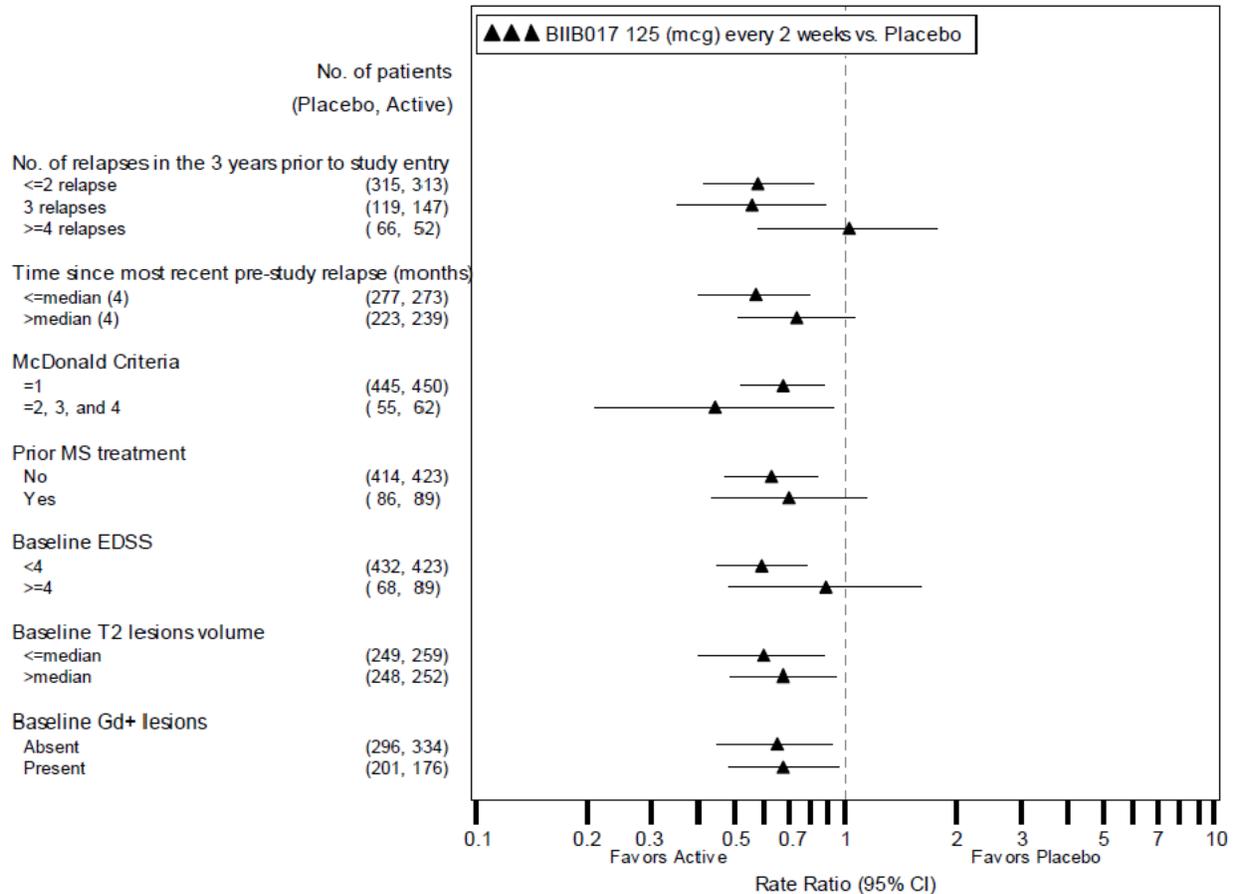
Figure 10 ARR (INEC confirmed) at year 1 - q2W dose – by demographic subgroup - Forest Plot



NOTE: Rate ratio (active/placebo) and (95% CI) based on negative binomial regression model, adjusted for baseline EDSS (<4 v s. >=4), baseline relapse rate, baseline age (<40 v s. >=40), except for the subgroup factor of interest.

- (a) Region 1 includes Canada, United States, Belgium, France, Germany, Netherlands, Spain, and United Kingdom.
- (b) Region 2 includes Bulgaria, Croatia, Czech Republic, Estonia, Greece, Latvia, Poland, Romania, Russia, Serbia, and Ukraine.
- (c) Region 3 includes Chile, Colombia, Georgia, India, Mexico, New Zealand and Peru.

Figure 11 ARR (INEC confirmed) at year 1 - q2W dose - by baseline disease characteristic - Forest plot



NOTE: Rate ratio (active/placebo) and (95% CI) based on negative binomial regression model, adjusted for baseline EDSS (<4 v s. >=4), baseline relapse rate, baseline age (<40 v s. >=40), except for the subgroup factor of interest.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor proposes to market the drug at a dose of 125µg subcutaneously every 2 weeks. Dosing at both every 2 weeks and every 4 weeks was studied. The table below summarizes the results of the primary and pre-specified secondary endpoints for both doses.

Table 53 Summary of results of primary and secondary endpoint for BIIB017 q4W and q2W

Endpoint at year 1	Dose	
	BIIB017 q4W	BIIB017 q2W
	p-value for pre-specified analysis	

Endpoint at year 1	Dose	
	BIIB017 q4W	BIIB017 q2W
	p-value for pre-specified analysis	
ARR	0.014	0.007
New or newly enlarging T2 lesions	0.0008	<0.0001
Proportion of subjects relapsed	0.02	0.0003
Disability progression by EDSS	0.038	0.038

For the q4W group the ARR remained stable, i.e. the benefit was sustained, from year one to two. The rate did decline further in year 2 compared to year one for the q2W group. The same pattern was seen for the proportion of subjects relapsed, i.e. the benefit was sustained in year 2 in the BIIB017 q4W group but was somewhat greater in year 2 for the BIIB017 q2W group. Over 2 years the proportion of subjects with sustained disability progression by EDSS and the time to sustained disability progression remained significantly lower in the BIIB017 q2W group compared to placebo but the confidence interval just crossed 1.0 for the BIIB017 q4W group. In the second year the number of new or newly enlarging T2 lesions on MRI is higher in the BIIB017 q4W group compared to the two groups randomized from placebo in the first year to BIIB017 in the second year. The number of subjects with no new lesions in the BIIB017 q4W group in the second year is comparable to the two groups on placebo in year one and considerably lower than that for the BIIB017 q2W group in year two. (Sponsor Table 156).

Reviewer comment:

(b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See discussion in section 6.1.8.

6.1.10 Additional Efficacy Issues/Analyses

Study 302

At the time of data cutoff, 517 subjects had entered Study 302, and 508 subjects had received at least 1 dose of study treatment. Only 17 subjects in the BIIB017 every 4 weeks group and 13 subjects in the BIIB017 every 2 weeks group who were

continuously exposed to BIIB017 in Study 301 had completed Year 1 of Study 302 and consequently had 3 years of exposure to BIIB017

The following is extracted from the Summary of Clinical Efficacy

Relapse data were analyzed for the Study 302 ITT Population, which included 247 subjects in the BIIB017 every 4 weeks group and 261 subjects in the BIIB017 every 2 weeks group. The following is a summary of the efficacy results available to date:

- The adjusted annualized relapse rate at 1 year was 0.410 (95% CI: 0.260, 0.645) in the BIIB017 every 4 weeks group and 0.203 (95% CI: 0.116, 0.355) in the BIIB017 every 2 weeks group.
- The estimated proportion of subjects relapsed at Week 36 was 0.186 and 0.104 in the BIIB017 every 4 weeks and every 2 weeks groups, respectively.
- At the time of data cutoff, 24-week sustained disability progression (based on combined Study 301 and 302 data) had been confirmed for 21 subjects (8.5%) in the BIIB017 every 4 weeks group and 16 subjects (6.1%) in the BIIB017 every 2 weeks group.
- Among the 37 subjects with available MRI data at the time of data cutoff, a mean of 3.7 new or newly enlarging T2 lesions was detected among the 19 subjects in the BIIB017 every 4 weeks group, and a mean of 1.1 lesions was detected among the 18 subjects in the BIIB017 every 2 weeks group.
- The available data from the extension study at the time of data cutoff suggest that the clinical and MRI measures of MS disease activity remained stable with continued BIIB017 treatment.

7 Review of Safety

See primary safety review for this BLA by Dr. Gerald Boehm.

8 Postmarket Experience

There is no postmarket experience with pegylated-interferon- β .

9 Appendices

9.1 Literature Review/References

None

9.2 Labeling Recommendations

Refer to the approved label.

9.3 Advisory Committee Meeting

Not applicable.

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/s/

LAWRENCE D RODICHOK
01/16/2014

JOHN R MARLER
07/15/2014

Safety Team Leader Memo
BLA 125499

Review and Evaluation of Clinical Data
Safety Team Leader Memorandum

BLA:	125499
Drug:	PEGylated interferon beta-1a; BIIB017 (PLEGRIDY and PLEGRIDY PEN)
Route:	Subcutaneous injection
Indication:	Relapsing forms of multiple sclerosis
Sponsor:	Biogen
Submission Date:	5/15/13
Review Date:	1/23/14
Reviewer:	Sally Usdin Yasuda, Safety Team Leader Division of Neurology Products

1. Background

BIIB017, the PEGylated form of interferon beta-1a, has been proposed for use in relapsing forms of multiple sclerosis (MS). According to the applicant, as a beta interferon, BIIB017 modulates immune responses thought to play a role in the pathogenesis of MS, although the exact mechanism of action of interferon beta-1a in MS is unknown. The proposed dosing regimen is 125 µg administered subcutaneously every 2 weeks. The currently approved interferon beta products used to treat MS are Avonex (interferon beta-1a) that is given by intramuscular injection once weekly, Rebif (interferon beta 1-a) that is given subcutaneously three times a week, and Betaseron (interferon beta 1-b) that is given subcutaneously every other day. According to the applicant, pegylation shields a protein from enzymatic degradation or other clearance processes. The applicant reports that BIIB017 has a longer half-life compared to unmodified interferon beta-1a, and that there is no change in the pharmacological or safety profiles of interferon beta 1-a in nonclinical studies. The applicant postulates that renal elimination is a major excretory pathway for PLEGRIDY. Approved pegylated interferons in the United States include Pegintron (pegylated interferon alpha-2b used for chronic hepatitis C) and Pegasys (pegylated interferon alpha-2a used for chronic hepatitis B and for chronic hepatitis C).

This memorandum primarily summarizes the findings of Dr. Jerry Boehm's primary safety review of the BIIB017 BLA. Please refer to his review for more detail.

2. Summary of Findings from the Safety Review

2.1 Sources of Data, Exposure, and Demographics

The safety database supporting this supplement contains data from 1664 subjects who were exposed to at least 1 dose of BIIB017 (729 every 4 weeks, 740 every 2 weeks) in clinical trials in healthy volunteers, volunteers with renal impairment, and adults with MS. There were 4 Phase 1 trials (196 exposed subjects) and 2 Phase 3 trials (1468 exposed in trials 105MS301 and 105MS302). Through the 120 Day Safety Update, in the Phase 3 trials 1350 MS patients were exposed to BIIB017 for at least 6 months (670 in the every 2 weeks group), 1182 were exposed for at least 1 year (588 in the every 2

Safety Team Leader Memo
BLA 125499

weeks group), and 648 were exposed for at least 2 years (334 in the every 2 weeks group). The exposure exceeds ICH guidelines (300-600 for 6 months, 100 for 1 year, and 1500 total), including for 6 months and 1 year at the proposed dose. Compliance was high in Studies 301 and 302, with 93% of all BIIB017 treated subjects receiving all planned injections during the first year, and 99% of subjects in the overall experience that received all planned injections through the 120 day Safety Update.

105MS301 is a 2 year trial in patients with relapsing-remitting MS (RRMS) where subjects were randomized to placebo (n=500 dosed), BIIB017 125 µg every 2 weeks (n=500 dosed), or BIIB017 125 µg every 4 weeks (n=512 dosed) during the first year. Subjects were titrated to their target randomized dose using the following schedule: initiation 63 µg, Week 2 94 µg, week 4 125 µg ; at Week 6 subjects randomized to every 2 weeks received 125 µg and subjects randomized to every 4 weeks received placebo. The first year of the study (placebo controlled) has been completed. During the second year, BIIB017 is administered as 125 µg either every 2 weeks or every 4 weeks (ongoing); there have been 666 subjects dosed in each group, with dose frequency blinded. 105MS032 is an extension trial in patients with RRMS and is ongoing. The safety analysis uses data primarily from the placebo controlled phase of the first year of 105MS031 and the pooled data from 105MS031 and 302 to summarize the overall Phase 3 safety experience. I agree with Dr. Boehm that the data provided generally were adequate to assess the safety of BIIB017.

Dr. Boehm notes that the applicant included treatment related adverse events (AEs) for Avonex and Rebif as AEs of special interest in the Plegridy BLA, and compared safety data for Plegridy to the available safety data for Avonex and Rebif.

Demographics – In the Phase 3 trials overall, the mean age was approximately 37 years, the range was 18-19 years to 65 years, with most subjects in the range of 20-49 years. Female subjects accounted for 71% of subjects. Approximately 82% of patients were white, and approximately 11% Asian. There were 183 investigational sites worldwide. The countries enrolling the most subjects are Poland (386), Ukraine (189), India (170), Russian Federation (145), and Serbia (134); Dr. Boehm reports that all other countries, including the US and Canada, each enrolled fewer than 100 subjects.

2.3 Significant Safety Findings

2.3.1 Deaths

Overall, through the 120 day Safety Update cutoff, the applicant reported 6 deaths among subjects exposed to BIIB017 in the development program trials, all occurring during trial 105MS301. Two deaths occurred during the placebo-controlled phase in BIIB017 subjects (2/1012, 0.2%) vs 1 placebo patients (2/500, 0.4%). Four deaths occurred during the second year (uncontrolled phase). There were 2 additional deaths after the 120 day Safety Update cutoff. I agree with Dr. Boehm that the safety data did not suggest an increased mortality risk in subjects exposed to BIIB017 based on a small number of events and that there did not appear to be a clustering of unusual causes of death. As Dr.

Safety Team Leader Memo
BLA 125499

Boehm notes, missing details in some cases complicate assessment of potential association with exposure to BIIB017. The cases are summarized below.

In the placebo controlled phase of 105MS301, the reported causes of death for the placebo patients were subarachnoid hemorrhage and unknown, and the reported causes of death for the BIIB017 patients were septic shock and unknown. Septic shock occurred in Subject 618-320, a 40 y.o. female randomized to BIIB017 every 4 weeks who was hospitalized for sepsis and UTI 3 days after her first injection. Her hospital course was complicated by decubitus ulcer formation and intestinal obstruction from which she recovered and she was discharged. She received her 2nd injection of BIIB017 and 12 days later was hospitalized, unconscious and with a high grade fever. Two days later the subject died. The investigator believes the subject was experiencing septic shock on admission, but no supporting laboratory results are available. “Unknown” cause of death was reported for Subject 613-308, a 19 year old female randomized to BIIB017 every 2 weeks. She received her 2nd injection of study treatment 2 days prior to the event. Before her death, she was ambulatory, her functional status was good, and her activities of daily living were unaffected. She died in her sleep without evidence suggestive of seizure during sleep. No autopsy was performed. Results of all laboratory tests prior to death were unremarkable and ECG results had been normal. It is difficult to determine the role of BIIB017 in either of these deaths.

There were 4 deaths in patients taking BIIB017 following the placebo controlled phase of 105MS301. Subject 621-301 was a 47 year old male who received placebo for the first year and then started BIIB017 every 4 weeks in the second year. He was diagnosed with squamous cell cancer of the oral cavity after 4 injections of BIIB017. Symptoms related to the diagnosis began 4 months earlier. He discontinued BIIB017, refused treatment for the cancer, and died 6 months later. Subject 496-303 died as a result of a motor vehicle accident in adverse weather conditions. I agree that these deaths were unlikely related to study drug. Subject 436-305 was a 47 y.o. female with a history of anterior wall myocardial infarction who died unexpectedly at home. There was no other information available, and I agree that the assessment of the relationship of this death to BIIB017 is not possible. Subject 630-303 was a 19 year old female treated with BIIB017 every 2 weeks in year 1 and year 2 of the trial whose death was attributed to sepsis. Events began 5 days after her 35th injection of study treatment, with signs and symptoms of infection. No autopsy was performed. It is not possible to rule out a role for BIIB017, given its immunomodulatory properties, although as Dr. Boehm notes in his review, BIIB017 did not appear to be associated with an increased risk of infections in the BLA database trials.

Dr. Boehm summarized the 2 additional deaths after the cutoff date for the 120 day Safety update. Subject 610-313 was a 42 y.o. female from India with no relevant medical history who died on Day 726 having received placebo in Year 1, and BIIB017 every 4 weeks in year 2. Starting on Day 414 she experienced 3 SAEs of infection, including infected skin ulcer, urinary tract infection, and sepsis, the latter resolving on Day 589. The lowest WBC recorded was during screening (5.19×10^9), and the last available WBC count from week 95 was 7.6×10^9 . During her last visit on Day 659 she had an

Safety Team Leader Memo BLA 125499

indwelling urinary catheter and her skin ulcer was healing. On Day 723 she experienced worsening weakness; she refused to go to the hospital and was receiving IV fluids at home. It was reported that she had bilateral crepitation thought due to aspiration, and screaming episodes thought due to encephalopathy caused by sepsis. She had decreased urine output, blood pressure of 60/40 mm Hg, and pulse was 100 bpm. She remained home until her death. According to the investigator, the cause of death was infected bed sore and urinary tract infection considered related to study treatment. No autopsy was performed. It is not possible to determine the role of BIIB017. Subject 613-307 was a 25 y.o. female from India with a medical history of weight loss, who was hospitalized due to the SAE of meningitis on Day 43 of 105MS032. She had completed 105MS301 (placebo in Year 1 and BIIB017 every 2 weeks in Year 2). During Study 301 her lowest WBC was 4.8×10^9 (Day 271) and the rest of her WBC were $> 5.8 \times 10^9$. One week after beginning treatment for meningitis, she experienced urinary tract infection, pneumonia, and dyspnea for which she was treated. On Day 52 the SAE of meningitis was considered resolved and the pneumonia resolved two weeks later but the urinary tract infection was ongoing. Study treatment was interrupted on an unknown date due to the SAE of meningitis, and restarted on Day 57. The meningitis was considered related to study treatment by the investigator, and the pneumonia was considered not related. Approximately 6 weeks after meningitis resolved, the subject withdrew consent to participate in the trial. She remained at home with dyspnea, multiple bedsores, and quadriplegia and required a feeding tube, central IV line, indwelling bladder catheter and tracheostomy tube. Approximately 1 month after withdrawing from the trial, the subject died at home, with cause of death reported as major RRMS with recurrent pneumonia, considered not related to study treatment by the investigator.

2.3.2 Other Serious Adverse Events

Dr. Boehm notes that 20% (298/1468) of BIIB017 patients experienced 1 or more SAEs during the Phase 3 trials. During Year 1 of 105MS301, 14% of BIIB017 every 4 weeks, 11% of BIIB017 every 2 weeks, and 15% of placebo patients experienced one or more SAEs. Those that were reported by at least 2 BIIB017 patients and more frequently than placebo were Dengue fever, MS, paraparesis, and intervertebral disc disorder that each occurred in 2 BIIB017 subjects (1 in each dose group, $<1\%$) and in no placebo subjects. Overall in Phase 3 trials, the only SAE reported by at least 1% of BIIB017 subjects was MS relapse (13%, 185/1468). UTI (n=9) and pneumonia (n=5) were the only other SAEs reported by at least 5 BIIB017 patients. Other SAEs of potential interest included sepsis (n=4), ALT increased (n=3), AST increased (n=3), angioedema (n=2) hepatitis, toxic (n=2), transaminases increased (n=2), acute hepatic failure (n=1), anaphylactic reaction (n=1), Basedow's disease (n=1), blood bilirubin increased (n=1), drug induced liver injury (n=1), febrile neutropenia (n=1), grand mal convulsion (n=1), hypersensitivity (n=1), leucopenia (n=1), partial seizures (n=1), retinal detachment (n=1), septic shock (n=1), suicidal ideation (n=1), thrombocytopenia (n=1), urticaria (n=1). There was a single SAE reported from Phase 1 studies that was gastroenteritis in a patient with end-stage renal disease. Dr. Boehm notes that there were no SAEs of aplastic anemia, pancytopenia, acute pancreatitis, acute renal failure, rhabdomyolysis, Stevens Johnson Syndrome, or toxic epidermal necrolysis. Dr. Boehm reviews potentially important SAEs in the sections of AEs of special interest, and I discuss these in Section

Safety Team Leader Memo BLA 125499

2.3.4 (Significant Adverse Events/Submission-Specific Safety Concerns) of my memo. I agree with Dr. Boehm that there does not appear to be evidence of an increased risk of SAEs with BIIB017 from the placebo controlled phase of Trial 105MS301, and that the individual types of SAEs reported overall generally appear consistent with the safety profile of the approved interferon beta-1a treatments.

2.3.3 Dropouts

Dr. Boehm shows that in Year 1 of 105MS301, a higher percentage of BIIB017 patients (14% in q 2 weeks, and 12% in q 4 weeks) than placebo patients (9%) discontinued from the study, and adverse events (AEs) were the reason for higher discontinuation in BIIB017 (5%) compared to placebo (1%). Dr. Boehm shows that the AEs leading to discontinuation more frequently among BIIB017 subjects than placebo in 105MS301 Year 1 were influenza-like illness (1% overall in BIIB017 vs 0 in placebo), and injection site reaction, pyrexia, suicidal ideation, and depression, each less than 1% for BIIB017 and none in placebo. In Phase 1 trials, two subjects from 105HV103 (a 4 week treatment period in which subjects were exposed to 2 doses of BIIB017 125 µg SC delivered by prefilled syringe or autoinjector) discontinued for AEs: 1 for elevated AST and one for lymphopenia and neutropenia.

2.3.4 Significant Adverse Events/Submission-Specific Safety Concerns

2.3.4.1 *Flu-like symptoms* (FLS)

BIIB017 was associated with an increased risk of flu-like symptoms (preferred term of influenza like illness) in the controlled portion of 105MS031, with 47% of both the every 2 week (239/512) and every 4 week (234/500) BIIB017 patients experiencing a flu-like symptom AE compared to 13% (63/500) of the placebo patients.¹ Dr. Boehm shows that there is very little difference in FLS over time when examined by monthly intervals over 48 weeks, although the sponsor felt that FLS occurred most often in the first 12 weeks. The mean time from the most recent injection to FLS was approximately 1.4 days, and for the events that occurred within 2 days of the most recent injection, the duration was 2.8 days in the every 4 week group and 3 days in the every 2 week BIIB017 group. Patients with FLS in the every 4 week group had a slightly lower percentage of days with FLS (7%) vs the every 2 week group (10%). Through the 120 day Safety Update, none of the FLS events using the narrow definition of influenza-like illness were classified as SAEs. In the placebo controlled phase of 105MS301, no placebo subjects discontinued due to FLS vs 2 % (8/500) and < 1% (4/512) in the BIIB017 every 4 and every 2 weeks groups, respectively. Overall in Phase 3 through the 120 day Safety Update, 1% (21/1468) of BIIB017 subjects discontinued for FLS: 2% (12/728) of every 4 weeks subjects vs 1% (9/740) of BIIB017 every 2 weeks subjects. Of those subjects who discontinued, overall in Phase 3 trials, 4% (32/378) and 6% (42/380) in the every 4 week and every 2 week group, respectively, had a FLS event classified as severe. The

¹ Using a broader search that included preferred terms of chills, hyperpyrexia, influenza-like illness, musculoskeletal pain, myalgia, pain, and pyrexia, 77% of the every 4 weeks and 78% of the every 2 weeks BIIB017 patients experienced one or more of these search terms for flu-like symptoms vs 33% of placebo patients. The discussions of flu-like symptoms in Dr. Boehm's review and in my memo are primarily based on the narrow search for influenza-like illness that defined a "flu-like symptom".

Safety Team Leader Memo
BLA 125499

incidence of FLS in the Phase 3 trials for BIIB017 are similar to those reported for Avonex or for Rebif, although in the Rebif and Avonex placebo groups, the incidence was higher than reported in this BLA. There were reportedly no serious FLS in the Rebif and Avonex controlled trials.

2.3.4.2 Injection site reactions

Beta-interferons have been associated with injection site reactions (ISRs), in some cases resulting in necrosis. In the present BLA, over 60% of BIIB017 treated subjects developed ISRs, primarily erythema, pain, and pruritus. In the placebo controlled phase of 105MS301, 11% (54/500) of placebo subjects vs 60% (298/500) of BIIB017 every 4 weeks and 66% (336/512) of every 2 weeks patients experienced ISR. Of these, ISRs were classified as severe for 3% of subjects in each BIIB017 group and none in the placebo group. The risk of ISRs was highest during the first 12 weeks of treatment and remained relatively high during the remainder of the first year of treatment. For the every 4 weeks group, 54 % of patients had ISRs in weeks 0-12 and 31-39% had ISRs for the remaining 12 week treatment periods in the first year. For the every 2 weeks group, 58% of patients had ISRs in weeks 0-12, and 38-38% had ISRs for the remaining 12 week periods.

Two BIIB017 subjects (<1%, 2/1468) had ISRs that were SAEs. Subject 570-310 (BIIB017 every 2 weeks) had a SAE that was an ISR that included erythema, edema, pain, and pruritus at the injection study (without necrosis) after having completed 6 injections, resulting in discontinuation of study treatment. She had experienced multiple non-serious ISRs. Anti-IFN beta-1a and anti-PEG status were negative throughout the trial. Subject 270-304 (BIIB017 every 2 weeks) had received 24 injections before the serious ISR occurred, 8 days after her last injection. She presented with mild erythema, pruritus, and necrosis at the injection site that was increasing in size and pain. She had no history of similar episodes or reaction and had no signs of poor hygiene.

Less than 1% of BIIB017 subjects (n=3 for every 4 weeks and n=5 for every 2 weeks) and no placebo subjects discontinued for ISRs in the placebo controlled phase of 105 MS031. Two additional BIIB017 subjects (both every 2 weeks) discontinued for ISRs during 105MS302.

Dr. Boehm shows that there does not appear to be strong evidence of difference in risk for ISRs when stratified by patients ever positive or never positive for binding antibodies (BAbs) or PEG antibodies. There were too few patients with ISRs and positive neutralizing antibodies (Nabs) to assess the risk of ISRs in that group.

Because there was no non-pegylated arm in this development program, rates of ISRs could not be directly compared to findings with other beta interferons. The risk of ISRs was 3% for Avonex vs 1% for placebo (and I note that according to the Avonex label, injection site pain was reported in 8% of subjects taking Avonex and 6% on placebo). For Rebif, ISRs were reported in approximately 90% of subjects taking Rebif and 39% taking placebo. According to those labels, injection site necrosis was reported in the

Safety Team Leader Memo
BLA 125499

Rebif treated subjects (1% of subjects who received Rebif 22 µg and 3% who received Rebif 44 µg), but not in the Avonex clinical trials.

2.3.4.3 Infections

In the placebo controlled phase of 105MS301, 39% of placebo subjects had one or more infection AEs compared to 37% of BIIB017 every 4 weeks and 33% of BIIB017 every 2 weeks patients. Of the AEs occurring in at least 1% of BIIB017 patients, Dr. Boehm reports that only urinary tract infection (placebo 4%, 21/500; BIIB017 6% 57/1012), oral herpes (placebo 1%, 7/500; BIIB017 3%, 26/1012) and cystitis (placebo < 1%, 2/500; BIIB017 1%, 15/1012) occurred more frequently in BIIB017 patients. He finds no meaningful difference in infection SAEs among treatment groups (placebo 1%, every 4 weeks 1%, every 2 weeks < 1%). Less than 1% in each treatment group discontinued for an infection AE. In the placebo controlled phase of 105MS031, potential opportunistic infections were reported in 2 placebo subjects (cryptosporidium gastroenteritis, and disseminated tuberculosis) and in 1 BIIB017 subject (every 2 weeks group; positive CMV immunoglobulin G test during a hospitalization for MS relapse after 4 injections of study medication; no symptoms of CMV infection; reason for testing was not provided). I agree with Dr. Boehm that exposure to BIIB017 did not appear to be associated with an increased risk of infections or opportunistic infections in the BLA database.

2.3.4.4 Cardiovascular disorders

According to the labeling of AVONEX and BETASERON, although beta interferons do not have any known direct cardiac toxicity, cases of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure have been reported in some cases temporally related to administration of AVONEX or BETASERON in the postmarketing setting, as noted in the Warnings and Precautions sections of those labels. Cardiac adverse events are not mentioned in Warnings and Precautions of the REBIF label.

In the placebo controlled phase of 105MS301, 7% of placebo subjects had 1 or more cardiovascular AEs vs 9% (43/500) of BIIB017 every 4 weeks subjects and 7% (38/512) of every 2 weeks subjects. Tachycardia was the only cardiovascular AE that occurred in at least 1% of BIIB017 patients (1% in BIIB017) and more than placebo (<1%). Cardiovascular SAEs experienced by BIIB017 patients were paraparesis (n=2), cerebral ischemia, cerebrovascular insufficiency, monoparesis, and paresis². One placebo subject (subarachnoid hemorrhage) and one BIIB017 subject (every 4 weeks, peripheral edema) discontinued for a cardiovascular AE. In the overall BIIB017 Phase 3 experience, 11% (78/728) of BIIB017 every 4 weeks and 10% (75/740) of every 2 weeks subjects experienced a cardiovascular AE, of which 7 subjects (<1%) and 4 subjects (<1%) in the BIIB017 every 4 weeks and every 2 weeks, groups, respectively reported SAEs. The SAEs were similar to those identified in the placebo controlled phase of 105 MS301, but also included 1 cardiac failure congestive. There were no additional discontinuations related to cardiovascular AEs.

² Biogen analyzed cardiovascular disorders using cardiovascular disorder SMQs: cardiac arrhythmias, cardiac failure, cardiomyopathy, cerebrovascular disorders, and ischemic heart disease.

Safety Team Leader Memo
BLA 125499

In the BIIB017 trials, patients with underlying cardiac disease were excluded, and as Dr. Boehm notes, this potentially limits the generalizability of these data to more heterogeneous populations. Because of this, and the limited size of the BLA database, I agree with Dr. Boehm that the absence of an increased risk is not surprising. I recommend that postmarketing summaries provided by Biogen should include events of cardiovascular AEs as this drug becomes more widely used in a less restricted population.

2.3.4.5 Hepatic disorders

Dr. Boehm notes that the approved beta interferons are associated with a risk of severe hepatic injury, and the labels for these products include warnings about this risk. The labels mention autoimmune hepatitis and hepatic failure resulting in transplant, and they document the increased risk of aminotransferase elevations and suggest monitoring of aminotransferases during treatment.

Dr. Boehm finds that BIIB017 is also associated with liver injury risk. Dr. Boehm observed increased aminotransferases up to > 3X ULN in BIIB017 compared to placebo, particularly in the every 2 weeks group in the placebo controlled portion of 105MS301. For greater elevations, there was no difference observed between BIIB017 and placebo, with very small numbers of events. Elevations of ALT >5X ULN occurred in 2% in each BIIB017 group and 1% in placebo, and elevations > 10 X ULN occurred in < 1% in each group, and elevations > 20X ULN occurred in 1 BIIB017 subject and no placebo subjects. Elevations of AST > 5X ULN occurred in < 1% in each group, and elevations of > 10X ULN or > 20% ULN occurred in < 1% of BIIB017 subjects and in no placebo subjects. The following table, extracted from a table in Dr. Boehm’s review, shows the increased risk of ALT and AST elevations up to ≥3XULN in Year 1. Total bilirubin > ULN was only slightly increased for BIIB017 (9% and 8% in every 4 weeks and every 2 weeks, respectively) vs 7% for placebo, and higher elevations did not occur more frequently for BIIB017 vs placebo.

Aminotransferase Outlier Results up to ≥ 3XULN in 105MS301, year 1

	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	Total
	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)
AST				
>ULN	15% (73)	19% (92)	33% (166)	26% (258)
≥3xULN	1% (7)	2% (11)	2% (12)	2% (23)

Dr. Boehm shows that the plot for mean ALT over time demonstrated maximum differences vs placebo at week 6 for the every 4 weeks group and at week 8 for the every 2 weeks group and that these mean differences persisted over the 48 week observation period. AST showed a similar pattern, although differences vs placebo were less than for ALT.

Safety Team Leader Memo
BLA 125499

Through the 120 day Safety Update, Dr. Boehm notes that 3 BIIB017 treated subjects in the Phase 3 trials (437-307, 435-308, and 523-325) experienced aminotransferase elevations $\geq 3X$ ULN with concurrent total bilirubin $> 2X$ ULN and no increase in alkaline phosphatase, meeting the definition of Hy's Law. Subject 435-308, was a 52 y.o. female from Poland with no relevant history and no history of alcohol abuse, who developed asymptomatic elevations in liver function tests (ALT 27X ULN, AST up to 34X ULN, bili $\sim 2X$ ULN) approximately 14 months after the start of study treatment that resolved beginning 1 month after interruption of study drug. Results for Hepatitis E and for autoimmune hepatitis were pending. AST levels were greater than ALT levels, consistent with alcoholic induced liver injury. Subject 437-307 was a 25 y.o female from Poland, with no relevant history y.o who developed acute hepatic failure with elevated liver enzymes (AST 29X ULN, ALT 24X ULN, bili 20X ULN) approximately 5 weeks after starting study drug (after 4 doses), and 4 weeks after receiving a course of high dose corticosteroids for MS relapse, Study drug was discontinued and she recovered. Four months later, she experienced a similar event after a course of corticosteroids for another MS relapse. High dose steroids could be an alternative explanation, although Dr. Boehm notes that the NIH Liver Tox web site states that hepatic complications of corticosteroids usually represent worsening or triggering of an underlying liver disease. Subject 523-505 was a 52 y.o. female from Serbia, with a history of nonalcoholic steatohepatitis (NASH) and cholelithiasis, who developed symptomatic elevations in liver function tests beginning after approximately 15 months of exposure to BIIB017. There was incomplete information about HepE and autoimmune hepatitis test results. Study drug was discontinued and liver tests had begun to resolve approximately 1 month later. Although all three cases had confounding factors, a role for BIIB017 cannot be ruled out.

Overall, in the Phase 3 experience, 5 subjects (in addition to 437-307 and 572-309) experienced elevations hepatic SAEs or SAEs related to liver laboratory tests, reversible and generally occurring within 9 months to 2 years after beginning BIIB017. Although one was confounded by concurrent administration of warfarin (subject 496-301, event began within 1 month of starting BIIB017), it is not possible to rule out the role of BIIB017 in any case. For all Phase 3 trials, 1 placebo subject and 10 BIIB017 patients discontinued for a hepatic AE (6 during the placebo-controlled phase of 105MS301 and 4 during the uncontrolled phase in year 2). For these cases also, it is generally not possible to rule out the role of BIIB017. Please refer to Dr. Boehm's review for details of the cases not previously discussed in this memo.

There were no hepatic SAEs and no hepatic enzyme elevations that were SAEs in Phase 1 trials. One subject from a phase 1 trial discontinued for AST elevation that began on Day 8 and resolved on Day 14, after receiving peginterferon beta-1a on Day 1. The patient was taking naproxen, associated with increased hepatic enzymes, at the time of injection and at 12 and 24 hours after injection.

Dr. Boehm discusses hepatic related AEs. In the overall Phase 3 experience, 23 BIIB017 patients experienced 25 AEs under the Hepatobiliary disorders SOC. These were hepatic pain (n=6), cholelithiasis (n=4), hyperbilirubinemia (n=4), hepatitis toxic (n=2), acute hepatic failure, bile duct stone, biliary colic, biliary dyskinesia, cholecystitis acute,

Safety Team Leader Memo
BLA 125499

cholecystitis chronic, drug induced liver injury, gall bladder disorder, and hepatic steatosis. The investigations SOC included hepatic lab test abnormalities reported as AEs. These included ALT increased (8% every 2 weeks, 6% every 4 weeks), AST increased (5% every 2 weeks, 4% every 4 weeks), and GGT increased (5% every 2 weeks, 4% every 4 weeks). In the placebo controlled phase of 105MS031 two placebo patients (hepatic pain) and 8 BIIB017 patients experienced hepatic AEs (n=4 in each BIIB017 group that included hepatic pain (n=4), hyperbilirubinemia (n=3), and acute hepatic failure). Hepatic lab test abnormalities in the Investigations SOC included the following, abstracted from Dr. Boehm’s review:

	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	Total
	N=500	N=500	N=512	N=1012
ALT increased	3% (13)	7% (33)	6% (31)	6% (64)
AST increased	2% (8)	4% (19)	6% (29)	5% (48)
GGT increased	1% (7)	3% (14)	4% (18)	3% (31)

Hepatic enzyme increased, alkaline phosphatase increased, transaminase increased, and liver function test abnormal were reported in <1% in any group.

In summary, BIIB017 is associated with liver injury risk that included Hy’s law cases. Dr. Boehm reports that the database included no deaths due to liver failure and no liver transplants. I agree that based on comparisons to data available for other interferons, the risk for BIIB017 appears generally comparable with other interferons. I agree with Dr. Boehm that as with the approved beta interferons, the BIIB017 label should include a Warnings and Precautions statement describing the liver injury risk.

2.3.4.6 Autoimmune disorders

The Warnings and Precautions section of the AVONEX label mentions post-marketing reports of autoimmune disorders of multiple target organs in AVONEX-treated patients that included idiopathic thrombocytopenia, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis, and the postmarketing section of REBIF mentions drug-induced lupus and autoimmune hepatitis.

In the overall Phase 3 experience for BIIB017, 9 (<1%, 9/1468) BIIB017 subjects had AEs related to autoimmune disorders as identified by the applicant. These events were autoimmune thyroiditis (n=6), rheumatoid arthritis (n=2), Basedow’s disease (in a subject diagnosed with hyperthyroidism during placebo year 1 that resolved during year 1), none of which led to study discontinuation. During the placebo controlled phase of 105MS031, 3 placebo subjects (<1%, 3/500) and 1 BIIB017 subject (<1%, 1/1012) experienced autoimmune AEs. These were autoimmune thyroiditis in the BIIB017 patients and autoimmune thyroiditis (n=1) and rheumatoid arthritis in the placebo subjects, none of which were SAEs or led to discontinuation.

I agree with Dr. Boehm, that BIIB017 did not appear to be associated with an increased risk of autoimmune disorder AEs vs placebo in year 1 of 105MS301. I also agree that

Safety Team Leader Memo
BLA 125499

given the limited size of the database, the risk of autoimmune disorder AEs with beta interferons cannot be discounted. I agree with Dr. Boehm that autoimmune disorders should be a topic of discussion in Biogen's postmarketing reviews.

2.3.4.7 Hypersensitivity/Allergic Reactions

Allergic reactions are noted as Warnings/Precautions for the other beta-interferons. In the Phase 3 experience, 16% of BIIB017 every 4 weeks patients and 19% of every 2 weeks patients had one or more hypersensitivity AEs. There were 2 SAEs of angioedema and 1 of generalized urticaria that could be related to study drug and that occurred approximately 1 month to 14 months after starting BIIB017. Eight patients discontinued for hypersensitivity AEs (4 in the placebo controlled phase vs no placebo subjects). In the placebo controlled phase of 105MS031, 14% (71/500) of placebo patients, 13% (67/500) BIIB017 every 4 weeks patients, and 16% (82/512) of every 2 weeks patients had a hypersensitivity AE. Those that occurred in at least 1% of BIIB017 patients and more commonly than placebo were pruritus (1% in placebo, 2% in every 4 weeks, and 4% in every 12 weeks), erythema (<1% in placebo and every 4 weeks, 2% in every 2 weeks), and rash (<1% in placebo and 1% in every 4 weeks or every 2 weeks). There did not appear to be an association between the presence of binding antibodies to BIIB017 or anti-Peg antibodies and hypersensitivity reactions. I agree with Dr. Boehm that there did not appear to be an increased risk of hypersensitivity AEs compared to placebo in year 1. There also does not appear to be a clear relationship between the risk of hypersensitivity AEs with dose.

2.3.4.8 Malignancies

Biogen identified 6 BIIB017 patients (6/1468) with malignant neoplasms (breast cancer n=2, basal cell carcinoma, cervical cancer, lip/oral cavity cancer, and thyroid neoplasm). I agree with Dr. Boehm that there are too few malignancies to allow for meaningful comparisons of rates in the trials to background rates.

2.3.4.9 Seizures

Seizures associated with the use of beta-interferons are described in the Warnings/Precautions of labeling for Avonex and Betaseron and will be included in PLR labeling for Rebif.

Dr. Boehm notes a slight increase in seizure AEs in the BIIB017 every 2 weeks group compared to the every 4 weeks group and the placebo group in year 1 of 105MS301, but notes that the number of events was too small to draw conclusions about the relationship of seizures and exposure. I agree that given the risk described for the other beta interferons, the labeling for BIIB017 should also include discussion of seizures associated with the use of beta interferons.

2.3.4.10 Depression and Suicide

Dr. Boehm notes that the applicant explored the relationship between BIIB017 and depression in suicide by analyzing the risk for events included under the depression and suicide/self-injury SMQ and by analyzing data from the Beck Depression inventory –II (BDI-II) questionnaire administered during clinical trials. There were no completed

Safety Team Leader Memo BLA 125499

suicides and no AEs coded to the preferred term suicide attempt. In the overall BIIB017 experience, the incidence of depression or suicide related AEs was 11% (78/728) and 10% (74/740) for the every 4 and every 2 week groups, respectively. Serious depression or suicide AEs occurred in 1 subject (<1%) in the every 4 weeks group (suicidal ideation) and in 2 subjects (<1%) in the every 2 weeks group (depression). Four subjects in the every 4 weeks group discontinued for a Depression and Suicide related AE compared to 3 patients in the every 2 weeks group. Dr. Boehm shows that depression and suicide related AEs appeared balanced among treatment groups in the placebo controlled phase of 105MS031, the most common being depression (4% placebo, 5% every 4 weeks, 4% every 2 weeks) and depressed mood (3% placebo, 2% every 4 weeks, and 1% every 2 weeks). In the placebo-controlled BIIB017 experience, Depression and Suicide SAEs were reported for 1 subject in each of the treatment groups, and 2 placebo subjects discontinued for this AE compared to 4 BIIB017 every 4 weeks subjects and 2 every 2 weeks subjects. Dr. Boehm shows that the mean BDI-II scores and changes from baseline were similar across treatment groups.

Given that depression and suicide are prominent warnings in the labels of the other beta-interferons, I agree with Dr. Boehm that because of the small database, the lack of a signal in this case does not discount the concern, and I agree that Biogen's postmarketing reviews should include specific discussions of depression and suicide.

2.3.5 Common Adverse Events

Overall, in the Phase 3 trials, 95% (1393/1468) of treated subjects experienced one or more AEs. In the placebo controlled phase of 105MS031, BIIB017 patients more frequently reported AEs (94%, 953/1012) vs placebo patients (83%, 417/500). Dr. Boehm lists the AEs reported by at least 2% of BIIB017 patients and were reported twice as frequently compared to placebo. Of these, the most common (>10% for BIIB017) were injection site erythema (59% in BIIB017 and 7% in placebo), influenza-like illness (47% in BIIB017 and 13% in placebo), pyrexia (44% in BIIB017 and 15% in placebo), myalgia (19% in BIIB017 vs 6% in placebo), chills (18% in BIIB017 vs 5% in placebo), injection site pain (14% in BIIB017 vs 3% in placebo), and injection site pruritus (12% in BIIB017 vs 1% in placebo). Dr. Boehm shows that there was little difference in AE risk when dosing treatment regimens were compared either in the placebo controlled phase of 105MS301 or in the Phase 3 trials overall.

2.3.6 Laboratory findings

Hematology

Dr. Boehm shows that, as with the approved beta interferon treatments, BIIB017 causes decreases in white blood cells (neutrophils and lymphocytes), red blood cells, and platelets. Hematology sample collection was performed at screening, baseline, and as every 2 weeks from Weeks 2 through 12, every 4 weeks from week 12 through week 24, then at week 36 and week 48. Declines in mean WBC from baseline were observed in week 4 and continued through the end of the first year of treatment, and appeared dosing related. At week 48 the observed WBC decline in the every 4 weeks group represented a 3% decrease from baseline and in the 2 weeks group a 10% decrease from baseline.

Safety Team Leader Memo
BLA 125499

There appeared to be little additional decline after the first year of treatment; there were few patients in each treatment arm after week 108, limiting ability to assess over a longer period of time.

In the placebo controlled phase of 105MS031, 1% (5/500) of placebo patients had potentially clinically significant (PCS) low WBC counts ($<3 \times 10^9/L$) vs 4% (21/500) in the BIIB017 every 4 weeks group and 7% (34/512) in the every 2 weeks group. Dr. Boehm shows that the decline in WBC counts was due to declines in both lymphocytes and neutrophils. PCS low results for lymphocytes and neutrophils are shown in the table below, from Dr. Boehm's review that suggests results that are related to dosing.

PCS low results for lymphocytes and neutrophils during 105MS301, year 1

	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
	N=500	N=500	N=512
PCS low lymphocyte criteria			
$<0.8 \times 10^9/L$	3% (17)	4% (20)	5% (27)
$<0.5 \times 10^9/L$	0	<1% (1)	<1% (2)
PCS low neutrophil criteria			
$<1.5 \times 10^9/L$	3% (15)	5% (24)	9% (44)
$\leq 1.0 \times 10^9/L$	<1% (2)	1% (5)	1% (5)

From Summary of Clinical Safety, pp.112-113

No subjects discontinued for low WBC counts. The only SAE for low WBC appeared to be related to treatment with methimazole as the WBC improved (and the low WBC resolved) after discontinuation of methimazole in that patient. There were no discontinuations or SAEs associated with low lymphocyte counts. There were no discontinuations for low neutrophil counts, but there was 1 patient with a SAE of febrile neutropenia (neutrophil count of $0.42 \times 10^9/L$) after approximately 6 months (13 injections) after starting BIIB017. The event resolved 4 days after treatment with cephalexin and ciprofloxacin with ANC $2.52 \times 10^9/L$. No action was taken with study drug but the subject withdrew consent and withdrew from the trial.

Dr. Boehm also shows that BIIB017 was associated with declines in mean hemoglobin, hematocrit, and platelets, although there did not appear to be a relationship with dosing regimen. The applicant did not find a difference by treatment in percentage of patients with low PCS hemoglobin results (≤ 100 g/L), with 4% (21/496) of placebo patients having 1 or more low PCS hemoglobin results vs 3% (17/496) of BIIB017 every 4 weeks patients and 4% (18/507) of every 2 weeks patients. Dr. Boehm evaluated results for more extreme outliers (≤ 80 g/L), and found that result in 1% in each group. Dr. Boehm also found that similar percentages of patients by treatment (including placebo) experienced PCS low platelet counts ($<100 \times 10^9$). Dr. Boehm reports that no AEs related to decreased hemoglobin led to discontinuation from a phase 3 trial. One subject had an SAE related to decreased hemoglobin that declined to 74 g/L requiring hospitalization and blood transfusion during year 2 when treated with BIIB017 every 2 weeks, in a patient with a history of iron deficiency anemia with decreased hemoglobin on placebo of 88g/L. One AE related to decreased platelets was an SAE and led to discontinuation

Safety Team Leader Memo BLA 125499

(negative anti-platelet antibodies), and 1 subject had a non-SAE of thrombocytopenia that led to discontinuation.

Chemistry – Changes in liver function tests have been previously discussed. Dr. Boehm shows changes from baseline to 48 weeks in other chemistry tests (BUN, creatinine, bicarbonate, sodium, potassium, chloride, glucose, and TSH) and does not find meaningful differences in mean change from baseline or in outliers (shift to low or high) when comparing BIIB017 treated patients to placebo in 105MS031.

Urinalysis – Dr. Boehm notes no meaningful differences in shift percentages by treatment for urinalysis parameters (specific gravity, pH, color, blood, glucose, ketones, protein, RBC, WBC, bilirubin, nitrite, and urobilinogen).

2.3.7 Vital Signs

Dr. Boehm shows mean changes from baseline to week 48 for vital sign parameters (systolic and diastolic blood pressure, pulse, and temperature) for trial 105MS301, and finds that the mean changes were small and similar across treatment groups. He also shows no important differences across treatments in the PCS vital sign analysis.

2.3.8 Special Safety Studies/Clinical Trials

Dr. Boehm reports on the result of a sub-study in 105MS032 that compared the experience of 39 patients following 2 doses of BIIB017 125 µg every 4 weeks or every 2 weeks using the manual pre-filled syringe vs the single-use autoinjector. There were no deaths or discontinuations. Treatment-emergent SAEs occurred in 2 subjects (MS relapse following injection with autoinjector and ureteric calculus following injection with the pre-filled syringe). The most common AEs were generally similar to those observed in Year 1 of 105MS031 or in Phase 3 overall, and were generally similar for prefilled syringe and autoinjector (although injection site pain was slightly higher in the prefilled syringe vs autoinjector, 28% vs 15%), but I note that the AEs of pyrexia, injection site, erythema, and influenza-like illness were lower in this sub-study compared to the overall Phase 3 experience.

2.3.9 Electrocardiograms

Biogen performed 12-lead ECGs at baseline and weeks 48 and 96 during trial 105MS031 and did not collect ECGs during trial 105MS032, and, as Dr. Boehm notes, the ability to detect important changes is limited. There did not appear to be any important difference between treatment groups in QTcF (change from baseline) during the placebo controlled phase of 105MS301, and Dr. Boehm does not note meaningful differences in PR, QRS, or RR interval. Similarly, there did not appear to be meaningful changes in QTcF outliers.

2.3.10 Immunogenicity

The presence of antibodies at baseline was generally low among subjects across all groups ($\leq 3\%$ in each group for BAbs, $\leq 2\%$ of Nabs, and $\leq 8\%$ for anti-PEG antibodies). Dr. Boehm notes that the applicant attributed the positive anti-IFN antibody results to false positivity or prior interferon exposure, and expected some patients to have anti-PEG

Safety Team Leader Memo
BLA 125499

antibodies at baseline given the presence of PEG in foods and medicines. Subjects exposed to BIIB017 and initially antibody negative infrequently developed BAbs ($\leq 8\%$ in each group), NAbs ($< 1\%$ in each group), or anti-PEG antibodies ($\leq 9\%$ in each group) in Year 1 of 107MS031. Dr. Boehm shows that there were few additional subjects who developed antibodies after the first year. Dr. Boehm notes that according to the Sponsor, this compares to 2-8.5% of subjects treated with Avonex during clinical trials who developed NAbs, and 12-46% of subjects treated with Rebif in clinical trials.

2.3.11 Dose-Dependency for Adverse Events

Generally, there did not appear to be differences identified between the BIIB017 doses given every 2 weeks or every 4 weeks, as shown by Dr. Boehm throughout his review, except for liver aminotransferase outliers and to a lesser extent in decline in WBC and PCS low neutrophils, where every 2 weeks had a higher rate of outliers than every 4 weeks.

2.3.12 Time-Dependency for Adverse Events

This is discussed in relevant review sections.

2.3.13 Drug Interactions

Drug-Demographic Interactions – The age range in the BIIB017 clinical trials was 18-65 years, and as Dr. Boehm notes there are therefore no safety data for pediatric or elderly populations. Dr. Boehm shows no meaningful differences in risk of common AEs when comparing BIIB0127 patients < 40 y.o. to those ≥ 40 y.o. Dr. Boehm also finds no meaningful difference in common AEs stratified by sex.

With regard to *race*, the majority of subjects were white (82% in each group in Phase 3 trials), and approximately 11% were Asian. AEs were not evaluated by race.

Patients with significant *underlying diseases* were excluded and there was no analysis of AE risk stratified by underlying disease for enrolled patients. Formal *drug interaction* studies were not conducted, although Dr. Boehm notes that Biogen provided an analysis of AEs in patients who received concomitant IV corticosteroids and did not find notable differences in AEs when comparing patients who received IV corticosteroids vs those who did not, except for MS relapse.

With regard to *geographic region*, fewer than 100 subjects were enrolled from the United States or from Canada. Analysis of AEs by geographic region was not conducted.

Dr. Boehm shows no evidence of increased risk of common AEs among patients who developed antibodies to interferon or PEG, given the limitations of the small numbers of AEs when stratified in this manner.

2.3.14 Human Reproduction and Pregnancy Data

A total of 14 pregnancies in 12 BIIB017-treated subjects were reported in the clinical program. Two ended in spontaneous abortion (at 6 and 4 weeks of pregnancy), 5 in elective abortion (none due to identification of a fetal anomaly), 3 in live birth (no

Safety Team Leader Memo
BLA 125499

complications for 2, unknown for 1), and for 2 the outcome was pending at the time of data cutoff.

A pregnancy registry should be considered as a postmarketing requirement.

2.3.15 Pediatrics and Assessment of Effects on Growth

Patients under the age of 18 years were not included in the BIIB017 trials.

2.3.16 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to Dr. Boehm, the applicant identified no reports of BIIB017 overdose, and concluded that BIIB017 did not suggest rewarding effects or abuse related behaviors. Dr. Boehm reports that an analysis of AE terms potentially suggestive of abuse demonstrated that these events occurred infrequently and were balanced across treatment groups. According to Dr. Boehm, the applicant concluded that BIIB017 is not associated with withdrawal or rebound based on similarity in percentages of patients by treatment that discontinued from study treatment and then experienced an AE. Dr. Boehm notes that the AEs in these patients were similar across treatment groups.

2.3.17 Postmarket Experience

Not applicable.

2.3.18 Summary of Significant Safety Concerns:

As Dr. Boehm has shown, the safety profile of BIIB017 is very similar to that of other beta interferons approved for use in MS. BIIB017 was associated with flu-like symptoms that were experienced in approximately half of the BIIB017 treated patients. Over 60% of BIIB017-treated patients developed injection site reactions, two of whom had SAEs. As with other beta interferon treatments, hypersensitivity reactions were reported after treatment with BIIB017, although overall the risk was not increased compared to placebo in year 1. There were a small number of seizure-related events. BIIB017 did not appear to be associated with an increased risk of cardiac adverse events, depression/suicide AEs, or autoimmune disorder AEs that are mentioned in the labeling of the other beta interferons, but this is not unexpected given the size of the database. As with the other beta interferons approved for MS, BIIB017 is associated with a risk for hepatotoxicity. In addition, as with the approved beta interferon treatments, BIIB017 causes decreases in white blood cells, red blood cells, and platelets.

2.3.19 Postmarketing Risk Management Plan

Biogen has not proposed a postmarketing risk management plan. I agree with Dr. Boehm's recommendation that all postmarketing reviews by Biogen (for example PSURs) should include specific discussions of events of hepatic toxicity, hematological toxicity, autoimmune disorders, depression/suicidality, and infections/opportunistic infections as well as cardiac toxicity.

2.3.20 Conclusions

I agree with Dr. Boehm's assessment that there are no safety issues that preclude approval of this NDA. Adverse events associated with BIIB017 are generally consistent

Safety Team Leader Memo
BLA 125499

with those of other beta interferons approved for use in MS. I agree with Dr. Boehm that all postmarketing reviews by Biogen (for example PSURs) should include specific discussions of events of hepatic toxicity, hematological toxicity, autoimmune disorders, depression/suicidality, and infections/opportunistic infections as well as cardiac toxicity. I recommend that a pregnancy registry be considered as a postmarketing requirement.

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/s/

SALLY U YASUDA
01/23/2014

SAFETY REVIEW

Application Type	BLA
Application Number(s)	125499
Priority or Standard	Standard
Submit Date(s)	05/15/13
Received Date(s)	05/16/13
PDUFA Goal Date	05/16/14
Division / Office	DNP/ODE1
Reviewer Name(s)	Gerard Boehm, MD, MPH
Review Completion Date	01/13/14
Established Name (Proposed) Trade Name	PEGylated interferon beta-1a PLEGRIDY and PLEGRIDY PEN
Therapeutic Class Applicant	Interferon Biogen
Formulation(s)	Subcutaneous injection prefilled pen
Dosing Regimen	125µg every 2 weeks
Indication(s)	Relapsing forms of Multiple Sclerosis
Intended Population(s)	MS patients

Table of Contents

7 REVIEW OF SAFETY.....	4
Safety Summary	4
7.1 Methods.....	7
7.1.1 Studies/Clinical Trials Used to Evaluate Safety	7
7.1.2 Categorization of Adverse Events	14
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	14
7.2 Adequacy of Safety Assessments	15
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	15
7.2.2 Explorations for Dose Response.....	16
7.2.3 Special Animal and/or In Vitro Testing	17
7.2.4 Routine Clinical Testing	17
7.2.5 Metabolic, Clearance, and Interaction Workup	19
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	19
7.3 Major Safety Results	19
7.3.1 Deaths.....	19
7.3.2 Nonfatal Serious Adverse Events	23
7.3.3 Dropouts and/or Discontinuations	24
7.3.4 Significant Adverse Events	26
7.3.5 Submission Specific Primary Safety Concerns	57
7.4 Supportive Safety Results	57
7.4.1 Common Adverse Events	57
7.4.2 Laboratory Findings	59
7.4.3 Vital Signs	66
7.4.4 Electrocardiograms (ECGs)	67
7.4.5 Special Safety Studies/Clinical Trials	68
7.4.6 Immunogenicity	68
7.5 Other Safety Explorations.....	71
7.5.1 Dose Dependency for Adverse Events	71
7.5.2 Time Dependency for Adverse Events.....	71
7.5.3 Drug-Demographic Interactions	71
7.5.4 Drug-Disease Interactions.....	73
7.5.5 Drug-Drug Interactions.....	73
7.5.6 Adverse Events by Antibody Status	73
7.6 Additional Safety Evaluations	79
7.6.1 Human Carcinogenicity	79

7.6.2	Human Reproduction and Pregnancy Data.....	79
7.6.3	Pediatrics and Assessment of Effects on Growth	79
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	79
7.7	Additional Submissions / Safety Issues	80
8	POSTMARKET EXPERIENCE.....	80
9	APPENDICES	81
9.1	Literature Review/References	81
9.2	Labeling Recommendations	81
9.3	Advisory Committee Meeting.....	81

7 Review of Safety

Safety Summary

This review considers the safety data for BII017 (PLEGRIDY) as presented in Biogen's BLA 125499. BII017 is the PEGylated form of interferon beta-1a. Biogen asserts that as a beta interferon, BII017 modulates immune responses that are believed to play a role in the pathogenesis of Multiple Sclerosis (MS). Non-PEGylated beta interferons including Avonex, Rebif, and Betaseron are FDA approved for the treatment of MS.

Investigators conducted clinical trials using BII017 in Multiple Sclerosis (MS), patients. For BLA 125499, Biogen conducted trials to support the indication of "treatment of patients with relapsing forms of multiple sclerosis". Existing FDA approved treatments for relapsing forms of MS include interferons, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate.

The BII017 BLA submission summarizes safety data for 1,664 exposed subjects from clinical trials in healthy volunteers, volunteers with renal impairment, and adults with MS. The BII017 development program consisted of 4 Phase I trials (196 exposed subjects), and 2 Phase III trials (1,468 exposed, in trials 105MS301, 105MS302). 105MS301 is a 2-year trial in patients with relapsing-remitting Multiple Sclerosis (RRMS) where subjects were randomized to placebo, BII017 125ug every 2 weeks or every 4 weeks during the first year (completed). During the second year, investigators administer BII017 125ug either every 2 weeks or every 4 weeks (ongoing). 105MS302 is an extension trial in patients with RRMS (ongoing). Biogen presented comparative safety analyses using the data from the placebo controlled phase of the first year of 105MS301. Biogen also pooled data from 105MS301 and 105MS302 to summarize the overall Phase III trial BII017 safety experience

The number of individuals exposed to BII017 in the BLA trials exceeds ICH guidelines and investigators exposed adequate numbers of subjects to the intended recommended dose (125ug every 2 weeks). Biogen reported that 1,664 subjects were exposed to at least one dose of BII017 (728 every 4 weeks, 740 every 2 weeks). Through the 120 Day Safety Update (SU) submission, 1,350 MS patients were exposed to BII017 for at least 6 months, 1,182 were exposed for at least 1 year, and 648 were exposed for at least 2 years.

I identified no significant unresolved deficiencies in the BLA safety submission. Biogen submitted all necessary summaries and supporting data. There were no notable inconsistencies across the data sources (summaries, reports, data sets, etc.). The routine clinical safety testing in the MS clinical trials seemed appropriate and capable of identifying major safety signals with BII017. The coding of adverse events in the

BIIB017 BLA appeared adequate and allowed for accurate estimation of adverse event risks.

Deaths occurred infrequently in the BIIB017 clinical trials and the safety data did not suggest an increased mortality risk in subjects exposed to BIIB017. In the controlled phase of trial 105MS301, mortality risk was highest in the placebo group. In reviewing the individual narratives for deaths in patients exposed to BIIB017, there did not appear to be a clustering of unusual causes of death. Missing details for some of the deaths complicated assessment of potential association with BIIB017.

20% (298/1,468) of MS subjects exposed to BIIB017 experienced one or more serious adverse events (SAEs). The only SAE that occurred in $\geq 1\%$ of BIIB017 exposed patients was MS relapse (13%, 185/1,468). UTI (n=9), and pneumonia (n=5) were the only other SAEs reported by at least 5 patients. During the placebo controlled phase of 105MS301, SAEs were reported slightly more frequently by placebo patients compared to BIIB017 patients. No individual SAE was reported by at least 1% of BIIB017 patients and more commonly compared to placebo. I identified few unexpected SAEs of potential concern in the BIIB017 trials.

6% (92/1,468) of MS subjects exposed to BIIB017 experienced one or more AEs leading to discontinuation. The AEs leading to discontinuation of at least 3 BIIB017 treated patients were influenza like illness (n=21), pyrexia (n=8), injection site erythema (n=7), ALT increased (n=6), multiple sclerosis relapse (n=5), depression (n=4), suicidal ideation (n=4), fatigue (n=3), headache (n=3), and injection site pain (n=3). During the placebo controlled phase of 105MS301, the AEs leading to discontinuation more frequently among BIIB017 subjects compared to placebo were generally related to flu like symptoms and injection site reactions.

Common AEs that occurred more frequently among BIIB017 MS subjects included injection site erythema, influenza like illness, pyrexia, myalgia, chills, injection site pain, injection site pruritus, body temperature increased, vomiting, pain, ALT increased, and hyperthermia.

AEs of Special Interest

Biogen identified a number of AEs of special interest for which they provided in-depth analyses. The list of AEs of special interest included the safety related issues associated with the approved interferon beta MS therapies.

As with the currently available beta interferons, BIIB017 was associated with flu-like symptoms (FLS). Almost half of BIIB017 treated patients experienced FLS. Among BIIB017 treated subjects, there was little meaningful difference in FLS event occurrence over time during year 1 of treatment. No FLS events in the BIIB017 trials were classified as SAEs, and roughly 1% of BIIB017 treated patients discontinued for FLS.

Localized skin reactions at the injection site, in severe cases resulting in necrosis, have occurred in patients treated with beta interferons. Biogen reported an increased risk of injection site reactions (ISRs), mostly erythema, pain, and pruritis, in patients treated with BIIB017. Over 60% of BIIB017 treated subjects developed ISRs. Two BIIB017 exposed subjects had ISRs that were SAEs and <1% of BIIB017 subjects discontinued for ISRs. Development of ISRs did not appear to be associated with the presence of antibodies to BIIB017 or PEG.

Currently approved MS beta interferon treatments are associated with increased risk of serious allergic reactions. Biogen identified a limited number of hypersensitivity adverse events in the Phase III trials, including three SAEs (angioedema n=2, urticaria n=1) that were potentially attributable to BIIB017. BIIB017 did not appear to be associated with an increased risk of hypersensitivity adverse events compared to placebo in year 1 of trial 105MS301. Risk for hypersensitivity AEs in BIIB017 did not appear to be related to development of the measured BIIB017 or PEG antibodies.

Currently approved MS beta interferon treatments are associated with seizures. Biogen identified a limited number of seizure related adverse events in the BIIB017 safety database. There was a slight numeric increase in seizure AEs in the BIIB017 every 2 weeks group compared to the every 4 weeks group and the placebo group in year 1 of trial 105MS301, although the small number of events precludes firm conclusions about causality.

Exposure to BIIB017 did not appear to be associated with an increased risk of cardiac adverse events, depression/suicide AEs, or autoimmune disorder AEs in the BLA database trials. Given the limited size of the BLA database, the absence of an increased risk for these events is not surprising and does not overturn the current understanding regarding the risks for these events with beta interferons.

The approved beta interferon MS treatments are associated with a risk of severe hepatic injury and the labels for these products include information about this risk. The safety data submitted with the BLA suggest that BIIB017 also is associated with liver injury risk. BIIB017 patients had a higher risk of aminotransferase elevations 3x ULN compared to placebo. In addition, there were 2 "Hy's Law" cases (aminotransferase elevations 3x ULN associated with total bilirubin >2xULN) potentially causally related to BIIB017. The database included no deaths due to liver failure and no liver transplants. Based on comparisons to available data, the risks for aminotransferase elevations and hepatic injury with BIIB017 appeared similar to other interferons. The available data are not sufficiently robust to rule out small but potentially important increases in risk for hepatic injury with BIIB017 compared to other beta interferons. As with the approved beta interferons, the BIIB017 label should include a Warnings and Precaution statement describing the liver injury risk. Liver related AEs should be closely monitored following approval.

The additional analyses of treatment emergent AEs that Biogen performed did not suggest that BIIB017 was associated with infections, including opportunistic infections.

As with the approved interferon beta treatments, BIIB017 causes decreases in white blood cells (neutrophils and lymphocytes), red blood cells, and platelets. Despite these findings, there were few SAEs or discontinuations due to abnormal hematological lab results. There were no discontinuations from study treatment or SAEs associated with low lymphocyte counts and no patients discontinued for low neutrophil counts, but there was one patient with a SAE of febrile neutropenia. No AEs related to decreased hemoglobin led to discontinuation from a phase III clinical trial. One subject had an SAE related to decreased hemoglobin, but interpretation of the case was complicated by the subject's history of anemia. One AE related to decreased platelets was an SAE and led to discontinuation, and another (non SAE) led to discontinuation.

The remaining lab data, vital sign data and ECG data collected during the clinical trials did not suggest other BIIB017 related deleterious effects.

Biogen reported that exposed subjects infrequently developed BIIB017 blocking or neutralizing antibodies, or antibodies to PEG.

Conclusions/Recommendations

There are no safety issues that preclude approval of this NDA.

Specific safety labeling recommendations will be presented and discussed with the review team.

All post marketing reviews (e.g. PSURs) should include specific discussions of events of hepatic toxicity, hematological toxicity, autoimmune disorders, depression/suicidality, and infections/opportunistic infections.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The BIIB017 development program included 4 Phase I trials (healthy volunteers (HV): 105HV101, 105HV102, 105HV103, renal impairment and HV 105R101) and 2 Phase III trials (105MS301, 105MS302). 105MS301 is a 2-year trial in patients with relapsing-remitting Multiple Sclerosis (RRMS) with randomization to placebo, BIIB017 125 µg every 2 weeks, or BIIB017 125 µg every 4weeks during the first year (completed) and

treatment with either BIIB017 every 2 weeks or BIIB017 every 4 weeks during the second year (ongoing). 105MS302 is an extension trial in patients with RRMS (ongoing) and enrolled patients continue on their same BIIB017 dose from 105MS301. Biogen presented safety data for the BLA using a cutoff date of 10/24/12, and for the 120 day Safety Update using a cutoff date of 3/27/13. I summarize information from the development program clinical trials in the following tables.

Summary of Phase I trials, BIIB017 Development Program

Trial	Description	Number of subjects Dosed		
		Placebo	IFNB-1a	BIIB017
105HV101	Blinded, randomized, single-dose, BIIB017 dose- and route-finding trial in healthy volunteers (HV). Single-dose BIIB017 SC or IM, or liquid IFN β -1a 30 μ g IM BIIB017 starting dose was 63 μ g (equivalent to IFN β -1a 30 μ g in in vitro activity assays); highest dose 188 μ g. Subjects were monitored in the clinic for 3 days after a single dose, with a follow-up visit 4 weeks after the last dose.	-	12	48
105HV102	Double-blinded, randomized, parallel-group, placebo-controlled, multiple-dose, BIIB017 dose-ranging trial in HV. Subjects received BIIB017 or placebo (inert ingredients). BIIB017 was administered at 63 μ g to 188 μ g SC every 2 weeks (4 BIIB017 doses) or every 4 weeks (2 BIIB017 doses). The treatment period was 6 weeks, with a safety follow-up visit 4 weeks after the last dose	10	-	58
105HV103	Open-label, randomized, crossover trial of BIIB017 delivered by prefilled syringe or autoinjector (prefilled pen) in HV. Subjects were exposed to 2 doses of BIIB017 125 μ g SC delivered by prefilled syringe and a prefilled pen (autoinjector) The treatment period was approximately 4 weeks (29 days) with a safety follow-up visit 3 weeks after the last dose	-	-	55

Safety Review
Gerard Boehm, MD, MPH
BLA 125499
PLEGRIDY, PEGylated interferon beta-1a

105R101	Open-label, single-dose, PK/PD and safety trial of BIIB017 in HIV and subjects with renal impairment. Group 1 (normal renal function) BIIB017 125 µg SC (N = 6) Group 2 (mild renal impairment) BIIB017 63 µg SC (N = 3) and 125 µg SC (N = 6) Group 3 (moderate renal impairment) BIIB017 125 µg SC (N = 6) Group 4 (severe renal impairment) BIIB017 63 µg SC (N = 2) and 125 µg SC (N = 6) Group 5 (ESRD) BIIB017 125 µg SC (N = 6) Subjects were monitored in the clinic for 3 days after a single dose, with a safety follow-up visit 5 weeks after the last dose	-	-	35
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From Table 2, Summary of Clinical Safety, pp 15-16.

Summary of Phase III trials

Trial	Description	Number of Subjects Dosed		
		Placebo	BIIB017 125 µg every 4 weeks	BIIB017 125 µg every 2 weeks
105MS301	Double-blind, randomized, global, multicenter, parallel-group, placebo-controlled trial in MS subjects Year 1 – Subjects were exposed to placebo (inert ingredients) or BIIB017 125 µg SC every 2 weeks or every 4 weeks	500	500	512
	Year 2 – All subjects were exposed to BIIB017 125 µg SC every 2 weeks or every 4 weeks (dose frequency blinded)	-	666	666
105MS302*	Dose-frequency blinded, randomized, global, multicenter, parallel-group, extension trial in MS subjects All subjects continued exposure to BIIB017 with the dose regimen assigned in Year 2 of trial 105MS301	-	247	261

From Table 3, Summary of Clinical Safety, p.17.

*Trial 105MS302 included a sub-study in which 39 patients (q 4 week n=17, q 2 weeks n=22) administered their BIIB017 dose using an autoinjector, prefilled pen.

Trial 105MS301 provides the majority of the submitted safety data and is the only source of Phase III trial placebo-comparative safety data, so I will provide additional details about this trial below.

Trial 105MS301 is a double-blind, randomized, global, multicenter, parallel-group, placebo- controlled trial in MS subjects. During year 1, subjects were exposed to placebo (inert ingredients) or BIIB017 125 µg SC every 2 weeks or every 4 weeks. Subjects were titrated to their target randomized dose using the following schedule: Initiation 63µg, Week 2 94µg, Week 4 125µg. At week 6, subjects randomized to every 2 weeks received 125ug and subjects randomized to every 4 weeks received placebo (Study report 105MS301, p.49). During Year 2, all subjects were exposed to BIIB017 125 µg SC every 2 weeks or every 4 weeks (dose frequency blinded).

Biogen conducted trial 105MS301 at 183 investigational sites in Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, the Czech Republic, Estonia, France, Georgia, Germany, Greece, India, Latvia, Mexico, the Netherlands, New Zealand, Peru, Poland, Romania, the Russian Federation, Serbia, Spain, the Ukraine, the United Kingdom (UK), and the United States (US) (105MS301 Study Report, p.38). The countries enrolling the most subjects were Poland (386 subjects), the Ukraine (189 subjects), India (170 subjects), the Russian Federation (145 subjects), and Serbia (134 subjects); all other countries each enrolled fewer than 100 subjects (105MS301 Study Report, p.118). The trial used central laboratories to evaluate MRIs (b) (4) clinical lab samples (b) (4) and ECGs (b) (4) (105MS301 Study Report, Appendix 16.1.10, Table 1).

The trial included patients with relapsing MS, aged 18 to 65 years, and required females of childbearing age to use effective contraception (105MS301 Study Report, p.53). I provide safety related exclusion criteria for 105MS301 in the following table:

Safety Related Exclusion Criteria Trial 105MS301

<p>Underlying diseases or conditions</p>	<p>History of severe allergic or anaphylactic reactions or known hypersensitivity Known allergy to any component of the BIIB017 formulation History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, and renal, or other major disease History of malignant disease (with the exception of basal cell and squamous cell carcinomas of the skin that had been completely excised and were considered cured). History of seizure disorder or unexplained blackouts OR history of a seizure within 3 months prior to Baseline. History of suicidal ideation within 3 months prior to Baseline or an episode of severe depression within 3 months prior to Baseline. Clinically significant abnormal ECG values as determined by the</p>
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	<p>Investigator. Known history of HIV. Known history or positive test result for hepatitis C antibody, or current hepatitis B infection History of hypersensitivity or intolerance to acetaminophen (paracetamol), ibuprofen, naproxen, or aspirin that would preclude use of at least one of these during the trial. History of drug or alcohol abuse (as defined by the Investigator) within 2 years prior to Day 1.</p>
Abnormal screening test results	<p>Alanine transaminase/serum glutamate pyruvate transaminase (ALT/SGPT) greater than 2 times the upper limit of normal (>2 ULN) or aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) >2 ULN or bilirubin >1.5 ULN. Total white blood cell (WBC) count < 3,700 /mm³ Absolute neutrophil count (ANC) of 1,500 /mm³ Platelet count <150,000 c/mm³ Hemoglobin <10 g/dL in female subjects; <11 g/dL in male subjects Serum creatinine >ULN Prothrombin time (PT) or activated partial thromboplastin time (aPTT)>1.2 ULN</p>
Prior treatments	<p>Prior treatment not allowed : BIIB017, Total Lymphoid Radiation, Cladribine, Fingolimod, T-cell or T-cell Receptor Vaccine, Any therapeutic monoclonal antibody (e.g., rituximab, natalizumab, alemtuzumab)</p> <p>Within past 1 year not allowed: Cytosan, Mitoxantrone</p> <p>Within past 6 months not allowed: Interferon (<i>Prior treatment could not have exceeded 4 weeks</i>) Cyclosporin, Plasma Exchange, Intravenous Immunoglobulin (IVIg), Azathioprine, Mycophenylate, Methotrexate</p> <p>Within past 4 weeks not allowed: Systemic Corticosteroids</p> <p>Within past 50 days not allowed: Copaxone</p> <p>Treatment with another investigational drug or approved therapy for investigational use within the 6 months prior to randomization</p>
MS disease activity related	<p>Progressive forms of MS An MS relapse that had occurred within the 50 days prior to randomization and/or the subject had not stabilized from a previous relapse prior to randomization (Day 1).</p>
Pregnancy related	<p>Female subjects considering becoming pregnant while in the</p>

	<p>trial. Female subjects of childbearing potential who had a positive pregnancy test at either the Screening Visit or the Day 1 (Baseline) visit could not be enrolled into this trial. Female subjects who were pregnant or currently breastfeeding.</p>
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105MS301 Study Report pp. 53-56

I review the routine clinical testing requirements during 105MS301 below, in section 7.2.4. In the following paragraphs I discuss pre-specified requirements for withdrawal and for withholding or discontinuing treatment for laboratory results.

Biogen required investigators to permanently withdraw participants for safety related reasons including pregnancy, severe depression (defined as any episode of depression that required hospitalization, or at the discretion of the Investigator) or suicidal ideation, medical emergency that necessitated permanent discontinuation of treatment or unblinding of treatment assignment, medical reasons or non-compliance (Investigator's discretion), and if the subject experienced a protocol-specified change in laboratory values that necessitated permanent discontinuation of treatment (Study Report 105MS301, p.56).

In the following table I provide Biogen's protocol-specified change in laboratory values and the required action for these values.

Laboratory Criteria Requiring Withholding or Permanent Discontinuation of Treatment

Parameter	Result	Required Action
White Blood Cell Count	<1,500/mm ³	The Investigator* should repeat the test as soon as possible. If the retest value confirms WBC <1,500/mm ³ , the next dose of study treatment should be withheld, and the WBC should be retested in 2 weeks (prior to the next dose). If on retesting the WBC remains <1,500/mm ³ , the next dose of study treatment should also be withheld, and the WBC should be retested in 2 weeks (prior to the next dose). If on retesting the WBC remains <1,500/mm ³ and has persisted for 4 weeks, the subject must permanently discontinue study treatment.
	<500/mm ³	The Investigator* should repeat the test as soon as possible and if the retest value confirms WBC <500/mm ³ , the Investigator will be informed of the lab value immediately. Study treatment will be withheld and retesting will be performed as documented in the above required action for WBC <1,500/mm ³ . Medical evaluation should be conducted as appropriate
Absolute Neutrophil Count	<750/mm ³	The Investigator* should repeat the test as soon as possible. If the retest value confirms ANC <750/mm ³ , the next dose of study treatment should be withheld, and the ANC should be retested in 2 weeks (prior to the next dose). If on retesting the ANC remains <750/mm ³ , the next dose of study treatment should also be withheld, and the ANC should be re-tested in 2 weeks (prior to the next dose). If on retesting the ANC remains <750/mm ³ and has persisted for 4 weeks, the subject must permanently discontinue study treatment.
	<100/mm ³	The Investigator* should repeat the test as soon as possible and if the

		retest value confirms ANC <100/mm ³ , the Investigator will be informed of the lab value immediately. Study treatment will be withheld and retesting will be performed as documented in the above required action for ANC <750/mm ³ . Medical evaluation should be conducted as appropriate.
Platelets	<75,000/mm ³	The Investigator* should repeat the test as soon as possible. If the retest value confirms platelets <75,000/mm ³ , the next dose of study treatment should be withheld, and the platelets should be retested in 2 weeks (prior to the next dose). If on retesting the platelets remain <75,000/mm ³ , the next dose of study treatment should also be withheld, and the platelets should be retested in 2 weeks (prior to the next dose). If on retesting the platelets remain <75,000/mm ³ and have persisted for 4 weeks, the subject must permanently discontinue study treatment.
	<25,000/mm ³	The Investigator* should repeat the test as soon as possible and if the retest value confirms platelets <25,000/mm ³ , study treatment will be withheld and re-testing will be performed as documented in the above required action for platelets <75,000/mm ³ . Medical evaluation should be conducted as appropriate.
Hemoglobin	<8.5 g/dL	The Investigator* should repeat the test as soon as possible. If the retest value confirms hemoglobin <8.5g/dL, the next dose of study treatment should be withheld, and the hemoglobin should be retested in 2 weeks (prior to the next dose). If on retesting the hemoglobin remains <8.5 g/dL, the next dose of study treatment should also be withheld, and the hemoglobin should be retested in 2 weeks (prior to the next dose). If on retesting the hemoglobin remains <8.5g/dL and has persisted for 4 weeks, the subject must permanently discontinue study treatment.
	<8.0 g/dL	The Investigator* should repeat the test as soon as possible and if the retest value confirms hemoglobin <8.0g/dL, study treatment will be withheld and retesting will be performed as documented in the above required action for hemoglobin <8.5g/dL. Medical evaluation should be conducted as appropriate.
ALT or AST	>5 x ULN	The Investigator* should repeat the test as soon as possible. If the retest value confirms ALT or AST > 5× ULN, the next dose of study treatment should be withheld, and liver tests (ALT, AST, alkaline phosphatase, and total bilirubin) should be retested within 1 to 2 weeks. If on retesting the ALT or AST remain > 5× ULN, the subject must permanently discontinue study treatment. Elevated AST or ALT should return to <3× ULN in order to resume dosing. Once dosing has restarted, check AST or ALT weekly for a month, then monthly for 2 months, and then revert to the normal laboratory testing schedule. If the retest value confirms ALT or AST > 5× ULN again, the subject must permanently discontinue study treatment.
ALT or AST and total bilirubin	ALT or AST ≥3× ULN and total bilirubin >2× ULN in combination	The Investigator* should repeat the test as soon as possible. If the retest value confirms ALT or AST ≥3× ULN and total bilirubin > 2× ULN in combination, the subject must permanently discontinue study treatment.

*WBC and ANC data (including the differential) that was obtained after the Screening visit were not to be sent to the sites and were not to be reviewed by any site personnel, as these data could potentially compromise the blind of the trial. All other laboratory data were reviewed by the sites.
From Study Report 105MS301, Table 4, pp.63-5.

7.1.2 Categorization of Adverse Events

Biogen defined AEs as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment” (Study Report 105MS301, p.84). Investigators elicited AEs by general questioning of subjects at trial visits. Investigators recorded the date(s) (onset/resolution) of the event, treatment given, and whether the event led to withdrawal from the trial. Protocols required investigators to follow up reported AEs until they resolved/returned to baseline. Investigators provided opinions about relationship of AE to treatment and classified the AE as mild, moderate, or severe (CRF review).

Biogen coded the reported verbatim terms for AEs to preferred terms using MedDRA dictionary version 15.0 (Summary of Clinical Safety, p.22). In their AE data sets, Biogen provided the investigator verbatim terms and the preferred terms for all AEs. I reviewed the AE data set to assess the AE term coding process. In general, the coding process seemed appropriate and allowed for reliable estimates of AE risks.

Biogen included treatment emergent AEs (AEs present prior to first dose and subsequently worsened in severity, or not present prior to first dose but subsequently appeared) in their analyses (Summary of Clinical Safety, p.22). Biogen presented several routine analyses of AEs including deaths, serious AEs, AEs leading to discontinuation, common AEs, and AEs by investigator reported severity. In addition, Biogen provided detailed analyses for select AEs of special interest. Biogen selected these AEs of special interest based on the safety profile of the interferons approved for the treatment of MS.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Biogen did not pool data from the Phase I trials due to differences in populations, duration of exposures, and differences in doses administered (Summary of Clinical Safety p.19).

The only safety data pooling that Biogen performed in the BLA was to summarize the overall Phase III trial BIIB017 experience. For the overall BIIB017 safety experience, Biogen presented pooled data from 105MS301 (year 1 and 2) and 105MS302. For comparative safety analyses, Biogen presented the results from the placebo controlled phase (year 1) of trial 105MS301.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Biogen reported exposure to BIIB017 that met the ICH guidelines for chronically administered drugs. 1,664 individuals received 1 or more doses of BIIB017 during the development program studies.

Phase I trials

Biogen reported that 196 subjects (167 healthy volunteers, 29 with renal impairment) were exposed to BIIB017 during Phase I trials (Summary of Clinical Safety, p.25). Two of these trials used single dose exposure (105HV101, 105RI101). Trial 105HV102 had a 6 week treatment period and trial 105HV103 had a 4 week treatment period.

Phase III trials

In Table 2 from the 120 day Safety Update, Biogen summarized the exposure to BIIB017 during Phase III trials 301 and 302. Investigators exposed 1,468 patients (every 4 weeks n=728, every 2 weeks n=740) to BIIB017 through the 120 Day Safety Update cutoff date. In the following table I summarize exposure by duration in these trials.

Exposure by duration, BIIB017 Phase III trials

Duration of exposure	Every 4 weeks	Every 2 weeks	Total
At least 1 dose	728	740	1468
>=24 weeks	680	670	1350
>=48 weeks	594	588	1182
>=96 weeks	314	334	648
>=144 weeks	76	71	147
Total person years	1183.2	1202.6	2385.7

From 120 day Safety Update, Table 2 pp.23-26.

Compliance is important when considering exposure because in these clinical trials study drug was administered every 2 or 4 weeks, so any missed doses could have a notable impact on exposure. At the Division's request, Biogen provided a summary of compliance in the BIIB017 Phase III trials.

Biogen felt that compliance was high in Studies 301 and 302. To support this assertion, they noted that 93% of BIIB017 treated patients received all planned injections during the first year of trial 105MS301 (94% of every 4 week and 92% of every 2 week patients). Through the 120 day Safety Update cutoff date, 99% of patients in the overall

BIIB017 experience received all planned injections. (120 Day Safety Update, Table 4). These data support that the exposure estimates accurately reflect the actual exposure when considering compliance.

Demographics of the target population

For the overall BIIB017 experience, a majority of the subjects were females and the average age of participants was 36.9 years (Summary of Clinical Safety Appendix Table 106). I summarize demographic data the overall BIIB017 experience below.

Summary of Demographic Data for BIIB017 overall Phase III trials

	BIIB017 125 mcg SC		
	Every 4 weeks	Every 2 weeks	Total
Number of Subjects	728	740	1468
Mean Age	36.6	37.2	36.9
Age by categories			
<18 years	0	0	0
18-19 years	1% (10)	1% (10)	1% (20)
20-29	27% (196)	24% (174)	25% (370)
30-39	33% (237)	35% (259)	34% (496)
40-49	27% (200)	28% (209)	28% (409)
50-59	11% (81)	12% (86)	11% (167)
60-65	<1% (4)	<1% (2)	<1% (6)
>65	0	0	0
Sex			
Female	71% (514)	71% (522)	71% (1036)
Male	29% (214)	29% (218)	29% (432)
Race			
White	81% (592)	82% (609)	82% (1201)
Asian	12% (85)	11% (82)	11% (167)
Other	6% (46)	6% (45)	6% (91)
Black	<1% (3)	<1% (3)	<1% (6)
Not reported	<1% (2)	<1% (1)	<1% (3)

From Summary of Clinical Safety Appendix Table 106

7.2.2 Explorations for Dose Response

Biogen proposes one maintenance dosing regimen for BIIB017, 125 ug SC every 2 weeks. In the phase III clinical trials, Biogen exposed 728 subjects to every 4 weeks dosing and 740 subjects to every 2 weeks dosing regimens. In their presentation of the safety data, Biogen included data from both the every 4 weeks and every 2 weeks dosing regimen groups to allow for comparison of risks by dose. Biogen included a

BIIB017 188 ug dose in 2 Phase I trials, but the small trial population sizes and limited durations of exposure did not allow for meaningful analyses of safety at this dose.

7.2.3 Special Animal and/or In Vitro Testing

Biogen reported that a 5-week, repeated-dose, rhesus monkey toxicity study found no treatment-related changes in food consumption, body weight, serum chemistry, coagulation analysis, urinalysis, ophthalmology, ECGs, physical evaluations, organ weights, or gross or histological changes. Biogen did note a slight increase in body temperature (1°F to 3°F) within 4 to 8 hours after the first and second BIIB017 dose, but not with subsequent doses. Biogen also reported a reversible, dose-dependent, decrease in lymphocyte count in all BIIB017-treated monkeys.

Biogen reported that BIIB017 did not show evidence of genotoxicity in an in vitro bacterial mutation test (Ames assay) and in an in vitro mammalian chromosome aberration test in peripheral blood lymphocytes.

Biogen noted that a 5-week repeated-dose hormone study in rhesus monkeys conducted to evaluate effects of BIIB017 on menstrual cyclicity found mild and reversible effects at the highest BIIB017 dose tested. Biogen commented that Type I interferons, both unmodified and pegylated, currently in use as therapeutics in humans have, as a class, been identified as abortifacient but not teratogenic in animal studies.

7.2.4 Routine Clinical Testing

Safety assessments included monitoring of spontaneous adverse event (AE) reporting, physical examination, vital signs, electrocardiograms (ECG), hematology, blood chemistry, TSH, urinalysis, and immunogenicity assessments. Other safety assessments included subject assessment of injection pain and clinician assessment of the injection site. During 105MS301 and 105MS302, investigators administered the Beck Depression Inventory-II (BDI-II) questionnaire.

Biogen required the following schedule for safety assessments during year 1 of 105MS301:

Safety assessments during 105MS301, year 1

Tests and Assessments		Year 1 Treatment Period									
Visit Week	Screening	Baseline (Day 1)	Wk 2	Wk 4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 36
Medical History	•	•									
Physical Examination	•	•								•	
Vital Signs	•	•	•	•	•		•			•	•
12-Lead ECG	•	•									

Safety Review
Gerard Boehm, MD, MPH
BLA 125499
PLEGRIDY, PEGylated interferon beta-1a

Hematology/Blood Chemistry Sample Collection	•		•	•	•	•	•	•			•	•
HCV Ab, HBsAg, HBsAb, HBcAb, PT, aPTT	•											
Serum Pregnancy Test	•											
Urine Pregnancy Test			•		•		•	•	•	•	•	•
Urinalysis Sample Collection	•		•					•			•	•
Antibody sampling			•				•			•		•
BDI-II			•					•			•	

From Study Report 105MS301, p.72

At week 48 (end of year 1, beginning of year 2) or end of trial, investigators performed a physical exam, history, recorded vital signs, and collected hematology/chemistry, ECG, urine pregnancy test, UA, and an antibody sample.

During year 2 of 105MS301, investigators evaluated participants every 2 weeks through week 56, and then at week 60, 72, 84, and 96. During year 2 of 105MS301, investigators collected Hematology/Chemistry samples at each visit, urine pregnancy at each visit except weeks 50 and 54, and UA at each visit except weeks 50 through 56. Antibody samples were collected at weeks 60, 72, and 96. Post trial follow up was done at week 100 for all subjects, and at week 108 for those subjects who experienced a change in EDS at week 96 and who did not enter the 105MS302 (105MS301, pp.72-76).

During 105MS302, investigators evaluate participants at baseline (enrollment) and then every 12 weeks, through week 96. Investigators also assess patients at the post treatment follow up visit (week 100), at early withdrawal visits, and at relapse evaluations. Investigators record AEs and concomitant medications at each visit. In the following table I summarize the scheduled safety assessments during 105MS302.

Safety assessments during 105MS302

Tests and Assessments	BL/ (Day 1)	Wk 12	Wk 24	Wk 36	Wk 48	Wk 60	Wk 72	Wk 84	Wk 96
Updated Medical History	•								
Physical Examination	•		•		•				•
Vital Signs	•	•	•	•	•		•		•
Hematology/Blood Chemistry Sample Collection	•	•	•	•	•		•		•
Urine Pregnancy Test	•		•		•	•	•	•	•
Urinalysis Sample Collection	•	•	•	•	•	•	•	•	•
Antibody sampling	•		•		•		•		•

BDI-II		•	•	•	•		•		
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From Study Report 105MS302, Table 4, p.46

7.2.5 Metabolic, Clearance, and Interaction Workup

The serum half-life of PLEGRIDY is prolonged compared with non-pegylated interferon beta-1a. Serum concentration of PLEGRIDY was dose-proportional in healthy subjects. Subcutaneous administration of PLEGRIDY resulted in approximately 4-, 9-, and 13-fold higher exposure (AUC_{168h}) values and approximately 2, 3.5 and 5-fold higher C_{max} , following single doses of 63 (6 MIU), 125 (12 MIU), and 188 (18 MIU) micrograms respectively, compared to intramuscular administration of 30 (6 MIU) micrograms non-pegylated interferon beta-1a. Biogen postulates that renal elimination is a major excretory pathway for PLEGRIDY.

The half-life ($t_{1/2}$) of PLEGRIDY is approximately 2-fold longer than non-pegylated interferon beta-1a in healthy volunteers. In multiple sclerosis patients, the $t_{1/2}$ (mean \pm SE) of PLEGRIDY was 78 ± 15 hours at steady state. The mean steady state clearance of PLEGRIDY was 4.1 ± 0.4 L/hr.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As noted above, Plegridy is a PEGylated interferon beta 1-a. There are currently 2 approved non-PEGylated interferon beta 1-a products, Avonex and Rebif. Biogen identified the treatment related AEs for Avonex and Rebif and included these as AEs of special interest in Plegridy BLA. In addition, Biogen compared safety data for Plegridy to the available safety data for Avonex and Rebif. Biogen did not compare Plegridy safety to Betaseron (interferon beta 1-b).

7.3 Major Safety Results

7.3.1 Deaths

Reviewer Summary

The safety data did not suggest an increased mortality risk in subjects exposed to BIIB017. Deaths occurred infrequently in the BLA submitted trials. In the controlled phase of trial 105MS301, mortality risk was higher in the placebo group than the BIIB017 treatment groups. In reviewing the individual narratives for deaths in patients exposed to BIIB017, there did not appear to be a clustering of unusual causes of death. Missing details for some of the deaths complicated assessment of potential association with BIIB017.

Overall

Through the 120 day Safety Update cutoff, Biogen reported 6 deaths among subjects exposed to BIIB017 in development program trials. All 6 deaths occurred during trial 105MS301. Two deaths occurred during the first year (placebo-controlled phase) and 4 deaths occurred during the second year (uncontrolled phase). Biogen reported 2 additional deaths that occurred after the 120 day Safety Update cutoff.

Deaths, Placebo-controlled phase

There did not appear to be an increased mortality risk among BIIB017 patients during the placebo controlled phase of 105MS301, based on a small number of events. During this first year of trial 105MS301, 2 placebo patients (0.4%, 2/500) died compared to 2 BIIB017 (0.2%, 2/1012) patients. The reported causes of death for the placebo patients were subarachnoid hemorrhage and unknown. The reported causes of death for the BIIB017 patients were septic shock and unknown. I provide additional details for the BIIB017 deaths below.

Subject 618-320, a 40 year old female, was randomized to BIIB017 every 4 weeks. Three days after her first injection, she was hospitalized for sepsis and UTI, and her hospital course was complicated by decubitus ulcer formation, and intestinal obstruction. She recovered from these events and was discharged. The subject received her 2nd injection of study treatment and 12 days later was hospitalized, unconscious and with a high-grade fever. Based on information provided by the subject's family, the Investigator believes that the subject was probably experiencing septic shock on admission; however, no supporting laboratory results are available. Two days later the subject died. The Investigator assessed the septic shock as severe and classified the relationship to study treatment as "not related."

Subject 613-308, a 19 year old female, was randomized to BIIB017 every 2 weeks. She received her 2nd injection of study treatment in the trial 2 days prior to the onset of the event. Before her death, the subject was ambulatory, her functional status was good, and her activities of daily living were unaffected. Her muscle tone was normal. Except for decreased muscle power in the right upper and lower limbs (4+/5) and an exaggerated right plantar reflex, no functional limitations had been noted. She died in her sleep. Relatives reported that the death was silent and sudden. There was no evidence of tongue biting, bedwetting, injuries, or signs suggestive of seizure during sleep. No autopsy was performed. Results of all laboratory tests prior to the subject's death were unremarkable. In addition, the subject's ECG results from 25 January 2011 and 05 February 2011 were normal.

Deaths, After Year 1 105MS301

Biogen reported 4 deaths in BIIB017 treated patients following the placebo controlled phase of trial 105MS301. The reported causes of death were oral cancer, motor vehicle accident/basilar skull fracture, sepsis, and unknown.

Biogen identified non-study drug related explanations for 2 of these deaths. One death (621-301) occurred in a 47 year old male patient who received placebo for the first year and then started BIIB017 (every 4 weeks) in the second year of 105MS301. After 4 injections of BIIB017, he was diagnosed with squamous cell cancer of the oral cavity,

and he stated that symptoms related to this diagnosis began 4 months earlier. He discontinued from the trial, refused treatment for the cancer, and died 6 months later. Given that the symptoms of cancer began around the time of initiation of BIIB107, it is unlikely that the event was related to exposure to study drug. A second death (496-303) was the result of a motor vehicle accident. The patient attempted to pass another vehicle, in a no pass zone, with adverse weather conditions including sleet and ice, resulting in an accident.

The third BIIB017 death (630-303) was attributed to sepsis. I provide additional details about that death below.

Subject 630-303, a 19 year old female, was treated with BIIB017 every 2 weeks in both year 1 and 2 of trial 105MS301. Five days after her 35th injection of study treatment, the subject presented with mild respiratory distress, non-painful abdominal distension, and constipation that was described as infrequent passing of flatus and non-passage of stools for approximately 2 days. She was admitted to the hospital for further evaluation. Vital signs at presentation revealed tachypnea (respiratory rate not provided), blood pressure of 120/82 mmHg, and pulse rate of 84 bpm. Physical examination found “crepitations” in both lung fields. There was no pallor, cyanosis, jaundice, or edema. The neck veins were not engorged, and the neck glands were not enlarged. The abdomen showed no organomegaly, rigidity, or tenderness. Hematological examination on admission showed HGB of 7.4 g/dL (ref. range 12.0 to 16.0 g/dL) with hypochromia, anisocytosis, and microcytosis. Total WBC count was 9,800/mm³ (ref. range 4,300 to 10,800/mm³) with 90% neutrophils (ref. range 45% to 70%) and 10% lymphocytes. The ESR was 112 mm/h (ref. range 0 to 15 mm/h). Platelets were “adequate”. Her serum sodium was 123 mmol/L (ref. range 136 to 146 mmol/L) and potassium was 3.1 mmol/L (ref. range 3.5 to 5.0 mmol/L). C-reactive protein was 16.85 mg/dL (ref. range < 0.50 mg/dL).

Treatment with IV amoxicillin/clavulanic acid; moist oxygen, budesonide, and ipratropium/albuterol inhalation; and bisacodyl enema was started. Two days later, abdominal x-ray showed gross distension of the stomach and intestinal loops. On the following day serum sodium and potassium improved to 133 mmol/L and 3.4 mmol/L, respectively. Two days later, ABG analysis showed pH of 7.533, partial pressure of oxygen of 69.7 mm, and partial pressure of carbon dioxide of 15.7 mm (ref. ranges not provided). A chest xray showed signs of pneumonia. Treatment with amoxicillin/clavulanic acid was discontinued.

The subject’s condition deteriorated on the next day with worsening respiratory distress and development of sepsis. ABG analysis revealed low oxygen saturation (value not provided). Chest x-ray showed increased bronchovascular markings. Laboratory examination showed persistent anemia with HGB of 7.5 g/dL, and some decrease in WBC at 6,000/mm³, with 83% neutrophils and 15% lymphocytes, and CRP at 8.30 mg/dL. Serology test for malaria was negative. The subject was transferred to the ICU, where she received a transfusion of 1 unit of packed RBC for anemia. According to the Investigator, the low HGB level of the subject was possibly secondary to infection. Treatment with IV piperacillin/tazobactam and IV amikacin was started for pneumonia and sepsis.

Two days later, examination of stool sample showed no visible or occult blood; and no ova, cysts, or parasites; a few white blood cells per high-power field were also seen. No blood, sputum, or other specimens were collected for culture during the hospitalization. The subject's condition did not improve while in the ICU. The next day, she developed cardiopulmonary failure. Resuscitation attempts with IV atropine, IV epinephrine, and endotracheal intubation were not successful. No autopsy was performed. The Investigator noted that the subject developed signs and symptoms of infection, which can be related to the study due to immunomodulation.

The fourth death (436-305) involved a 47 year old female who died unexpectedly, at home, and the investigator was unable to provide any other information about the event. The patient had a medical history of an anterior wall myocardial infarction. Due to the limited available information, assessment of the relationship of this death to BIIB017 is not possible.

In addition to the 6 deaths described above, Biogen identified 2 additional deaths reported after the data cutoff date for the 120 day Safety Update. I summarize those deaths below.

Subject 610-313 (Placebo in Year 1 and BIIB017 every 4 weeks in Year 2, 105MS301), a 42-year-old female from India with no relevant medical history, died on Day 726. During her participation in trial 301, the subject experienced 3 SAEs of MS relapse from Day 175 through Day 414. Starting on Day 414, the subject experienced 3 SAEs of infection, including infected skin ulcer, urinary tract infection, and sepsis, with the latter resolving on Day 589. The lowest recorded WBC count for this subject during the trial was the screening WBC count (5.19×10^9). The last available WBC count (7.6×10^9) was from week 96 (Sponsor response to Information Request 10/21/13). During the subject's last trial visit on Day 659, she had an indwelling urinary catheter in place and the skin ulcer was healing. Her treating physician reported that she was stable until Day 723, at which point she experienced worsening weakness. She refused to go to the hospital and was receiving intravenous (IV) fluids at home. The Investigator reported that it was likely that the subject had a new MS relapse involving the arms and neck muscles, that she had bilateral crepitation probably due to aspiration, and screaming episodes probably due to encephalopathy caused by sepsis. Her urine output decreased, blood pressure was 60/40 mmHg, and pulse was 100 beats per minute. She remained at home until her death on Day 725. Per the Investigator, the causes of death were infected bed sore and urinary tract infection which were considered related to study treatment. No autopsy was performed.

Subject 613-307 (BIIB017 every 2 weeks group, trial 105MS302), a 25-year-old female from India with a medical history of weight loss, was hospitalized due to the SAE of meningitis on Day 43 of 105MS302. Prior to entering 105MS302, she completed 105MS301 during which she received placebo in Year 1 and BIIB017 every 2 weeks in Year 2. During 105MS301, her lowest WBC count was 4.8×10^9 (Day 271) and the rest of her WBC results were $>5.8 \times 10^9$ (Sponsor response to Information Request 10/21/13). She presented with severe headache, vomiting, difficulty moving limbs, and a 4-day history of constipation; she had a seizure the same day. Examination revealed neck rigidity, confusion, and slurred speech. Cerebrospinal fluid (CSF) test results showed elevated proteins and mild lymphocytosis, but the culture was negative. She was diagnosed with meningitis. Treatment for meningitis included IV mannitol, IV ceftriaxone,

and IV amikacin. Two days later, she experienced dizziness and headache and was treated with IV tramadol hydrochloride. CSF analysis results were reported to be within normal limits, and her neck stiffness was gradually decreasing. One week after admission, she experienced urinary tract infection, pneumonia, and dyspnea. Additionally, she had hoarseness and hypoxia, with oxygen desaturation to 90% on room air; physical examination showed bilaterally decreased air entry and “crepitus” present; chest x-ray revealed subtle infiltrates in the mid lower zones bilaterally and a congestive pattern. Treatment included oral fluconazole, IV levofloxacin, IV ceftazidime, IV etophylline, IV theophylline, and inhaled ipratropium/salbutamol. Dyspnea resolved on the same day. The following day, Day 52, the SAE of meningitis was considered resolved, with improved proteins from CSF analysis. The pneumonia resolved 2 weeks later but urinary tract infection was ongoing. Study treatment was interrupted on an unknown date due to the SAE and was restarted on Day 57. The pneumonia was assessed as severe and not related to study treatment the by the Investigator. The meningitis was assessed as moderate and considered related to study treatment by the Investigator. According to the Discharge Summary, the diagnosis was RRMS with bacterial meningitis, followed by bulbar (brain stem) relapse with chest infection and a urinary tract infection. Approximately 6 weeks after the meningitis resolved, the subject withdrew consent to participate in the trial. She remained at home with dyspnea, multiple bedsores and quadriplegia and required a feeding tube, central IV line, indwelling bladder catheter, and tracheostomy tube. Approximately 1 month after withdrawing from the trial, the subject died at home, with cause of death reported as major RRMS with recurrent pneumonia, which were considered not related to study treatment by the Investigator.

7.3.2 Nonfatal Serious Adverse Events

Reviewer Summary

Except for MS relapse, SAEs occurred infrequently during the BLA submitted trials. There did not appear to be evidence of an increased risk of SAEs with BIIB017 from the placebo controlled phase of trial 105MS301. The individual types of SAEs reported in the BLA appeared consistent with the safety profile of the approved interferon beta-1a treatments.

Overall Phase III experience

20% (298/1,468) of BIIB017 treated patients experienced 1 or more SAEs during the Phase III trials (120 Day SU Table 31). The only SAE reported by at least 1% of BIIB017 subjects was Multiple sclerosis relapse (13%, 185/1468). UTI (n=9) and Pneumonia (n=5) were the only other SAEs reported by at least 5 BIIB017 patients. Less frequently occurring SAEs of potential interest included sepsis (n=4), ALT increased (n=3), AST increased (n=3), angioedema (n=2), hepatitis toxic (n=2), transaminases increased (n=2), acute hepatic failure (n=1), anaphylactic reaction (n=1), Basedow’s disease (n=1), blood bilirubin increased (n=1), drug induced liver injury (n=1), febrile neutropenia (n=1), grand mal convulsion (n=1), hypersensitivity (n=1), leucopenia (n=1), partial seizures (n=1), retinal detachment (n=1), septic shock (n=1), suicidal ideation (n=1), thrombocytopenia (n=1), urticaria (n=1). There were no SAEs of aplastic anemia, pancytopenia, acute pancreatitis, acute renal failure, rhabdomyolysis, Stevens Johnson Syndrome, or toxic epidermal necrolysis (120 Day SU Table 31).

105MS301, Year 1

During year 1 (placebo controlled phase) of 105MS301, 14% of BIIB017 every 4 week, 11% of BIIB017 every 2 week, and 15% of placebo patients experienced one or more SAEs. In the following table, I list the SAEs reported by at least 2 BIIB017 patients and more frequently compared to placebo.

SAEs reported by at least 2 BIIB017 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)

Summary of Clinical Safety, Table 12 and Appendix Table 27

I include review of potentially important SAE narratives in the relevant sections of the AEs of special interest, below.

Phase I studies

A single SAE was reported from the Phase I studies. An end stage renal disease patient experienced an SAE of gastroenteritis.

7.3.3 Dropouts and/or Discontinuations

In year 1 of 105MS301, a higher percentage of BIIB017 patients discontinued compared to placebo patients. AEs were the reason for the higher discontinuation risk with BIIB017. In the following table I summarize the reasons for discontinuation during year 1 of 105MS301.

Reasons for discontinuation during year 1 of 105MS301

	Placebo	BIIB017 125 mcg SC		
		Q 4 weeks	Q 2 weeks	Total
	N=500	N=501	N=515	N=1016*
Discontinuations for any reason	9% (44)	12% (62)	14% (74)	13% (136)
Adverse event	1% (5)	5% (24)	5% (24)	5% (48)
Loss to f/u	<1% (3)	<1% (4)	<1% (2)	<1% (6)
Consent w/d	6% (30)	6% (30)	7% (35)	6% (65)

Investigator decision	0	<1% (1)	<1% (4)	<1% (5)
Death	<1% (2)	<1% (1)	<1% (1)	<1% (2)
Other	<1% (4)	<1% (2)	2% (8)	1% (10)

Adapted from Table 9, Study report 105MS301

*Includes all enrolled patients (4 BIIB017 patients were enrolled but not dosed).

AEs leading to discontinuation

Reviewer Summary

BIIB017 was generally well tolerated and trial participants infrequently discontinued for AEs. During the placebo controlled phase of trial 105MS301, BIIB017 treated subjects discontinued slightly more frequently compared to placebo subjects. The AEs leading to discontinuation more frequently among BIIB017 subjects compared to placebo were generally related to flu like symptoms and injection site reactions.

Overall Phase III experience

Through the 120 Day Safety Update cutoff date, AEs led to discontinuation of 6% (92/1468) of BIIB017 patients enrolled in the Phase III trials. The AEs leading to discontinuation of at least 3 BIIB017 patients were influenza like illness (n=21), pyrexia (n=8), injection site erythema (n=7), ALT increased (n=6), multiple sclerosis relapse (n=5), depression (n=4), suicidal ideation (n=4), fatigue (n=3), headache (n=3), and injection site pain (n=3). Less frequently occurring, but potentially important, AEs leading to discontinuation were angioedema (n=2), thrombocytopenia (n=2), transaminases increased (n=2), acute hepatic failure (n=1), anaphylactic reaction (n=1), drug induced liver injury (n=1), hemoglobin decreased (n=1), and hepatitis toxic (n=1) (120 Day Safety Update, Table 34).

105MS301, Year 1

During year 1 of 105MS301, the AEs leading that most commonly led to discontinuation among BIIB017 patients, and that were more frequent compared to placebo were influenza like illness, injection site reaction, pyrexia, suicidal ideation, and depression. In the following table I identify the AEs leading to discontinuation of at least 2 BIIB017 patients during year 1 of trial 105MS301.

AEs leading to discontinuation of at least 2 BIIB017 patients from 105MS301, year 1

	Placebo	BIIB017 125 mcg SC		
		Q 4 weeks	Q 2 weeks	Total
	N=500	N=500	N=512	N=1012
Discontinuations for any AE	1% (7)	5% (24)	5% (25)	5% (49)
Influenza like illness	0	2% (8)	<1% (4)	1% (12)

Injection site erythema	0	<1% (3)	<1% (3)	<1% (6)
Pyrexia	0	<1% (1)	<1% (4)	<1% (5)
Suicidal ideation	0	<1% (2)	<1% (2)	<1% (4)
Depression	0	<1% (2)	<1% (1)	<1% (3)
Fatigue	0	<1% (1)	<1% (2)	<1% (3)
Headache	0	<1% (2)	<1% (1)	<1% (3)
Hyperthermia	0	<1% (2)	0	<1% (2)
Transaminase elevated	0	0	<1% (2)	<1% (2)

Summary of Clinical Safety, Table 14

I include review of potentially important AE leading to discontinuation narratives in the relevant sections of the AEs of special interest, below.

Phase I Trials

Two subjects from the Phase I trial 105HV103 discontinued for AEs. One subject was discontinued for elevated AST, and one subject was discontinued for lymphopenia and neutropenia. No other Phase I subjects discontinued from trials for AEs.

7.3.4 Significant Adverse Events

AEs of Special Interest

Based on their understanding of safety related issues with interferon beta therapies, Biogen identified a number of AEs of special interest for which they provided in-depth analyses. Specifically, Biogen provided additional analyses for flu-like symptoms, injection site reactions, infections, cardiovascular disorders, hepatic disorders, autoimmune disorders, hypersensitivity events, malignancies, seizures, and depression/suicide. I discuss those analyses in the following sections.

Flu-like symptoms

Reviewer Summary

As with the approved beta interferons, BIIB017 was associated with an increased risk of FLS. Almost half of BIIB017 treated patients experienced FLS. Among BIIB017 treated subjects, there was little meaningful difference in FLS event occurrence over time for the examined intervals during year 1 of treatment. No FLS events in the BIIB017 trials were classified as SAEs, and roughly 1% of BIIB017 treated patients discontinued for FLS.

Methods

Biogen did not require investigators to ask specific questions or use written questionnaires to elicit flu-like symptoms (FLS) AEs, so information about these events is based on reporting from trial participants. The protocol required participants to record FLS in a diary. Given the risk of FLS, for the first 26 weeks of trial 105MS301, investigators instructed participants to take acetaminophen or NSAIDs prior to study medication dosing and for 24 hours after administration (trial 105MS301 Protocol v.5, p 879).

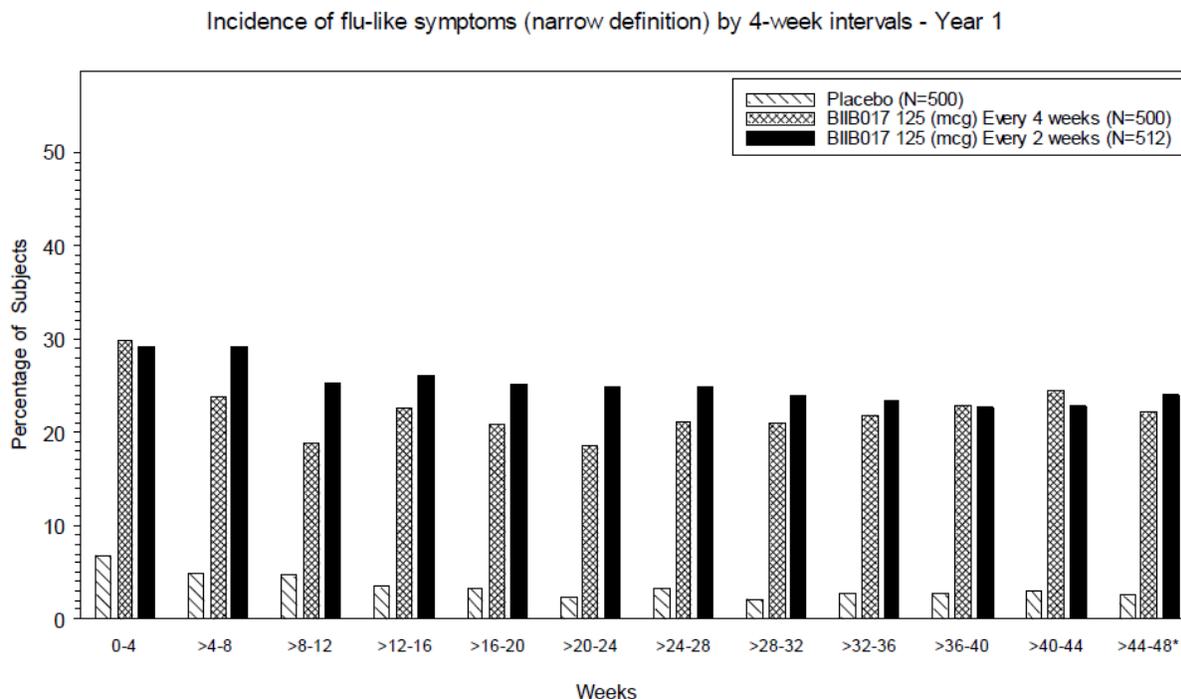
Biogen analyzed FLS AEs using 2 approaches. Biogen first identified AEs with the preferred term of influenza like illness, and then separately performed a broader search using a collection of preferred terms including: chills, hyperpyrexia, influenza-like illnesses, musculoskeletal pain, myalgia, pain, and pyrexia. The purpose of the second search was to increase sensitivity (capture more potential cases), albeit at the expense of specificity. The majority of the discussion of these events will be based on the narrow definition of FLS, unless specifically noted otherwise.

Results

During the placebo controlled phase of 105MS301 (first year), 47% of both the every 2 week (239/512) and every 4 week (234/500) BIIB017 patients experienced a FLS AE compared to 13% (63/500) of the placebo patients (Clinical Study Report Table 238). Using the broader, pooled endpoint, 77% (386/500) of the every 4 weeks and 78% (401/512) of the every 2 weeks BIIB017 patients experienced one or more of the included FLS AEs compared to 33% (165/500) of placebo patients (Clinical Study Report Table 239).

Biogen analyzed the frequency of FLS events over time, using 4-week intervals. Biogen felt that FLS occurred most frequently in the first 12 weeks of treatment. Their graph of these events suggests that there was little meaningful difference in FLS event occurrence for the examined intervals during year 1 of treatment. I provide that graph below.

Figure 2: Incidence of Flu-Like Symptoms (Narrow Definition) By 4-Week Intervals



The mean time from most recent injection to FLS was 1.5 days and 1.4 days in the in the every 4 week and every 2 week BIIB017 groups, respectively. Focusing on the FLS events reported within 2 days of the most recent injection, the duration of FLS was 2.8 days and 3.0 days in the every 4 week and every 2 week BIIB017 groups, respectively. Patients with FLS in the every 4 week group had a slightly lower percentage of trial days with FLS (7%) compared to the every 2 week group (10%). (Summary of Clinical Safety, p.76).

Through the 120 day Safety Update, none of the FLS events (narrow definition) in the BIIB017 trials were classified as SAEs (120 Day Safety Update, p.53).

In the placebo-controlled phase of 105MS301, no placebo subjects discontinued study treatment due to FLS compared to 2% (8/500) and <1% (4/512) in the BIIB017 every 4 and every 2 weeks groups, respectively (Appendix Table 37). Considering all Phase III trials, 1% (21/1468) of BIIB017 subjects discontinued treatment for FLS through the 120 day Safety Update (120 Day Safety Update, Table 43). When considering dose, 1% (9/740) of BIIB017 every 2 week patients discontinued for FLS compared to 2% (12/728) of every 4 week patients (120 Day Safety Update, Table 43).

Considering all Phase III trials, 4% (32/378) of patients with FLS in the every 4 week group and 6% (42/380) in the every 2 week group had an event that was classified as severe. (120 Day Safety Update Table 39).

Since Biogen did not include a non-PEGylated beta interferon arm in 105MS301, there are no data that allow direct comparisons of FLS risk to the approved beta interferon products. Biogen did compare FLS risk observed with BIIB017 to the risks described in labeling for other beta interferons. Potentially important differences among the development programs for these treatments related to trial design, conduct, and populations could limit the validity of any such comparisons.

Biogen noted that the incidence of FLS observed in the pivotal Phase 3 studies with Avonex was 49% in Avonex-treated subjects and 29% in placebo-treated subjects. In the pivotal Phase 3 clinical trial of Rebif, FLS were reported by 56% and 59% of subjects treated with Rebif 22 µg and 44 µg, respectively, compared with 51% of placebo-treated subjects. In both the Rebif and Avonex placebo-controlled experience, there were no serious FLS reported.

Injection Site Reactions

Reviewer Summary

Localized skin reactions at the injection site, in severe cases resulting in necrosis, have occurred in patients treated with beta interferons. Biogen reported an increased risk of injection site reactions (ISRs), mostly erythema, pain, and pruritis, in patients treated with BIIB017. Over 60% of BIIB017 treated subjects developed ISRs. Two BIIB017 exposed subjects had ISRs that were SAEs and <1% of BIIB017 subjects discontinued for ISRs. Development of ISRs did not appear to be associated with the presence of antibodies to BIIB017 or PEG.

Methods

For their analyses of ISR risks, Biogen used the events included in the SOC “General Disorders and Administration Site Conditions”.

Results

The most commonly reported individual ISR preferred terms included injection site erythema, injection site pain, and injection site pruritis. In the placebo controlled phase of 105MS301, 11% (54/500) of placebo patients experienced ISRs compared to 60% (298/500) of BIIB017 every 4 week patients, and 66% (336/512) of every 2 week patients (SCS Table 15, pp. 80-81).

Biogen found that the risk for ISR was highest during the first 12 weeks of treatment, and remained relatively high for the duration of the 1st year of treatment. Biogen provided an analysis that examined the risk for ISRs in 12 week intervals during the placebo controlled phase of trial 105MS301. During the first year of treatment, for the

BIIB017 every 4 weeks group, the percentage of patients with ISRs was 54% (269/500) in weeks 0-12, and ranged between 31-39% for the remaining 12 week treatment periods. For the every 2 weeks group, the risk for ISRs was 58% (299/512) for weeks 0-12, and ranged from 38-48% for the remaining 12 week treatment periods (Study Report 105MS301, Appendix Table 47).

Of all BIIB017 patients (trials 105MS301 and 105MS302), 2 (<1%, 2/1468) had ISRs that were SAEs (SCS, pp. 77-78). In the following paragraphs, I provide information about these events.

Subject 570-310 (BIIB017 every 2 weeks), a 36-year-old female, completed 6 injections of study treatment prior to the onset of the serious ISR event. The ISR included erythema (20 × 10 cm), edema, pain, and pruritus at the injection site in the left thigh. The investigator did not report injection-site necrosis. Study treatment was discontinued, and the subject was withdrawn from the trial due to the serious ISR. She was treated with IM dexamethasone and oral cetirizine and the event resolved within approximately 1 month. The subject also had experienced multiple nonserious events of injection-site erythema/pain/edema a few days after each prior study treatment injection that were assessed as mild or moderate. The subject's anti-IFN β -1a and anti-PEG status were negative throughout the trial.

Subject 270-304 (BIIB017 every 2 weeks group) was a 24-year-old female, who had received 24 injections of study treatment when the serious ISR was reported. Eight days after her last injection of study treatment in Year 1, she presented with mild erythema, pruritus, and necrosis at the injection site that was progressively increasing in size and pain. She had no history of similar episodes or reaction and had no signs of poor hygiene. Her vital signs were unremarkable with no signs of fever or sepsis. Physical examination showed a 2 cm x 3 cm necrotic lesion in the abdominal area with induration, pain, tenderness, and 2 moderately raised areas of possible abscess. She was hospitalized with a diagnosis of gangrenous cellulitis. Treatment included intravenous (IV) cefazolin, oral tramadol, intramuscular parecoxib, and oral amoxicillin/clavulanate. The SAE was considered resolved with sequela of abdominal wall cellulitis 4 days after onset. The Investigator reported that the lesion may have become infected when the subject scratched a pruritic area. No action was taken with study treatment, and the subject continued study treatment as scheduled.

During the placebo-controlled phase of 105MS301, no placebo patients and <1% of BIIB017 patients (every 4 week n=3; every 2 week n=5) had ISRs that led to study treatment discontinuation (SCS, p.79). Two additional BIIB017 patients (both every 2 weeks) discontinued for ISRs during trial 105MS302 (120 Day Safety Update, p.53).

Biogen reported that during the placebo controlled phase of 105MS301, investigators classified ISRs as severe for 3% of subjects in each of the BIIB017 groups, and for none in the placebo group (SCS, p.77).

In addition to AE reporting, Biogen required investigators to periodically assess injection sites in patients during clinical trials. During these assessments, investigators found

that ≥85% of subject’s injection sites had no erythema, induration, or tenderness, and were normal temperature (120 Day Safety Update, Table 53).

Biogen analyzed ISRs in relation to antibody status and did not find evidence that risk of ISRs was increased in patients who developed anti-BIIB017 or anti-PEG antibodies, although these analyses were limited by the relatively small number of patients with antibodies.

Given the low number of subjects (n=12) with ISRs and positive neutralizing antibodies (NAbs) at any time point during Year 1 of 105MS301, Biogen was not able to make meaningful assessment of risk of ISRs for this subpopulation. When examining the percentage of patients with ISRs stratified by the presence/absence of binding antibodies(BABs) at any time during the trial, there did not appear to be strong evidence of differences in risk. Similarly, when examining the percentage of patients with ISRs stratified by the presence of anti-PEG antibodies at any time during the trial, there did not appear to be strong evidence of differences in risk. In the following table, I provide the ISR risk for patients ever positive or never positive for binding and anti-PEG antibodies.

ISR AEs stratified by antibody result (ever positive or never positive for binding and anti-PEG antibodies)

Placebo	BIIB017			RR (Total/Placebo)
	Q 2 weeks	Q 4 weeks	Total	
% of Patients with ISRs, among those Ever Positive for Binding Antibodies				
16% (4/25)	75% (21/28)	70% (38/54)	72% (59/82)	4.5
% of Patients with ISRs among those Never Positive for Binding Antibodies				
11% (50/475)	59% (277/472)	65% (298/458)	62% (575/930)	5.6
% of Patients with ISRs, among those Ever Positive for PEG Antibodies				
13% (8/63)	61% (43/70)	64% (36/56)	63% (79/126)	4.8
% of Patients with ISRs, among those Never Positive for PEG Antibodies				
11% (46/437)	59% (255/430)	66% (300/456)	63% (555/886)	5.7

From Study report 105MS301, Tables 275, 276.

Biogen did not include a non-PEGylated beta interferon comparator arm in 105MS301, so there are no data that allow direct comparisons of ISR risk to any of the approved beta interferon products. Biogen did compare ISR risk observed with BIIB017 to the risks described in labeling for other beta interferons. Potentially important differences among the development programs for these treatments including trial design, conduct, and populations could limit the validity of any such comparisons.

Biogen noted that the incidence of ISRs in the pivotal Phase 3 trial was significantly greater in Rebif-treated subjects (89% in those treated with 22 µg and 92% in those

treated with 44 µg dose) compared to placebo (30%). In the Phase 3 placebo-controlled combined studies with Avonex, the incidence of ISRs was 3% in Avonex-treated subjects compared with 1% in placebo-treated subjects (Summary of Clinical Safety, p.160). In a controlled Phase 3 clinical trial comparing Rebif 44 µg SC with Avonex 30 µg IM, 83% of Rebif-treated subjects and 28% of Avonex-treated subjects reported ISRs (Panitch 2002).

In terms of severity, Biogen noted that in the pivotal Phase 3 placebo-controlled trial with Rebif, 1% of subjects who received Rebif 22 µg and 3% of subjects who received Rebif 44 µg developed necrosis at the site of injection. None of 351 subjects treated with Avonex in Phase III trials developed injection site necrosis (Summary of Clinical Safety, p.160).

Biogen concluded that for BIIB017, the overall incidence of ISRs was similar to that observed with Rebif, and that the incidence of injection site necrosis appeared to be lower with Avonex than with Rebif (Summary of Clinical Safety, p.160).

Infections

Reviewer Summary

Exposure to BIIB017 did not appear to be associated with an increased risk of infections or opportunistic infections in the BLA database trials.

Methods

Biogen examined the risk of infections and potential opportunistic infections (OIs) with BIIB017. For their analysis of infections, Biogen reviewed events included under the Infections and Infestations SOC. For their analysis of potential OIs, Biogen searched using an extensive list of infection related preferred terms that included potential OIs. Biogen provided, in the Appendix to their Statistical Analysis Plan, the actual list of potential OI events included in their search. The listed terms appeared adequate for the purpose of identifying OIs.

Results

In the placebo controlled phase of 105MS301, 39% of placebo patients had one or more Infection AEs compared to 37% of BIIB017 every 4 weeks patients and 33% of BIIB017 every 2 weeks patients. Of the individual infection AEs occurring in at least 1% of BIIB017 patients, only urinary tract infection (placebo 4%, 21/500; BIIB017 6%, 57/1012), oral herpes (placebo 1%, 7/500; BIIB017 3%, 26/1012), and cystitis (placebo <1%, 2/500; BIIB017 1%, 15/1012) occurred more frequently in BIIB017 patients (105MS301 Clinical Study Report, Table 285). There was no meaningful difference in infection SAEs among the treatment groups (placebo 1%, n=7; every 4 weeks 1%, n=5; every 2 weeks <1%, n=3). Furthermore, <1% of patients in each of the treatment groups discontinued for an infection AE.

In the placebo controlled phase of 105MS301, Biogen identified 2 placebo subjects and one BIIB017 subject (every 2 weeks group) with potential OIs. The potential OIs in the placebo subjects were cryptosporidium gastroenteritis and disseminated tuberculosis. The BIIB017 patient, who had received 4 injections of study medication, had a positive cytomegalovirus immunoglobulin G test, during a hospitalization for MS relapse. She did not have symptoms of CMV infection at the time of the test result. Biogen identified no additional potential OIs in trials 105MS301 or 105MS302 (120 Day Safety Update, p.57).

Cardiovascular disorders

Reviewer Summary

Exposure to BIIB017 did not appear to be associated with an increased risk of cardiac adverse events in the BLA database trials. Given the limited size of the BLA database, the absence of an increased risk is not surprising and does not overturn the current understanding regarding the risk of cardiac AEs observed with beta interferons.

Methods

Biogen explored the relationship between BIIB017 and cardiovascular disorders, with emphasis on ischemic cardiac events. Biogen's analyses used cardiovascular disorder SMQs to identify events. Biogen specifically included the Cardiac arrhythmias SMQ (all subSMQs are included except Congenital and neonatal arrhythmias SMQ), Cardiac failure SMQ, Cardiomyopathy SMQ, Cerebrovascular disorders SMQ, and Ischemic heart disease SMQ (Summary of Clinical Safety Statistical Analysis Plan, p.38). Biogen provided in their Statistical Analysis Plan a complete list of the cardiovascular preferred terms included in their search. Biogen excluded patients with underlying cardiac disease from participation in their trials, potentially limiting the generalizability of these data to more heterogeneous populations with cardiac disease.

In the placebo controlled phase of 105MS301, 7% (36/500) of placebo patients had one or more cardiovascular AEs compared to 9% (43/500) of BIIB017 every 4 weeks patients and 7% (38/512) of every 2 weeks patients. Tachycardia was the only cardiovascular event that occurred in at least 1% of BIIB017 patients and more frequently compared to placebo (BIIB017 1%, 13/1012; placebo <1%, 4/500) (105MS301 Study report, Table 57). Biogen noted that <1% of subjects (BIIB017 every 4 weeks 3/500, BIIB017 every 2 weeks 3/512, and placebo 2/500) had a serious cardiovascular AE. The cardiovascular SAEs that BIIB017 patients experienced were paraparesis (n=2), cerebral ischemia, cerebrovascular insufficiency, monoparesis, and paresis. One placebo patient (subarachnoid hemorrhage) and 1 BIIB017 patient (every 4 weeks, peripheral edema) discontinued for a cardiovascular AE (Summary of Clinical Safety p.88).

For the overall BIIB017 experience, 11% (78/728) of BIIB017 every 4 weeks and 10% (75/740) of every 2 weeks patients experienced a cardiovascular AE (120 Day Safety

Update Table 62). Serious cardiovascular disorders were reported by 7 subjects (<1%) and 4 subjects (<1%) in the BIIB017 every 4 and every 2 weeks groups, respectively. The SAEs experienced by these subjects were paraparesis (n=3), myocardial infarction (n=2), cerebral ischemia, cerebrovascular insufficiency, lacunar infarction, monoparesis, syncope, and cardiac failure congestive (120 Day Safety Update, Table 66). For the overall BIIB017 experience, one BIIB017 patient discontinued for a cardiovascular event (peripheral edema, mentioned above, from the placebo controlled phase) (120 Day Safety Update, p.58).

Hepatic Disorders

Reviewer Summary

The approved beta interferons are associated with a risk of severe hepatic injury and the labels for these products include information about this risk. Specifically, these labels mention autoimmune hepatitis, and hepatic failure resulting in transplant. These labels also document the increased risk of aminotransferase elevations and suggest monitoring of aminotransferases during treatment. Biogen proposed adding similar language to the BIIB017 labeling. The NIH LiverTox database web site notes, "Interferon beta is a well-known cause of mild hepatic injury and rarely can result in severe liver injury with jaundice"¹. LiverTox also states that the mechanism of hepatic injury with interferon beta is not known, but that some cases of liver injury are associated with autoimmune features.

The safety data submitted with the BLA suggest that BIIB017 also is associated with liver injury risk. BIIB017 patients had a higher risk of aminotransferase elevations 3x ULN compared to placebo. In addition, there were 2 unexplained "Hy's Law" cases (aminotransferase elevations 3x ULN associated with total bilirubin >2xULN). The database included no deaths due to liver failure and no liver transplants. Based on comparisons to available data, the risks for aminotransferase elevations and hepatic injury with BIIB017 appeared comparable with other interferons. The available data are not sufficiently robust to rule out smaller but potentially important increases in risk for hepatic injury with BIIB017 compared to other beta interferons. As with the approved beta interferons, the BIIB017 label should include a Warnings and Precaution statement describing the liver injury risk.

Methods

Biogen examined the risk of liver injury in the BIIB017 BLA safety database. This effort included review of review of lab results (aminotransferases and bilirubin) and liver related adverse events.

Liver-related lab test results

¹ <http://livertox.nlm.nih.gov/Interferon.htm>

In the placebo controlled phase of 105MS301, BIIB017 exposed patients were more likely to have elevations above multiples of ULN in aminotransferases, with the BIIB017 every 2 week group having the highest percentage of patients with such elevations. In the table below, I summarize the aminotransferase and bilirubin results.

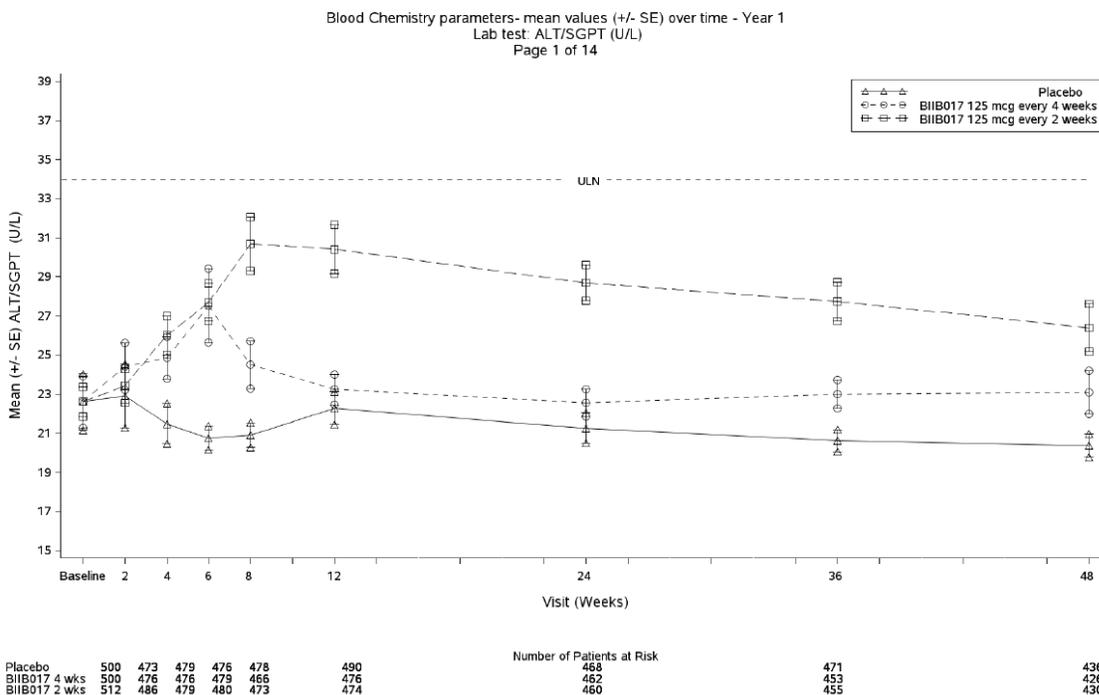
Aminotransferase and Bilirubin Outlier Results, 105MS301, year 1

	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	Total
	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)

From 105MS301 Clinical Study Report, Table 19.

Consistent with the data presented above, Biogen provided graphs of the mean aminotransferases over time. The plot for mean ALT over time demonstrated maximum differences compared to placebo at week 6 (every 4 weeks) and week 8 (every 2 weeks), and that the mean ALT differences compared to placebo persisted during the observation period. I provide that plot below.

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



The plot for mean AST over time (not shown) was similar, although the differences compared to placebo were less than with ALT.

Hepatic Adverse Events

No BIIB017 exposed patients died from liver injury related AEs and no patients underwent liver transplantation.

Concurrent Elevations of ALT/AST \geq 3x ULN and Total Bilirubin $>$ 2xULN

Through the 120 day Safety Update, Biogen reported that 3 BIIB017 treated subjects (437-307, 435-308, and 523-325) in the Phase III trials experienced aminotransferase elevations \geq 3xULN with concurrent total bilirubin $>$ 2x ULN (“Hy’s Law” cases)(120 Day Safety Update, p.66). In cases 435-308 and 523-325, Biogen identified no obvious non-study drug related etiology for the event, although there were factors that complicated interpretation of the cases. In case 437-307, Biogen identified high dose corticosteroid use as a potential confounding factor. I summarize those cases below.

ALT increased, AST increased, Blood Bilirubin increased

Subject 435-308 (BIIB017 every 4 weeks group), a 52-year-old female from Poland with no relevant medical history, was found to have asymptomatic elevation of liver transaminase levels including maximum ALT of 938 (normal range 6-34 U/L), AST of 1151 U/L (normal range 9-34

U/L), and bilirubin of 43 $\mu\text{mol/L}$ (normal range 3-21 $\mu\text{mol/L}$), all considered SAEs, approximately 14 months after the start of the study treatment. The subject had no history of similar events of increased liver enzymes. She had no history of alcohol abuse or herbal medication use. The subject was not hospitalized and remained free of symptoms and signs of liver injury throughout the events. Study treatment was interrupted as a result of the elevated liver transaminase levels. There were no treatments administered for the events. The event was considered resolved 1 month later. Approximately 3 months after interruption of study treatment, AST had decreased to 64 U/L and ALT, GGT, total bilirubin, and alkaline phosphatase were within normal limits. The Investigator assessed the SAEs of increased ALT, AST, and bilirubin levels as related to the study treatment. Of note, at the data cutoff, study treatment remained on hold, although there were no plans to restart treatment. As a result, the clinical database currently classifies this case as a BII017 treatment interruption and not a treatment discontinuation. Test results for Hepatitis E and for autoimmune hepatitis were pending at the time of the 120 Day Safety Update submission.

Acute hepatic failure

Subject 437-307 (BII017 every 4 weeks group), a 25 year-old female (Poland), enrolled in the trial and had no history of hepatitis and denied use of alcohol or recreational drugs. Her screening and baseline aminotransferase and bilirubin tests were normal and her screening tests for HepB and Hep C were negative. Approximately 5 weeks after the start of the study treatment (four doses of trial medication, Year 1) and 4 weeks after receiving a course of high-dose methylprednisolone for treatment of an MS relapse, she had no complaints but was noted to have icterus and significantly elevated liver transaminase and serum bilirubin levels (maximum AST of 998 U/L [ref. range: 9 to 34 U/L], ALT of 810 U/L [ref. range 6 to 34 U/L], and total bilirubin of 24 mg/dL [ref. range up to 1.2 mg/dL]). Her INR was reported as abnormal and the investigator reported she was encephalopathic. She was hospitalized and received fresh frozen plasma, and supportive therapy. Study treatment was discontinued permanently. Test results included a normal ultrasound, a positive HEp-2 test, a cytoplasmic fluorine pattern and no antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA) were detected (+++) and the COMBI test was positive. Acetaminophen was not measured, and biopsy was not mentioned in the reports. The initial diagnosis was autoimmune hepatitis and acute hepatic failure due to interferon. A liver transplant was initially considered but the patient improved. She subsequently recovered and was discharged from the hospital 18 days after onset. Four months after the first event of acute liver failure, she experienced a similar episode of acute liver failure (maximum AST of 1486 U/L, AST of 1038 U/L, total bilirubin of 7.5 mg/dL, INR 1.52) about 1 month after receiving a course of corticosteroids for the treatment of another MS relapse. She recovered and was discharged after approximately 12 days. This case was reviewed by an external hepatology expert who confirmed that the case was associated with corticosteroid use, given the recurrence of hepatic failure with corticosteroid rechallenge. The reports did not indicate that the patient was rechallenged with BII017. The investigator confirmed by phone contact in March 2013 that the subject was alive and well. (Narrative assembled from BLA submission narrative, lab data set, and update safety reports filed to the IND).

In a response to an Information request dated 10/21/13, Biogen provided Dr. (b) (4) comments on this specific case. Dr. (b) (4) wrote the following:

Based on the evidence thus far available, we cannot completely exclude a role for the study drug in the initiation of the hepatic events which appeared in 1/10. There were some changes in ASMA which seem to have been transient. The second episode of hepatitis noted in 6/10 may have been an exacerbation of an underlying process or the result of the readministration of Solumedrol. Overall I do not think it is likely the study drug was involved in the causation of the liver abnormalities noted and surely no recent (sic) to implicate the drug in the second episode. I recommend continued follow up. A liver biopsy would be helpful in determining the extent of injury but unlikely to be of use in establishing the cause. A test for hepatitis E might be useful.

The NIH LiverTox web site² states that corticosteroids can be associated with liver injury. In a discussion of corticosteroids, the Liver Tox website notes, "high doses of intravenous corticosteroids, largely methylprednisolone, have been associated with acute liver injury which can result in acute liver failure and death." The website also notes that "...the hepatic complications of corticosteroids usually represent the worsening or triggering of an underlying liver disease and rarely are the result of drug hepatotoxicity." Based on this information, and the liver injury recurrence following corticosteroid administration, it is unclear whether or not this AE was due to BIIB017.

Subject 523-325 (Placebo in Year 1 and BIIB017 every 4 weeks in Year 2 of 105MS301, BIIB017 every 4 weeks in 105MS302), a 53-year-old female from Serbia, had a baseline BMI of 40.7 kg/m², as well as non-alcoholic liver steatosis, cholelithiasis, and hypertension. She had no history of alcohol use, drug abuse, herbal medicine use, pancreatic problems, recent travel abroad, or contact with individuals who were ill. Concomitant medications included bisoprolol, valsartan/hydrochlorothiazide, and amlodipine. In addition, the subject was receiving dipyrone/fenpiverinium/pitofenone and paracetamol/pheniramine/ascorbic acid until approximately 1 week before the onset of events. The subject was originally treated with placebo during Year 1 of 105MS301. During the placebo-treatment period, the subject was observed to have maximum AST elevations of >5 × ULN and ALT elevations >2 × ULN, which waxed and waned and were assessed by the Investigator as not clinically significant. At that time, serum bilirubin remained within normal limits.

After being treated with BIIB017 every 4 weeks for approximately 13 months (including Year 2 of 105MS301 and approximately 2 months in 105MS302), the subject developed nausea, influenza-like illness, and nasopharyngitis. Treatment included dipyrone/fenpiverinium/pitofenone and paracetamol/pheniramine/ascorbic acid (doses unknown). Approximately 2 weeks later (Day 55 of 105MS302), subsequent laboratory testing demonstrated ALT 1074 U/L [ref. range 6 to 34 U/L] and AST 724 U/L [ref. range 9 to 34 U/L]. Total bilirubin was 21 µmol/L (ref. range 3 to 21 µmol/L) and ALP was 95 U/L (ref. range 35-123 U/L). BIIB017 was discontinued (last dose received on Day 57). On Day 61 (of 105MS302), the subject was hospitalized after reporting persistent nausea, loss of appetite, retching, feeling weak, and having dark-colored urine. Physical examination showed her as being moderately ill but without signs of chronic liver disease. The ALT reached a peak of 1264 U/L, the AST

2 <http://livertox.nlm.nih.gov/Corticosteroids.htm>

reached a peak of 798 U/L, and total bilirubin had increased to 50 µmol/L. No alkaline phosphatase testing was done. Virology tests for hepatitis A, B, and C were negative, and immunology tests for antinuclear antibody (ANA) IgG, antineutrophil cytoplasmic antibody (ANCA) IgG, antimitochondrial antibody (AMA) IgG, anti-parietal cell antibody IgG, anti-smooth muscle antibody (ASMA) IgG, and anti-liver-kidney microsome type 1 antibody (anti-LKM-1 Ab) IgG were negative. An abdominal ultrasound on Day 65 revealed a 20 mm stone in the gallbladder, but the examination was reported as otherwise unremarkable. Four days after hospital admission, ALT and AST levels had decreased (855 U/L and 528 U/L, respectively), and total bilirubin reached a peak of 59.2 µmol/L. Treatment included IV Hepasol, silymarin, and ursodeoxycholic acid. The subject was discharged from the hospital 1 month after admission. Approximately 1 week later, on (b) (6), liver function test levels had significantly decreased: ALT was 46 U/L, AST was 39 U/L, total bilirubin was 12 µmol/L, and GGT was 79 U/L. Approximately 2 months after discharge, the subject was evaluated by the gastroenterologist, whose final diagnosis was transient toxic liver disease. At that time the subject had no new symptoms and was feeling well, and her physical examination was normal.

Biogen recruited a panel of 3 hepatologists, (b) (4), to review and assess the role of BIIB017 in the liver injury AEs for subjects 435-308 and 523-325. In conducting their review, the panel used a structured causality tool by Rockey et al. The panel's consensus was that the events were probably related to BIIB017, but they noted several confounding factors that precluded definitive conclusions about causality. For subject 435-308, the panel noted a prior history of liver test abnormalities, elevation of AST>ALT (more consistent with alcohol induced liver injury), >1 year treatment with BIIB017 prior to liver injury, and missing information about hepatitis E and autoimmune hepatitis test results. For subject 523-325, the panel noted the history of non-alcoholic hepatic steatosis and obesity, >1 year treatment with BIIB017 prior to liver injury, history of cholelithiasis, and incomplete information about hepatitis E and autoimmune hepatitis test results.

Hepatic SAEs, Overall Phase III Trials

Through the 120 day Safety Update, for the overall Phase III experience, 4 subjects experienced hepatic SAEs. One of these events (437-307) was summarized above as a case of AST/ALT≥3xULN and Total Bilirubin >2 x ULN. I summarize the remaining 3 events below.

Subject 496-301 (placebo in Year 1 followed by BIIB017 every 2 weeks in Year 2), was a 39-year old female on warfarin for thrombophlebitis (beginning Day 56). She experienced elevations of liver transaminase > 5x ULN with a maximum ALT of 20 U/L (normal range 6-34 U/L) and AST of 176 U/L (normal range 9-34 U/L), respectively, approximately 4 weeks after warfarin was started. Her liver transaminase levels remained elevated (>1x ULN and <3x ULN) during the remaining 8 months of placebo treatment period. After completing the placebo controlled phase, she started BIIB017 every 2 weeks. On trial day 380, the same day as receiving her third injection of BIIB017, her AST was 344 U/L (ref. range 9 to 34 U/L), ALT 44 U/L (ref. range 6 to 34 U/L), total bilirubin 16µmol/L (ref. range 3-21 µmol/L), GGT 68 U/L (ref. range 4 to 49 U/L), and lactate dehydrogenase (LDH) 305 (ref. range 53 to 234 U/L). This was reported as a nonserious drug-induced liver injury AE (assessed as not related by the

Investigator). No action was taken, and no concomitant medications were given. On Day 394 (2 weeks after her last study treatment injection), the subject was hospitalized for the SAE of drug-induced liver injury. At the reporting of the SAE, AST reached a maximum value of 826 U/L (second event of post baseline ALT and AST >5 xULN) and ALT reached a maximum value of 84 U/L. The bilirubin remained in the normal range with a maximum value of 18 µmol/L. On admission, the subject was in satisfactory condition, pale, with hematomas on the lower legs and right buttock. The abdomen was soft with periumbilical tenderness, with no enlargement of the liver and spleen. The Investigator assessed the SAE as not related to study treatment but as a result of warfarin therapy that had been given as prophylaxis treatment of a previously reported limb venous thrombosis SAE. Study treatment and warfarin were discontinued permanently. The event was considered resolved 3 weeks after the onset with supportive treatment. Below is a table of liver related test results for this patient. (Information summarized from narrative submitted with the BLA and Biogen response to review questions dated 9/9/13).

Date	ALP (Ref. 31-106 U/L)	ALT (Ref. 6-34 U/L)	AST (Ref. 9-34 U/L)	GGT (Ref. 4-49 U/L)	TB (Ref. 3-21 µmol/L)	LDH (Ref. 53-234 U/L)
(b) (6) (Screening)	10	48	20	13	10	171
(b) (6) (Screening)	8	49	30	9	8	
(b) (6) (Day 1)	39	4	17	9	8	153
(b) (6)	41	4	31	11	6	178
(b) (6)	57	20	176	29	10	297
(b) (6)	51	4	31	15	8	175
(b) (6)	63	6	58	17	5	-
(b) (6)	55	13	57	24	9	226
(b) (6)	59	7	41	22	14	226
(b) (6)	52	13	74	25	13	188
(b) (6)	68	44	344	68	16	305
(b) (6)	108	84	826	151	18	356
(b) (6)	-	-	218 ^a	-	High ^b	-
(b) (6)	-	-	79 ^a	-	-	-
(b) (6)	-	-	35 ^a	-	-	-

^a Normal range: 8 to 39 U/L.

^b TB for this date was recorded as 30.2 µmol/L.

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; Ref. = reference range; TB = total bilirubin.

Subject 572-309 (BIIB017 every 2 weeks group), a 36-year-old female from the Ukraine with medical history of ALT and AST elevation and normal ALT and AST at baseline, was hospitalized due to SAEs of elevated ALT and AST 368 days after her first injection of BIIB017 and 17 days after her 26th injection of study treatment. There were no concomitant medications. Three days prior to hospitalization, ALT reached a peak of 392 U/L (ref. range 6 to 34 U/L) and AST reached a peak of 242 U/L (ref. range 9 to 34 U/L). Bilirubin remained in the normal range with a maximum value of 11 $\mu\text{mol/L}$ (ref range of 3 to 21 $\mu\text{mol/L}$). The subject was asymptomatic. Hepatitis tests were negative. Abdominal ultrasound showed no clinically significant findings. The subject had no history of alcohol use. Study treatment was interrupted as a result of the events. Treatment included IV arginine glutamate, oral polyenylphosphatidylcholine, and IM thiotriazoline. ALT and AST gradually decreased. Study treatment was restarted approximately 1 month after the onset of the event, at which time ALT was 58 U/L and AST was 38 U/L. One month after treatment was restarted, ALT and AST were within normal limits (28 U/L and 24 U/L, respectively). The Investigator assessed the SAEs of increased ALT and AST as related to study treatment. The subject continued in the trial.

Subject 523-321 (BIIB017 every 4 weeks group, 105MS302) a 52-year-old female from Serbia with a medical history of hypertension, goiter, and hypothyroidism, experienced toxic hepatitis on Day 21 of 105MS302 after receiving BIIB017 every 4 weeks for 2 years during 105MS301, during which she had experienced events of elevated ALT and AST $>5 \times \text{ULN}$ on Days 673, 679, and 690. The subject had no history of, alcohol or drug abuse, herbal medication use, smoking, gallstones, pancreatic problems, recent intake of alcohol, recent travel abroad, or contact with another individual with illness; she had been treated with methylprednisolone for MS relapse approximately 3 months prior to the onset of the event. On Day 1 of 105MS302, the subject had elevated ALT (466 U/L [ref. range 6 to 34 U/L]), AST (284 U/L [ref. range 9 to 34 U/L]), and lactate dehydrogenase (LDH; 243 U/L [ref. range 53 to 234 U/L]) results; total bilirubin was normal (12 $\mu\text{mol/L}$ [ref. range 3 to 21 $\mu\text{mol/L}$]). By Day 7, ALT reached a peak of 663 U/L, AST reached a peak of 493 U/L, GGT and LDH parameters were increasing, and total bilirubin remained normal (9 $\mu\text{mol/L}$). On Day 11, GGT reached a peak of 129 U/L (ref. range 0 to 38 U/L) and LDH reached a peak of 533 U/L (ref. range 220 to 460 U/L) while ALT and AST values were decreasing. On the same day, the subject was evaluated in an outpatient clinic. Symptoms included mild nausea and belching. There was no fever, chills, jaundice, rash, or abdominal pain. Serology for hepatitis B surface antigen, anti-hepatitis B core antibody, anti-hepatitis C antibody, and anti-hepatitis A immunoglobulin M antibody were negative. The subject was diagnosed with toxic hepatitis and study treatment was discontinued. On Day 18, total bilirubin reached a peak of 23 $\mu\text{mol/L}$, ALT was 403 U/L, and AST was 236 U/L. On Day 24, an abdominal ultrasound showed no clinically relevant findings. Liver function test values continued to decrease over time and returned to normal by Day 58, 57 days after her final dose of study treatment. The event of toxic hepatitis was assessed as moderate and related to study treatment by the Investigator.

In the 120 day Safety Update, Biogen identified 3 subjects, 117-301, 117-302, and 572-309 with SAEs related to liver laboratory test results included under the Investigations SOC (120 day Safety Update, p.91). I included the summary for subject 572-309 above with the cases of $\text{AST/ALT} \geq 3 \times \text{ULN}$ and total bilirubin $>2 \times \text{ULN}$. I summarize the remaining events below.

Subject 117-301 (BIIB017 every 4 weeks group), a 30 year old male with normal transaminases (AST 18 U/L, ALT 14 U/L, LDH (162U/L) and total bilirubin (6.84umol/L) at baseline, and no relevant medical history, developed elevated liver transaminases 582 days after first dose of BIIB017. Concomitant medications were ondansetron, naproxen, ranitidine, and sertraline. 11 days after his 42nd injection of study treatment, he had asymptomatic increases in ALT (84 U/L), AST (333 U/L), and LDH (584U/L, ULN 234U/L) with a total bilirubin of 8.6umol/L (ref. range 3-21umol/L). 2 days later, his ALT was 108U/L, AST was 339 U/L, LDH was 436U/L and total bilirubin was 12 umol/L. Study treatment was discontinued and he received no other treatment. 16 days after his first abnormal result, his liver related tests were normal with ALT 27U/L, AST 20U/L, LDH 164U/L and total bilirubin 8.6umol/L. Test results included ANA titer of 80 (units, ref. range not provided) with speckled pattern, smooth muscle antibody titer 40 (units, ref. range not provided), antineutrophil cytoplasmic antibody negative, mitochondrial antibody screen negative, and liver/kidney microsomal antibody <=20.

Subject 117-302 (BIIB017 every 2 weeks group), a 49-year-old male from the United States with normal liver transaminase levels at baseline and a medical history of bleeding ulcers, was found to have elevated levels of liver transaminases 270 days after beginning treatment with BIIB017. Concomitant medications included eszopiclone and nortriptyline. Approximately 5 days after the subject's 20th injection of BIIB017, he experienced fatigue, nausea, and FLS that were more prolonged than usual. No weight loss or jaundice were noted. Laboratory tests revealed significant transaminitis with ALT 808 (units not provided, ref. range 0 to 55) and AST 598 (units not provided, ref. range 0 to 40). Eight days later, ALT decreased to 173 U/L and AST decreased to 46 U/L. Bilirubin remained in the normal range, with a maximum of 10.26 µmol/L (ref. range of 3.42 to 20.52 µmol/L). CT scan of the liver showed small liver hemangioma. All medications were discontinued. Study treatment was permanently discontinued as a result of the event. Liver transaminase levels returned to normal limits approximately 2.5 months after the onset of the event.

For all Phase III trials, 10 BIIB017 patients discontinued for a hepatic AE. Six BIIB017 patients discontinued during the placebo controlled phase of 105MS301 and 4 additional patients withdrew during the uncontrolled phase (year 2).

In the placebo-controlled BIIB017 experience, 1 placebo subject, 3 BIIB017 every 4 weeks subjects, and 3 BIIB017 every 2 weeks subjects discontinued for hepatic AEs or hepatic enzyme elevations. In the BIIB017 every 4 weeks group, 1 subject (437-307) discontinued due to an SAE of acute hepatic failure that was considered to be related to IV corticosteroid treatment (described above) and 2 subjects (451-301, 483-308) discontinued due to hepatic enzyme elevations (AST/ALT>5xULN) that were not SAEs. In the BIIB017 every 2 weeks group, 1 subject (117-302) discontinued due to an SAE of elevated liver transaminases (described above) and 2 subjects (488-302, 567-308) discontinued study treatment due to hepatic enzyme elevations that were not SAEs (AST/ALT>5xULN) (Summary of Clinical Safety, p.92).

I briefly summarize the hepatic AEs leading to discontinuation in BIIB017 patients that were not summarized above with the SAEs.

Safety Review
Gerard Boehm, MD, MPH
BLA 125499
PLEGRIDY, PEGylated interferon beta-1a

451-301 This 29 year old female experienced elevations in aminotransferases that led to discontinuation. The events began 57 days after her first dose of study medication (last dose was 13 days prior to the event, total of 5 doses received). She had no history of hepatic abnormalities and her only concomitant medication was norgestimate/ethinylestradiol. Her screening aminotransferases, bilirubin and ALP were within normal limits. Her ALT and AST were first elevated on trial week 4. The table below summarizes her hepatic related labs.

Date	ALP (Ref. 31- 106 U/L)	ALT (Ref. 6-34 U/L)	AST (Ref. 9-34 U/L)	GGT (Ref. 4- 49 U/L)	TB (Ref. 3-21 µmol/L)
24 Nov 2010 (Screening)	33	13	17	9	4
16 Dec 2010	30	14	17	9	6
30 Dec 2010	34	19	23	10	6
14 Jan 2011	39	48	39	13	7
28 Jan 2011	43	80	60	16	6
10 Feb 2011	48	466	241	34	9
16 Feb 2011	53	441	263	73	4
02 Mar 2011	50	210	124	82	12
10 Mar 2011	45	210	123	66	9
23 Mar 2011	40	57	38	47	6
14 Apr 2011	31	16	21	22	6
23 Sep 2011 (EWV)	34	34	33	24	7

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; EWV = early withdrawal visit; GGT = gamma-glutamyl transferase; Ref. = reference range; TB = total bilirubin.

Her study treatment was stopped following the 2/10/11 results and was not restarted. She received no other treatment for these events.

483-308 This 39 year old female experienced elevations in aminotransferases and LDH that led to discontinuation. The events began on the day of her first dose of study treatment. She had no history of hepatic abnormalities and her only concomitant medication was dienogest/ethinylestradiol. She did have an elevated ALT (52U/L) at screening. The table below summarizes her liver related laboratory results.

Date	ALP (Ref. 31-106 U/L)	ALT (Ref. 6-34 U/L)	AST (Ref. 9-34 U/L)	GGT (Ref. 4-49 U/L)	TB (Ref. 3-21 µmol/L)	LDH (Ref. 53-234 U/L)
31 Mar 2011	45	52	33	20	10	211
11 May 2011	53	619	387	37	17	376
17 May 2011	60	664	410	55	11	356
25 May 2011	56	398	218	61	21	246
08 Jun 2011	51	144	85	54	22	196
23 Jun 2011	48	82	50	45	14	191
08 Jul 2011	55	44	36	33	8	174

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; Ref. = reference range; TB = total bilirubin.

Safety Review
Gerard Boehm, MD, MPH
BLA 125499
PLEGRIDY, PEGylated interferon beta-1a

Her study treatment was stopped following her first dose and was not restarted. She received no other treatment for these events.

488-302 This 21 year old female experienced elevations in aminotransferases that led to discontinuation. The events began 57 days after her first dose of study treatment (following her 5th dose of study medication). She had no history of hepatic abnormalities and her only concomitant medication was oxymetazoline. The table below summarizes her liver related laboratory results.

Date	ALP (Ref. 31- 106 U/L)	ALT (Ref. 6- 34 U/L)	AST (Ref. 9- 34 U/L)	GGT (Ref. 4-49 U/L)	TB (Ref. 3- 21 µmol/L)
27 Jul 2010 (Screening)	50	11	19	10	5
31 Aug 2010 (Day 1)	62	16	23	9	5
13 Sep 2010	66	17	28	10	7
30 Sep 2010	71	39	38	8	6
11 Oct 2010	66	78	53	10	8
26 Oct 2010	81	261	138	19	6
02 Nov 2010	89	355	197	39	5
16 Nov 2010	77	311	147	50	8
23 Nov 2010	85	390	205	66	9
07 Dec 2010	75	155	95	55	10
21 Dec 2010	65	49	37	35	14
12 Apr 2011 (EWV)	63	37	27	14	6

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; EWV = early withdrawal visit; GGT = gamma-glutamyl transferase; Ref. = reference range; TB = total bilirubin.

Study medication was stopped on 10/26/10 and was not restarted. She received no other treatment for these events.

567-308 This 38 year old male experienced elevations in aminotransferases that led to discontinuation. The events began 15 days after first dose of study treatment. He had no history of hepatic abnormalities, but did have chronic cholecystitis. He was taking no other medications at the time of the event. The table below summarizes liver related laboratory results.

Date	ALP (Ref. 31- 129 U/L)	ALT (Ref. 6-43 U/L)	AST (Ref. 11- 36 U/L)	GGT (Ref. 10- 61 U/L)	TB (Ref. 3-21 µmol/L)
15 Sep 2010 (Screening)	41	45	27	22	6
27 Oct 2010 (Day 1)	49	200	82	26	5
03 Nov 2010	50	215	107	36	6
10 Nov 2010	58	264	126	42	11
24 Nov 2010	58	314	153	46	8

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; GGT = gamma-glutamyl transferase; Ref. = reference range; TB = total bilirubin.

Study medication was stopped after the first dose and was not restarted. He was also treated with phospholipids.

During Year 2 of 105MS301, 4 subjects discontinued due to hepatic disorders or hepatic enzyme elevations. In the placebo to BIIB017 every 2 weeks group, 1 subject (496-301) discontinued due to an SAE of drug-induced liver injury that was considered to be related to warfarin treatment for a previous SAE of venous thrombosis (described above). In the BIIB017 every 4 weeks group, 2 subjects (433-308, 437-323) discontinued study treatment due to hepatic enzyme elevations (ALT>5xULN, AST>=3xULN; AST/ALT>5xULN) that were not SAEs. In the BIIB017 every 2 weeks group 1 subject (320-303) discontinued due to an elevated ALT (AST/ALT>5xULN) (Summary of Clinical Safety, pp.92-93).

I briefly summarize the hepatic AEs leading to discontinuation in BIIB017 patients that were not summarized above with the SAEs.

433-308 This 50 year old female experienced elevations in aminotransferases that led to discontinuation. The events began 294 days after her first dose, on the day she received her 25th dose of study treatment. She had no history of hepatic abnormalities and concomitant medications included latanoprost and alendronate . The table below summarizes liver related laboratory results.

Date	ALP (Ref. 31-106 U/L)	ALT (Ref. 6-34 U/L)	AST (Ref. 9-34 U/L)	GGT (Ref. 4-49 U/L)	TB (Ref. 3-21 µmol/L)	LDH (Ref. 53-234 U/L)
16 May 2011	44	19	19	14	24	173

(Screening)						
02 Jun 2011	43	31	25	12	23	156
16 Jun 2011	45	23	21	15	22	170
30 Jun 2011	46	18	18	13	22	150
13 Jul 2011	48	19	19	15	15	153
25 Aug 2011	47	15	17	11	23	153
17 Nov 2011	45	15	18	15	15	164
21 Mar 2012	51	20	20	17	12	145
02 May 2012	56	278	100	20	20	210
10 May 2012	58	282	91	49	15	181
17 May 2012	62	291	127	55	26	269
24 May 2012	55	209	86	45	21	176
31 May 2012	57	219	82	43	18	169
14 Jun 2012 (EWV)	57	228	90	38	15	211

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; EWV = early withdrawal visit; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; Ref. = reference range; TB = total bilirubin.

Study treatment was stopped on 5/2/12 and not restarted. She received no other treatment for the event.

320-303 This 41 year old female experienced elevations in aminotransferases that led to discontinuation. The events began 338 days after her first dose, following her 25th dose of study treatment. She had no history of hepatic abnormalities and was taking no other medications at the time of the event. The table below summarizes liver related laboratory results.

Date	ALP (Ref. 31- 106 U/L)	ALT (Ref. 6- 34 U/L)	AST (Ref. 9- 34 U/L)	GGT (Ref. 4- 49 U/L)	TB (Ref. 3-21 µmol/L)
20 Jun 2011 (Screening)	56	14	21	10	7
27 Jul 2011	58	12	23	11	9
10 Aug 2011	63	16	22	11	7
24 Aug 2011	55	20	25	10	9
08 Sep 2011	61	20	22	11	10
22 Sep 2011	55	19	21	11	10
19 Oct 2011	61	15	19	12	9
11 Jan 2012	62	17	23	10	7
04 Apr 2012	76	59	38	15	8
28 Jun 2012	117	452	285	86	13
26 Jul 2012 (EWV)	100	163	132	71	13

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; EWV = early withdrawal visit; GGT = gamma-glutamyl transferase; Ref. = reference range; TB = total bilirubin.

Study medication was stopped on 6/28/12 and not restarted. She received no other treatment for the event.

437-323 This 46 year old female experienced elevations in aminotransferases that led to discontinuation. The events began 365 days after her first dose, following her 27th dose of study treatment. She had no history of hepatic abnormalities and was taking paracetamol at the time of the event. The table below summarizes liver related laboratory results.

Date	ALP (Ref. 31-106 U/L)	ALT (Ref. 6-34 U/L)	AST (Ref. 9-34 U/L)	GGT (Ref. 4-49 U/L)	TB (Ref. 3-21 µmol/L)
16 Dec 2009 (Screening)	54	17	31	24	9
20 Jan 2012 (Day 1)	54	18	27	21	8
17 Mar 2010	51	19	29	22	11
07 Jul 2010	48	26	33	27	8
29 Sep 2010	59	26	36	31	8
22 Dec 2010	60	70	79	41	6
05 Jan 2011	76	169	152	97	9
19 Jan 2011	92	500	568	171	12
24 Jan 2011	133	860	1185	420	7
02 Feb 2011	141	501	469	477	13
16 Feb 2011	86	262	230	329	16
02 Mar 2011	78	170	222	242	4
16 Mar 2011	59	101	115	141	14
30 Mar 2011	58	60	88	102	7
06 Apr 2011 (EWV)	57	44	56	84	8

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; EWV = early withdrawal visit; GGT = gamma-glutamyl transferase; Ref. = reference range; TB = total bilirubin.

Study treatment was stopped on 1/19/11 and not restarted. She received no other treatment for the event.

Hepatic related AEs, Overall Phase III

In the overall Phase III experience, 23 BIIB017 patients experienced 25 AEs subsumed under the Hepatobiliary disorders SOC. The hepatobiliary AEs were hepatic pain n=6, cholelithiasis n=4, hyperbilirubinemia n=4, hepatitis toxic n=2, acute hepatic failure, bile duct stone, biliary colic, biliary dyskinesia, cholecystitis acute, cholecystitis chronic, drug induced liver injury, gall bladder disorder and hepatic steatosis (120 Day Safety Update Table 26). In addition, the Investigations SOC included hepatic lab test abnormalities that investigators reported as AEs. I summarize those AEs below.

Hepatic lab test abnormalities listed under the Investigations SOC, Overall Phase III trials

	BIIB017		
	Every 4 weeks	Every 2 weeks	Total
AE	N=728	N=740	N=1468
ALT increased	6% (41)	8% (56)	7% (97)
AST increased	4% (28)	5% (39)	5% (67)
GGT increased	4% (27)	5% (38)	4% (65)

Hepatic enzyme increased	<1% (4)	<1% (7)	<1% (11)
Blood alkaline phosphatase increased	<1% (5)	<1% (4)	<1% (9)
Blood bilirubin increased	<1% (7)	<1% (2)	<1% (9)
Transaminase increased	<1% (2)	<1% (4)	<1% (6)
Liver function test abnormal	<1% (1)	<1% (4)	<1% (5)

From 120 Day Safety Update, Table 26

Hepatic related AEs, Placebo controlled Phase 105MS301

During the placebo controlled phase of trial 105MS301, 2 placebo patients and 8 BIIB017 patients (every 4 weeks, n=4; every 2 weeks n=4) experienced hepatic AEs (105MS301 Clinical Study report, Table 59). Both placebo hepatic AEs were hepatic pain. The BIIB017 every 4 weeks hepatic AEs were hepatic pain (n=2), hyperbilirubinemia, and acute hepatic failure. The BIIB017 hepatic AEs were hepatic pain (n=2) and hyperbilirubinemia (n=2). In addition, the Investigations SOC included hepatic lab test abnormalities that investigators reported as AEs. I summarize those AEs below.

Hepatic lab test abnormalities listed under the Investigations SOC, 105MS301, year 1

	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	Total
AE	N=500	N=500	N=512	N=1012
ALT increased	3% (13)	7% (33)	6% (31)	6% (64)
AST increased	2% (8)	4% (19)	6% (29)	5% (48)
GGT increased	1% (7)	3% (14)	4% (18)	3% (31)
Hepatic enzyme increased	<1% (2)	0	<1% (4)	<1% (4)
Alkaline phosphatase increased	<1% (3)	<1% (2)	<1% (1)	<1% (3)
Transaminase increased	<1% (2)	0	<1% (3)	<1% (3)
Liver function test abnormal	0	0	<1% (2)	<1% (2)

From 105MS301 Clinical Study Report, Table 193

Phase I trials

There were no hepatic SAEs and no hepatic enzyme elevations that were SAEs in the Phase I trials. One subject from a phase I trial discontinued for AST elevation (105HV103 Subject 102-408). I provide information about that subject below.

Subject 102-408 was a 27-year-old female with no reported history of liver abnormalities. She was taking naproxen (at the time of injection, and at 12 and 24 hours after injection). She was randomized to PFS/autoinjector arm and received peginterferon beta-1a 125 mcg SC by PFS on Day 1. Her baseline and Day 2 AST levels were normal at 14 and 11 U/L, respectively. She experienced an AE of AST increased on Day 8 (156 U/L; reference range: 0 to 50 U/L) that resolved on Day 14. AST levels returned to normal (16 U/L) at the next assessment (Day 29).

ALT was within the reference range throughout the trial. No treatment was provided for the event. Study treatment was discontinued.

Hepatic Injury with approved beta interferons

In the pivotal Phase 3 placebo-controlled clinical studies with Avonex Hepatic AEs were reported for <1% placebo patients compared to 0 Avonex patients. Corresponding data are not available for Rebif.

In Avonex placebo-controlled Phase 3 studies, the incidences of elevations of transaminases >ULN was 19% and 29% in the placebo and Avonex treatment groups, respectively, for ALT; and 10% and 11% on placebo and Avonex groups, respectively, for AST. The incidence of elevations of liver transaminases >5 × ULN was balanced between Avonex and placebo groups (2% on placebo and 1% on Avonex for ALT; and <1% in both placebo- and Avonex-treated groups for AST).

Biogen cited a paper by Francis that included aminotransferase result information for Rebif. In a systematic review of pooled data from 6 controlled clinical studies which included 2,819 subjects followed for up to 12 months, the incidence of any elevation of AST or ALT (>ULN) was 19% in placebo-treated subjects and 47% and 64% in those who received Rebif 22 µg and 44 µg, respectively [Francis 2003]. Incidence of elevations of AST or ALT >5x ULN was 1.3% in the Rebif 22 µg group and 2.8% in the Rebif 44 µg group.

Within Phase 3 clinical studies, 1/351 Avonex-treated subjects experienced concurrent elevations of ALT and AST >3 × ULN and bilirubin >1.5 × ULN. In a separate trial comparing Avonex to daclizumab, Biogen reported that 1/920 Avonex subjects experienced ALT and AST >3 × ULN and bilirubin >1.5 × ULN. In clinical trials, 1 of 1658 Rebif-treated subjects (22 µg 3 times weekly group) experienced concurrent elevations of total bilirubin >3 × ULN and ALT >2.5 × ULN [Francis 2003].

Autoimmune disorders

Reviewer Summary

Biogen identified a limited number of autoimmune disorder adverse events in the Phase III trials. BIIB017 did not appear to be associated with an increased risk of autoimmune disorder adverse events compared to placebo in year 1 of trial 105MS301. Given the limited size of the BLA database, the apparent lack of an increased risk during the placebo controlled phase of 105MS301 does not overturn the current understanding regarding the risk of autoimmune disorder AEs observed with beta interferons.

Methods

Biogen summarized select autoimmune disorder AEs preferred terms and HLTs from the BIIB017 clinical trials.

Results

In the overall Phase III BIIB017 experience, 9 (<1%, 9/1468) subjects had AEs identified by Biogen's search criteria. The events reported for these patients were autoimmune thyroiditis (n=6), rheumatoid arthritis (n=2) and Basedow's disease. None of these events led to discontinuation. The Basedow's disease AE was the only autoimmune AE that was classified as an SAE. I summarize that event below.

Subject 457-307 (placebo Year 1, and BIIB017 every 4 weeks group in Year 2), a 49-year-old female, had been diagnosed with hyperthyroidism (assessed as mild and not related to study treatment) during Year 1, which resolved, and the subject completed treatment Year 1. In Year 2, on Day 25, the subject was admitted to the hospital for further evaluation of hyperthyroidism, and diagnostic tests revealed a high concentration of free thyroid hormones (triiodothyronine [T3] at 16.58 pmol/L [ref. range 3.10 to 6.80 pmol/L] and thyroxine [T4] at 43.39 pmol/L [ref. range 12.00 to 22.00 pmol/L]) and increased human thyroid receptor antibody level. The subject was subsequently diagnosed with Basedow's disease that was assessed as moderate and not related to study treatment by the Investigator. Study treatment was interrupted, and the SAE was resolved 12 days after onset following treatment with methimazole and oral lithium carbonate. Prior to discharge, the subject's free thyroid hormone levels decreased (T3 at 10.83 pmol/L and T4 at 32.90 pmol/L), and then decreased significantly lower (T3 at 7.43 pmol/L and T4 at 22.98 pmol/L). The subject continued study treatment.

During the placebo controlled phase of 105MS301, 3 placebo subjects (<1%, 3/500) and 1 BIIB017 subject (<1%, 1/1012) experienced autoimmune AEs. The autoimmune AE in the BIIB017 patient was autoimmune thyroiditis. The placebo subjects experienced autoimmune thyroiditis (n=2) and rheumatoid arthritis. None of these events were SAEs and none led to discontinuation.

Hypersensitivity/Allergic reactions

Reviewer Summary

Biogen identified a limited number of hypersensitivity adverse events in the Phase III trials, including three unexplained SAEs (angioedema n=2, urticaria n=1). BIIB017 did not appear to be associated with an increased risk of hypersensitivity adverse events compared to placebo in year 1 of trial 105MS301. Given the limited size of the BLA database, the apparent lack of an increased risk during the placebo controlled phase of 105MS301 does not overturn the current understanding regarding the risk of allergic reactions/hypersensitivity disorder AEs observed with beta interferons. Risk for hypersensitivity AEs did not appear to be related to development of BIIB017 or PEG antibodies.

Methods

Biogen searched for select hypersensitivity AE preferred terms and HLTs. Biogen provided a list of the searched terms in their Statistical Analysis Plan. Many of the included terms are suggestive of, but not specific for, hypersensitivity.

Results

In the overall Phase III trial experience, through the 120 Day Safety Update cutoff, 16% of BIIB017 every 4 weeks patients had one or more hypersensitivity AEs compared to 19% of every 2 weeks patients (120 Day Safety Update, p.71). The following table identifies the reported hypersensitivity AEs that occurred in at least 2 BIIB017 patients.

Hypersensitivity AEs reported by at least 2 BIIB017 patients in Phase III Trials

	BIIB017		
	Every 4 weeks	Every 2 weeks	Total
AE	N=728	N=740	N=1468
Cough	6% (46)	5% (36)	6% (82)
Pruritus	3% (20)	4% (27)	3% (47)
Rash	2% (12)	2% (14)	2% (26)
Erythema	<1% (7)	2% (17)	1% (24)
Edema peripheral	2% (16)	<1% (6)	1% (22)
Urticaria	1% (8)	2% (13)	1% (21)
Dyspnea	<1% (7)	2% (12)	1% (19)
Dermatitis allergic	<1% (6)	<1% (5)	<1% (11)
Pruritus generalized	<1% (5)	<1% (6)	<1% (11)
Hypotension	<1% (2)	<1% (5)	<1% (7)
Drug hypersensitivity	<1% (2)	<1% (4)	<1% (6)
Sneezing	<1% (4)	<1% (1)	<1% (5)
Face edema	0	<1% (4)	<1% (4)
Flushing	<1% (1)	<1% (3)	<1% (4)
Angioedema	<1% (1)	<1% (2)	<1% (3)
Asthma	<1% (1)	<1% (2)	<1% (3)
Blood pressure decreased	0	<1% (3)	<1% (3)
Chest discomfort	<1% (1)	<1% (2)	<1% (3)
Conjunctivitis allergic	<1% (1)	<1% (2)	<1% (3)
Eye pruritus	<1% (2)	<1% (1)	<1% (3)
Injection site urticaria	<1% (1)	<1% (2)	<1% (3)
Ocular hyperemia	<1% (2)	<1% (1)	<1% (3)
Injection site hypersensitivity	<1% (1)	<1% (2)	<1% (3)
Rash generalized	<1% (2)	<1% (1)	<1% (3)
Edema	0	<1% (2)	<1% (2)
Eyelid edema	0	<1% (2)	<1% (2)
Swelling face	<1% (1)	<1% (1)	<1% (2)

The following events were reported by 1 BIIB017 subject each: anaphylactic reaction, auricular swelling, bronchospasm, cyanosis, dermatitis atopic, eye swelling, generalized edema, hypersensitivity, localized edema, pharyngeal edema, rash pruritic, shock, swelling, wheezing
From 120 Day Safety Update Table 78

Seven of the above events were SAEs. Four of these had likely identified etiologies other than the trial medication, or did not appear to represent hypersensitivity. Subject 437-353, who had a history of asthma, had an asthma exacerbation that was treated and she continued in the trial without experiencing another similar event. Subject 623-

302 experienced chest tightness and difficulty breathing, which was diagnosed as an anaphylactic reaction, approximately 30 minutes after receiving IV gadolinium contrast agent, while undergoing an MRI scan. Subject 378-303 experienced right leg pruritus on trial day 269 and which did not recur. Subject 614-303 experienced hypotension/shock that was related to sepsis. I summarize the remaining 3 events below.

Subject 572-306 (BIIB017 every 2 weeks group), a 22-year-old male, with no relevant medical history completed the first year of BIIB017 every 2 week treatment, and on Day 86 of Year 2, three minutes after study treatment injection, the subject experienced angioedema on the neck area accompanied by dyspnea, pyrexia, and general weakness. No laboratory or diagnostic tests were performed. Treatment included diphenhydramine. The angioedema was considered resolved on the same day. Study treatment was discontinued, and the subject withdrew from the trial due to angioedema.

Subject 311-302 (placebo Year 1 to BIIB017 every 2 weeks Year 2), a 36-year-old female, completed Year 1 treatment with placebo and during Year 2 treatment reported the SAE of angioedema, 214 days after starting study treatment. Several hours after the last injection of study treatment, the subject presented to the emergency department with headache, high temperature, vomiting, dyspnea, and facial rash. She was hospitalized with diagnosis of angioneurotic edema. Study treatment was permanently discontinued, and the subject was withdrawn from the trial. Treatment included acetaminophen, antihistamines, and acetylsalicylic acid.

Subject 445-338 (placebo Year 1 to BIIB017 every 2 weeks Year 2), a 41-year-old female with no relevant medical history, completed Year 1 treatment with placebo, and in Year 2, 35 days after starting treatment with BIIB017 every 2 weeks, experienced generalized urticaria presenting with eruption of erythematous and purpuric lesions over the entire body. Study treatment was discontinued, and she withdrew from the trial. Treatment included IV dexamethasone, oral clemastin, oral cetirizine, oral calcium dobesilate, oral antihistamines and topical steroid. Following treatment, the appearance of new lesions was halted and existing lesions subsided, and the subject was discharged in good general condition.

In the overall BIIB017 Phase III experience, 8 patients discontinued for hypersensitivity AEs. The hypersensitivity AEs leading to discontinuation were angioedema (n=2), dermatitis allergic (n=2), urticaria (n=2), anaphylactic reaction, edema peripheral, and erythema (120 Day Safety Update Table 80).

In the placebo controlled phase of 105MS301, 14% (71/500) of placebo patients had a hypersensitivity AE compared to 13% (67/500) of BIIB017 every 4 weeks patients and 16% (82/512) of every 2 weeks patients. In the following table I identify the hypersensitivity AEs that occurred in at least 1% of BIIB017 patients and were more common compared to placebo.

Hypersensitivity AEs reported by at least 1% BIIB017 patients and more frequently than placebo 105MS301, year 1

	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	Total
AE	N=500	N=500	N=512	N=1012
Pruritus	1% (6)	2% (12)	4% (19)	3% (31)
Erythema	<1% (1)	<1% (4)	2% (8)	1% (12)
Rash	<1% (1)	1% (6)	1% (6)	1% (12)

105MS301 Clinical Study Report, Table 326

In the placebo controlled trials, there were 3 hypersensitivity SAEs in BIIB017 patients (<1%, 3/1012) compared to none in placebo patients. The 3 hypersensitivity SAEs (discussed above) were asthma, anaphylaxis following gadolinium, and pruritus of the right leg. These events had other, non-study drug etiologies or did not represent hypersensitivity.

In the placebo controlled trials, 3 BIIB017 every 4 weeks patients (<1%, 3/500) (dermatitis allergic, urticaria, edema peripheral) and 1 every 2 weeks patient (<1%/1/512) (anaphylactic reaction) discontinued for hypersensitivity AEs, compared to no placebo patients (0/500) (Summary of Clinical Safety Appendix Table 67).

Biogen also examined if presence of antibodies to BIIB017 or PEG was related to hypersensitivity AE risk and did not find evidence of an association. There were too few BIIB017 patients who developed NABs to assess the relationship to hypersensitivity AEs. Biogen found that 18% and 22% in the BIIB017 every 4 and every 2 weeks groups had hypersensitivity AEs and BAbs at any time during the trial compared with 14% and 16% in the BIIB017 every 4 and every 2 weeks groups, respectively, who never tested positive for BAbs. Similarly Biogen found that 12% and 13% in the BIIB017 every 4 and every 2 weeks groups had hypersensitivity AEs and anti-PEG Abs at any time point during the trial compared with 15% and 17% in the BIIB017 every 4 and every 2 weeks groups, respectively, who never tested positive for anti-PEG Abs.

Malignancies

Biogen's identified 6 BIIB017 patients (6/1468) with malignant neoplasms. The identified malignancies were breast cancer (n=2), basal cell carcinoma, cervical cancer, lip/oral cavity cancer, and thyroid neoplasm (120 Day Safety Update, Table 83). There were too few malignancies in these clinical trials to allow for meaningful comparisons of malignancy rates to background rates.

Seizures

Reviewer Summary

Biogen identified a limited number of seizure related adverse events in the BIIB017 safety database. There was a slight increase in the number of seizure AEs in the

BIIB017 every 2 weeks group compared to the every 4 weeks group and the placebo group in year 1 of trial 105MS301, but the number of events was too small to draw conclusions about the relationship of seizures and exposure. Given the current understanding of seizure risk and beta interferon use, Biogen's proposal for BIIB017 labeling for seizure risk seems appropriate.

Methods

Using the SMQ for convulsions, Biogen examined the risk of seizures with BIIB017.

Results

In the overall Phase III trials experience, through the 120 Day Safety Update cutoff, <1% (11/1468) of BIIB017 patients experienced a seizure (120 Day Safety Update, p.75). Five subjects who experienced seizures were in the BIIB017 every 4 weeks group and 6 subjects were in the every 2 weeks group. Six of these events were SAEs. No seizures led to discontinuation.

During the placebo controlled phase of 105MS301, 1 placebo subject (1/500), 1 BIIB017 every 4 weeks subject (1/500) and 3 every 2 weeks subjects (3/512) experienced a seizure. All five patients had histories of seizure disorders. Two seizure AEs (both in the every 2 weeks group) were SAEs. None of these seizures led to discontinuation.

Depression and Suicide

Reviewer Summary

Biogen did not find strong evidence of an increased risk of depression or suicide in their analyses of AE data or BDI-II results from year 1 of trial 105MS301. Given the limited size of the BLA database, the absence of an increased risk is not surprising and does not diminish concerns regarding the risk of depression with beta interferons.

Methods

Biogen explored the relationship between BIIB017 and depression and suicide in 2 ways. They analyzed the risk for events included under the depression and suicide/self-injury SMQ. In addition, they analyzed data from the Beck Depression Inventory-II (BDI-II) questionnaire that was administered during clinical trials. The BDI-II is a 21-item patient-reported outcome instrument that is used to assess the severity of depressive symptoms along two dimensions: cognitive affective and somatic. The global BDI score ranges from 0-63, with higher scores indicating greater depression severity. I summarize the results of Biogen's analyses below.

Results

In the BIIB017 Phase III trials, there were no completed suicides and no AEs coded to the preferred term suicide attempt. In the overall BIIB017 experience, the incidence of depression or suicide related AEs was 11% (78/728) and 10% (74/740) in the BIIB017 every 4 and every 2 weeks groups, respectively (120 Day Safety Update, Table 93).

The following table summarizes the Depression and Suicide related AEs reported by more than one BIIB017 subject.

Depression and Suicide related AEs reported by at least 2 BIIB017 patients in Phase III Trials

	BIIB017		
	Every 4 weeks	Every 2 weeks	Total
AE	N=728	N=740	N=1468
Depression	7% (50)	7% (49)	7% (99)
Depressed mood	3% (21)	1% (11)	2% (32)
Mood altered	<1% (7)	1% (8)	1% (15)
Affect lability	<1% (2)	<1% (6)	<1% (8)
Suicidal ideation	<1% (2)	<1% (2)	<1% (4)
Initial insomnia	0	<1% (2)	<1% (2)
Major depression	0	<1% (2)	<1% (2)
Mood swings	<1% (1)	<1% (1)	<1% (2)
Memory impairment	<1% (5)	<1% (5)	<1% (10)
Disturbance in attention	<1% (2)	0	<1% (2)

The Depression and Suicide related AEs reported by 1 subject were apathy, dysphoria, dyssomnia, emotional distress, feeling of despair, and crying
From 120 Day Safety Update Table 93

Serious depression or suicide AEs occurred in 1 subject (<1%) in the BIIB017 every 4 weeks group (suicidal ideation) and in 2 subjects (<1%) in the every 2 weeks group (depression, n=2). Four subjects in the BIIB017 every 4 weeks group discontinued for a Depression and Suicide related AE compared to 3 patients in the every 2 weeks group. The AEs leading to discontinuation were suicidal ideation (n=4), and depression (n=4) (120 Day Safety Update, Table 95).

Depression and suicide related AEs appeared balanced among treatment groups in the placebo controlled phase of 105MS301. The following table summarizes Depression and Suicide related AEs.

Depression and Suicide related AEs 105MS301, year 1

	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	Total
AE	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

105MS301 Clinical Study Report, Table 64

In the placebo-controlled BIIB017 experience, Depression and Suicide SAEs were reported for 1 subject in each of the treatment groups. Below I summarize details for the BIIB017 patients with a Depression or Suicide related SAE.

Subject 563-312, (BIIB017 every 4 weeks group) a 46-year-old female, with no history of depression or suicidal thoughts or attempts, had SAEs of irritability and suicidal ideation on Day 100, after receiving 8 injections of study treatment. Her symptoms included inability to sleep and irritability. Following a sleepless night, the subject had thoughts of wanting to shoot herself. Prior to starting the study treatment, the subject had only experienced shorter, less evident irritation during the night. The subject attributed her recent events to her concerns about her husband's heart disease. There were no treatments provided for the events. Study treatment was permanently discontinued. The events were considered resolved on the same day.

Subject 448-308 (BIIB017 every 2 weeks group), a 48-year-old female with a history of anxiety, depressive syndrome, coronary artery disease, hypertension, diabetes type 2, and fibromyalgia, was hospitalized on Day 71 due to the SAE of depression, 15 days after receiving her fifth and last injection of study treatment. Her symptoms on admission included weakness of the left arm and leg, severe pain and cramp in the left leg, and speech disorders. A psychological examination found evidence of secondary decrease in cognitive functions, mainly related to visuospatial organization. The subject was diagnosed with a depressive disorder requiring further treatment. Study treatment was permanently discontinued on the same day. Treatment included an antidepressant, and the event was considered resolved 7 days after the onset.

In the placebo controlled phase of 105MS301, 2 placebo subjects discontinued for a Depression and Suicide AE compared to 4 BIIB017 every 4 weeks subjects and 2 BIIB017 every 2 weeks subjects. The Depression and Suicide AEs leading to discontinuation of BIIB017 subjects were suicidal ideation (n=4), and depression (n=3). The placebo subjects discontinued for suicidal ideation (n=1) and major depression (n=1) (Summary of Clinical Safety Appendix Table 77).

BDI-II scores

In the placebo-controlled BIIB017 experience, the mean BDI-II scores and changes from baseline were similar across treatment groups. I summarize those data in the following table.

Mean BDI-II scores and changes from baseline during 105MS301, year 1

	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
Mean BDI-II Scores	N=500	N=500	N=512

Baseline	10.7	10.0	10.3
Week 12	10.0	9.4	9.7
Change from baseline at week 12	-0.7	-0.6	-0.3
Week 24	10.1	9.6	9.4
Change from baseline at week 12	-0.5	-0.1	-0.6
Week 48	10.2	9.2	9.4
Change from baseline at week 48	-0.6	-0.5	-0.5

From 105MS301 Clinical Study Report, Table 332

Biogen also examined the incidence of depression, suicidal tendency, and suicide attempt according to BDI-II (score >18). In the placebo-controlled BIIB017 experience the incidence of a BDI-II score >18 was similar across treatment groups (31% placebo versus 28% and 27% in the BIIB017 every 4 and every 2 weeks groups, respectively) and remained unchanged or stable over time (105MS301 Clinical Study Report, Table 324).

7.3.5 Submission Specific Primary Safety Concerns

N/A

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overall Phase III trials

In the Phase III BIIB017 trials, 95% (1393/1468) of treated subjects experienced one or more AEs. When viewed by dosing regimen, there appeared to be little difference in AE risk with 95% (690/728) of every 4 weeks patients experiencing AEs compared to 95% (703/740) of every 2 weeks patients. In the following table, I list the AEs that occurred in at least 5% of BIIB017 patients.

Common AEs (>=5%), Overall Phase III trials

	BIIB017		
	Every 4 weeks	Every 2 weeks	Total
	N=728	N=740	N=1468
Any AE	95% (690)	95% (703)	95% (1393)
Injection site erythema	60% (435)	64% (471)	62% (906)
Influenza like illness	52% (378)	53% (390)	52% (768)
Pyrexia	42% (305)	44% (325)	43% (630)
Headache	41% (298)	42% (313)	42% (611)

Multiple Sclerosis relapse	32% (236)	26% (196)	29% (432)
Myalgia	19% (140)	19% (143)	19% (283)
Chills	17% (127)	17% (129)	17% (256)
Injection site pain	16% (114)	18% (131)	17% (245)
Nasopharyngitis	16% (117)	14% (102)	15% (219)
Asthenia	16% (113)	13% (95)	14% (208)
Injection site pruritus	12% (85)	15% (109)	13% (194)
Back pain	12% (90)	13% (94)	13% (184)
Arthralgia	13% (93)	12% (88)	12% (181)
Fatigue	11% (80)	14% (100)	12% (180)
Pain in extremity	11% (79)	10% (77)	11% (156)
Nausea	9% (67)	10% (77)	10% (144)
Urinary tract infection	9% (68)	9% (68)	9% (136)
Vertigo	8% (57)	6% (48)	7% (105)
Upper respiratory tract infection	6% (43)	8% (57)	7% (100)
Depression	7% (50)	7% (49)	7% (99)
ALT increased	6% (41)	8% (56)	7% (97)
Body temperature increased	6% (45)	7% (51)	7% (96)
Oropharyngeal pain	6% (43)	7% (53)	7% (96)
Vomiting	7% (51)	6% (44)	6% (95)
Muscular weakness	6% (46)	6% (48)	6% (94)
Parasthesia	6% (44)	5% (39)	6% (81)
Dizziness	5% (40)	7% (51)	6% (91)
Hypoesthesia	7% (52)	5% (38)	6% (90)
Pain	6% (44)	6% (41)	6% (85)
Insomnia	6% (41)	6% (42)	6% (83)
Cough	6% (46)	5% (36)	6% (82)
ALT increased	4% (28)	5% (39)	5% (67)
Diarrhea	6% (41)	4% (26)	5% (67)
GGT increased	4% (27)	5% (38)	4% (65)
Hyperthermia	5% (35)	4% (27)	4% (62)
Pharyngitis	5% (35)	4% (26)	4% (61)

From 120 Day Safety Update, Table 27

In the placebo controlled phase of 105MS301, BIIB017 treated patients more frequently reported AEs (94%, 953/1012) compared to placebo patients (83%, 417/500). In the following table, I list the AEs reported by at least 2% of BIIB017 patients (any dosing group) and that were reported twice as frequently compared to placebo.

AEs reported by at least 2% of BIIB017 patients (any dosing group) and that were reported twice as frequently compared to placebo during 105MS301, year 1

AE	Placebo	BIIB017		
		Every 4 weeks	Every 2 weeks	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)
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)

105MS301 Clinical Study Report, Table 195

7.4.2 Laboratory Findings

Hematology

As with the approved interferon B treatments, BIIB017 causes decreases in white blood cells (neutrophils and lymphocytes), red blood cells, and platelets.

WBCs

BIIB017 led to declines in mean WBC from baseline that appeared dosing related. Declines in mean WBC were observed in week 4 of the trial and continued through the end of the first year of treatment. In the following table I provide the declines in mean WBC by treatment and trial week.

Mean WBC change from baseline by treatment and trial week during trial 105MS301, year 1

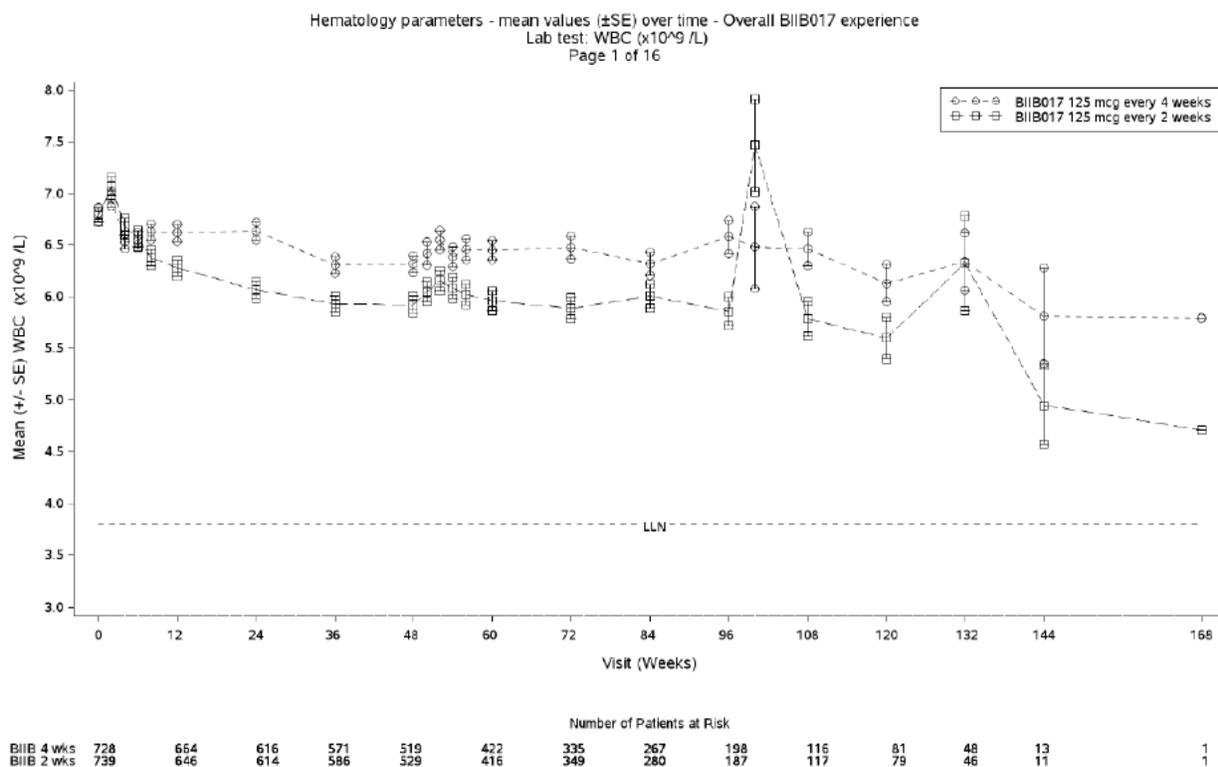
Trial Week	Mean change from baseline in WBC		
	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
Week 2	0.279	0.184	0.319
Week 4	0.228	-0.243	-0.109
Week 6	0.163	-0.279	-0.126
Week 8	0.093	-0.203	-0.411
Week 12	0.334	-0.122	-0.435
Week 24	0.214	-0.168	-0.580
Week 36	0.179	-0.484	-0.750
Week 48	0.140	-0.386	-0.775

From 105MS301 Study Report, Table 332

At week 48, the observed WBC decline in the every 4 weeks group represented a 3% decrease from baseline and in the every 2 weeks group represented a 10% decrease from baseline (Summary of Clinical Safety, p.112).

Biogen provided a graph of mean WBC counts for the overall BIIB017 experience. This graph suggests that there was little additional decline in WBC counts after the first year of treatment.

Figure 6: Hematology Parameters – Mean Values (+/- SE) Over Time – Overall BIIB017 Experience



The observed declines in mean WBC counts were associated with increased risk for potentially clinically significant (PCS) low WBC counts ($<3.0 \times 10^9$ /L) among BIIB017 treated patients. In the placebo controlled phase of 105MS301, 1% (5/500) of placebo patients had a PCS low WBC count compared to 4% (21/500) in the BIIB017 every 4 weeks group and 7% (34/512) in the every 2 weeks group (Summary of Clinical Safety, p.112).

The decline in WBC with BIIB017 was due to declines in both lymphocytes and neutrophils. In the following table, I summarize the mean changes from baseline for lymphocytes and neutrophils by treatment during the placebo controlled phase of 105MS301.

Lymphocyte and neutrophil mean changes from baseline by trial week and treatment during 105MS301, year 1

Trial Week	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
Mean change from baseline, lymphocytes ($\times 10^9$ /L)			
Week 2	0.148	0.106	0.148
Week 4	0.063	0.013	0.031
Week 6	0.135	0.038	0.044
Week 8	0.059	-0.067	-0.064

Week 12	0.080	-0.039	-0.062
Week 24	0.078	-0.057	-0.148
Week 36	0.088	-0.095	-0.158
Week 48	0.046	-0.100	-0.209
	Mean change from baseline, neutrophils ($\times 10^9/L$)		
Week 2	0.099	0.030	0.128
Week 4	0.146	-0.263	-0.165
Week 6	0.006	-0.342	-0.195
Week 8	0.024	-0.148	-0.337
Week 12	0.229	-0.092	-0.378
Week 24	0.106	-0.124	-0.420
Week 36	0.073	-0.372	-0.573
Week 48	0.080	-0.254	-0.536

From 105MS301 Study Report, Table 332

The mean changes for monocytes, basophils, and eosinophils were small and not meaningfully different across treatment groups (data not shown).

The graphs of mean lymphocyte and neutrophil counts for the overall BIIB017 experience (not shown) were similar to the graph of mean WBC counts provided above. These graphs suggest that there was little additional decline in lymphocyte or neutrophil counts after the first year of treatment. There were fewer than 100 patients in each treatment arm after week 108, limiting the ability to assess these parameters for longer periods of time.

As with WBC counts, BIIB017 treated patients had higher risks for potentially clinically significant low lymphocyte and neutrophil counts in the placebo controlled phase of 105MS301. In the table below, I provide the risks for low PCS results for lymphocytes and neutrophils.

PCS low results for lymphocytes and neutrophils during 105MS301, year 1

	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
	N=500	N=500	N=512
PCS low lymphocyte criteria			
< $0.8 \times 10^9/L$	3% (17)	4% (20)	5% (27)
< $0.5 \times 10^9/L$	0	<1% (1)	<1% (2)
PCS low neutrophil criteria			
< $1.5 \times 10^9/L$	3% (15)	5% (24)	9% (44)
$\leq 1.0 \times 10^9/L$	<1% (2)	1% (5)	1% (5)

From Summary of Clinical Safety, pp.112-113

No subjects discontinued for low WBC counts. The only SAE for low WBC count occurred in subject 457-307 and the event appeared to be related to treatment with methimazole. Subject 457-307 received placebo in the first year of 105MS301 and

BIIB017 every 4 weeks during year 2. The subject was also being treated with methimazole for hyperthyroidism. During a hospitalization for MS relapse, the subject had a WBC of 0.9x10⁹/L. Following discontinuation of methimazole, her WBC improved to 2.8x10⁹/L. Her low WBC count subsequently resolved and she continued in the trial.

There were no discontinuations from study treatment or SAEs associated with low lymphocyte counts. No patients discontinued for low neutrophil counts but there was one patient with a SAE of febrile neutropenia (Summary of Clinical Safety, p.112-113). I summarize that event below.

Subject 524-348 (BIIB017 every 4 weeks group), a 35-year-old female with normal WBC values at screening, was hospitalized due to febrile neutropenia approximately 6 months (13 injections) after starting study treatment. She presented with fever (>38°C), sore throat, and dysphagia. Her WBC count was 1.28 × 10⁹/L and her neutrophil count was 0.42 × 10⁹/L. No samples for culture or microbiology testing from the throat, blood, urine, or stools were collected. She was treated with cephalexin and ciprofloxacin. A source of infection was not identified. Her symptoms improved, and she was discharged from the hospital. Four days later WBCs were 4.38 × 10⁹/L and ANC was 2.52 × 10⁹/L, and the event was considered resolved. The Investigator assessed the SAE of leukopenia as moderate and related to study treatment. No action was taken with study treatment by the Investigator, but the subject withdrew consent and withdrew from the trial.

Hemoglobin, Hematocrit and Platelets

As with WBC counts, BIIB017 was associated with declines in mean Hemoglobin, Hematocrit and platelets. In the following table, I summarize the declines in mean Hemoglobin, Hematocrit, and Platelets during the controlled phase of 105MS301.

Hemoglobin, hematocrit, and platelet mean changes from baseline by trial week and treatment during 105MS301, year 1

Trial Week	Mean change from baseline, Hemoglobin (g/L)		
	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
Week 2	-1.3	-2.6	-1.2
Week 4	-1.6	-3.3	-2.5
Week 6	-2.0	-3.9	-3.4
Week 8	-1.1	-4.2	-4.1
Week 12	-1.8	-4.0	-4.6
Week 24	-1.7	-4.2	-5.6
Week 36	-1.3	-4.0	-5.3
Week 48	-1.2	-5.0	-5.5
	Mean change from baseline, Hematocrit (%)		
Week 2	-0.3	-0.7	-0.4
Week 4	-0.4	-1.0	-0.7
Week 6	-0.3	-1.1	-1.0
Week 8	-0.2	-1.1	-1.2
Week 12	-0.3	-1.0	-1.4
Week 24	-0.4	-1.1	-1.6

Week 36	-0.2	-1.1	-1.6
Week 48	-0.0	-1.1	-1.6
	Mean change from baseline, Platelets (x10 ⁹ /L)		
Week 2	2.8	22.2	15.3
Week 4	0	0	0.2
Week 6	3.7	-2.5	-0.3
Week 8	-0.1	-3.1	-8.7
Week 12	1.0	-6.0	-13.1
Week 24	-1.5	-10.9	-23.2
Week 36	-0.9	-12.8	-26.5
Week 48	2.8	-9.9	-22.1

From 105MS301 Study Report, Table 332

Biogen noted that there was little difference by treatment in the percentage of patients with low PCS hemoglobin results (≤ 100 g/L). Biogen found that 4% (21/496) of placebo patients had one or more low PCS hemoglobin results compared to 3% (17/496) of BIIB017 every 4 weeks patients and 4% (18/507) every 2 weeks patients (Summary of Clinical Safety, Table 18). To look for more extreme low hemoglobin outliers, I analyzed Biogen's hematology lab data set. I first identified the patients with a post baseline hemoglobin result using the values identified as "year 1 post-baseline" (APHASEC variable). I then identified the percentage of patients with a hemoglobin result ≤ 80 g/L. In this analysis, 1% (5/499) of placebo patients, 1% (5/496) every 4 week patients and 1% (4/507) of every 2 week patients had a hemoglobin ≤ 80 g/L.

During this search, I identified one BIIB017 subject with an extremely low hemoglobin result (39g/L) but this appeared to be an error. Subject 480-329, in the BIIB017 every 2 weeks treatment group, had a baseline hemoglobin of 121g/L, and did not have a hemoglobin result lower than baseline through week 12. At week 24 the subject had a hemoglobin of 39g/L. This event was identified as an AE, but not an SAE, and no treatment (ex. transfusion, iron replacement) was recorded (Clinical Study Report 105MS301, Adverse Event Listing, p.4056). A repeat hemoglobin test 6 days later was 149 g/L. For the remainder of the trial, this subject's lowest hemoglobin was 119g/L.

Similar percentages of patients by treatment experienced PCS low platelet counts ($\leq 100 \times 10^9$). $< 1\%$ (3/499) of placebo patients had a low PCS platelet count compared to $< 1\%$ (1/496) of BIIB017 every 4 weeks patients and 1% (6/507) of every 2 weeks patients (Summary of Clinical Safety, Table 18).

No AEs related to decreased hemoglobin led to discontinuation from a phase III clinical trial. One subject had an SAE related to decreased hemoglobin. Subject 626-310, a 45 year old female with a history of iron deficiency anemia, treated with ferrous sulfate, experienced decreased hemoglobin on placebo during year 1 of 105MS301 (lowest result was 88g/L at week 24). During year 2, when treated with BIIB017 every 2 weeks, her hemoglobin declined to 74g/L and she was hospitalized and treated with a blood

transfusion and oral ferrous sulfate. One month later, her hemoglobin was 98g/L (last available result).

One AE related to decreased platelets was an SAE and led to discontinuation, and another (non SAE) led to discontinuation. I summarize those events below.

Subject 437-322 (placebo Year 1 to BIIB017 every 4 weeks Year 2), a 32-year-old female was hospitalized for an SAE of thrombocytopenia on Day 395, approximately 2 months after beginning treatment with BIIB017 in Year 2. There was no relevant medical history. Her platelet count was $180 \times 10^9/L$ at baseline. While on placebo, she had AEs of low platelet counts on Day 15 ($51 \times 10^9/L$) and Day 85 ($65 \times 10^9/L$). Both of these events resolved within 2 weeks of onset without intervention. On Day 393 platelet count was $35 \times 10^9/L$ and she was hospitalized 2 days later with platelet count of $14 \times 10^9/L$ which decreased to a low of $8 \times 10^9/L$ the following day. The event was associated with some bruising on the legs. Anti-platelet antibodies were negative. Treatment included platelet transfusion and the SAE resolved but nonserious thrombocytopenia continued until Day 407, at which time platelet count was $173 \times 10^9/L$. Study treatment was discontinued and the subject was withdrawn from the trial as a result of the event.

Subject 481-308 (BIIB017 every 2 weeks group), a 36-year-old female had thrombocytopenia on Day 169 that led to discontinuation of study treatment. There was no relevant medical history. At screening, the subject's platelet count was $273 \times 10^9/L$. On Day 169, her platelet count was $30 \times 10^9/L$ and study treatment was discontinued. Platelets decreased to $16 \times 10^9/L$ 6 days later. Treatment included oral prednisolone. The event resolved approximately 1 month after the onset. Platelet count was $234 \times 10^9/L$ at the Early Withdrawal visit.

Chemistry

Biogen presented results for a number of blood chemistry tests including BUN, creatinine, sodium, potassium, chloride, bicarbonate, glucose, and TSH. For the majority of these tests, there did not appear to be meaningful differences in mean change from baseline or outliers (shift to low or high) when comparing BIIB017 treated patients to placebo patients in trial 105MS301. I summarize those data below. Results for liver related lab tests are presented with hepatic events in the events of special interest section above.

Chemistry tests, week 48 mean changes from baseline, during 105MS301

Chemistry parameter	Mean change from baseline, Week 48		
	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
BUN (mmol/L)	0.0882	0.0874	0.0433
Creatinine (umol/L)	0.387	0.563	-1.517
Bicarbonate (mmol/L)	-0.52	-0.85	-0.55
Sodium (mmol/L)	0.8	0.9	0.9
Potassium (mmol/L)	0.04	0.08	0.00
Chloride (mmol/L)	0.2	0.4	0.5
Glucose (mmol/L)	0.0446	0.0102	-0.0590
TSH (mIU/L)	0.414	-0.316	0.596

From Study Report 105MS301 Table 355

Biogen did not provide an analysis of PCS chemistry lab values and instead identified the percentage of patients in each treatment group with a shift to low (normal or unknown to low, high to low) or a shift to high (normal or unknown to high or low to high). I summarize those results below.

Chemistry shift analysis during 105MS301, year 1

Chemistry parameter		Percent shift to low or high by treatment		
		Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
BUN	Shift low	<1% (1/498)	0/496	<1% (1/507)
	Shift high	4% (18/497)	2% (10/494)	3% (14/504)
Creatinine	Shift low	<1% (2/499)	0/496	<1% (1/507)
	Shift high	3% (13/499)	2% (11/496)	3% (13/505)
Bicarbonate	Shift low	6% (30/496)	5% (26/492)	4% (21/504)
	Shift high	<1% (1/499)	0/496	<1% (1/504)
Sodium	Shift low	<1% (1/499)	<1% (1/496)	<1% (3/506)
	Shift high	8% (40/497)	6% (31/494)	8% (41/503)
Potassium	Shift low	1% (5/497)	1% (7/492)	<1% (5/502)
	Shift high	5% (26/497)	3% (16/493)	3% (17/506)
Chloride	Shift low	<1% (1/498)	<1% (3/496)	<1% (4/506)
	Shift high	1% (6/499)	<1% (2/496)	<1% (3/507)
Glucose	Shift low	9% (46/491)	11% (55/489)	12% (59/496)
	Shift high	26% (123/472)	25% (117/474)	23% (111/476)
TSH	Shift low	3% (13/470)	5% (25/463)	6% (27/496)
	Shift high	4% (19/481)	3% (14/469)	6% (31/480)

From Study Report 105MS301 Table 379

Urinalysis

For urinalysis results, Biogen provided a table that identified the percentage of patients that shifted to low or high for each parameter (specific gravity, pH, color, blood, glucose, ketones, protein, RBC, WBC, bilirubin, nitrite, and urobilinogen). There did not appear to be meaningful differences in shift percentages by treatment for the urinalysis parameters (105MS301 Clinical Study Report, Table 382).

7.4.3 Vital Signs

Biogen provided mean change from baseline and PCS analyses for vital sign parameters collected during 105MS301.

The vital sign parameter mean changes from baseline were small and similar across treatment groups for the time points assessed. In the following table, I provide the vital sign mean changes from baseline at week 48 (last scheduled trial visit, placebo controlled phase) for trial 105MS301.

Vital signs, week 48 mean changes from baseline, during 105MS301

Vital sign parameter	Mean change from baseline, Week 48		
	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
Systolic BP (mmHg)	0.6	1.1	0.7
Diastolic BP (mmHg)	-0.1	0.1	0.8
Pulse (Bpm)	0.3	0.5	0.4
Temperature (°C)	-0.03	-0.01	-0.07

From Study Report 105MS301 Table 385

Biogen's vital sign PCS analyses did not identify any important differences in frequency of vital sign outliers across treatment. I summarize that information below.

Vital sign outlier results during trial 105MS301, year 1

Vital sign parameter	% with post baseline PCS result		
	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
SBP (>150 if ≤150 at baseline or a >40 increase from baseline)	8% (38/498)	5% (25/499)	4% (22/512)
SBP (<90 if ≥90 at baseline or >30 decrease from baseline)	4% (21/498)	3% (17/499)	4% (23/512)
DBP (>100 if ≤100 at baseline or a >30 increase from baseline)	3% (16/498)	3% (16/499)	3% (13/512)
DBP (<50 if ≥50 at baseline or >20 decrease from baseline)	6% (31/498)	5% (25/499)	5% (27/512)
Pulse (>120 if ≤120 at baseline or >20 increase from baseline)	13% (67/498)	13% (67/499)	12% (63/512)
Pulse (<50 if ≥50 at baseline or >20 decrease from baseline)	9% (46/498)	6% (32/499)	8% (42/512)
Temperature (>38°C with ≥1°C increase from baseline)	<1% (1/486)	<1% (1/487)	<1% (3/499)

From Study Report 105MS301 Table 387

7.4.4 Electrocardiograms (ECGs)

Biogen performed 12-lead ECGs at baseline and weeks 48 and 96 during trial 105MS301. Biogen did not collect ECGs during trial 105MS302. Given the small number of ECGs, the ability to detect important changes is limited.

During the placebo controlled phase of 105MS301, at the end of the first year, the mean change from baseline for QTcF among placebo subjects was 2.6msec compared to 2.6 for subjects in the BIIB017 every 4 weeks group and 2.7msec for subjects in the BIIB017 every 2 weeks group (Clinical study report 105MS301, Table 392). There did

not appear to be meaningful differences by treatment in the PR, QRS, or RR intervals (data not shown).

In addition to the mean change analyses, Biogen provided analyses of QTcF outliers (absolute and change from baseline). There did not appear to be meaningful differences by treatment in these outlier analyses. I summarize the results below.

QTcF outlier results during trial 105MS301, year 1

QTcF Outlier criteria	% with post baseline result		
	Placebo	BIIB017	
		Every 4 weeks	Every 2 weeks
QTcF>450msec	<1% (3/441)	<1% (2/439)	<1% (2/449)
QTcF>480msec	0	0	0
QTcF increase from baseline >30msec	2% (8/441)	2% (10/438)	5% (21/448)
QTcF increase from baseline >60msec	0	0	<1% (1/448)

From ISS Appendix Table 260

7.4.5 Special Safety Studies/Clinical Trials

Trial 105MS302 included a sub-study that compared the experience of 39 patients following 2 doses of BIIB017 125ug every 4 weeks or every 2 weeks using the manual pre-filled syringe to the experience following 2 doses using the single-use autoinjector. None of the patients discontinued the sub-study, but 5 patients did not complete the last follow up visit (telephone). None of the sub study patients died. Treatment-emergent SAEs occurred in 2 subjects (MS relapse following injection with the autoinjector, and ureteric calculus following injection with the prefilled syringe). None of the AEs in the sub study led to treatment discontinuation. The most common AEs ($\geq 10\%$) reported following the use of the prefilled syringe and autoinjector, respectively, were pyrexia (33% and 33%), injection-site erythema (28% and 23%), headache (13% and 18%), influenza-like illness (18% and 15%), injection-site pain (23% and 15%), myalgia (18% and 15%), arthralgia (10% and 13%), chills (15% and 13%), and fatigue (10% and 3%)(Summary of Clinical Safety, p.30).

7.4.6 Immunogenicity

In trials 105MS301 and 105MS302, Biogen evaluated development binding antibodies to IFN B-1a (BAbs), neutralizing antibodies to IFN B-1a (NAbs), and antibodies to polyethylene glycol (anti-PEG). Biogen explained that for IFN- B-1a antibodies they used a tiered approach that involved a screening ELISA to detect binding antibodies, followed by further characterization and titration of positive samples in a cell-based neutralizing antibody assay. In addition, the presence and titer level of anti-PEG binding antibodies in human serum was determined using an ELISA (Study Report 105MS301, pp.83-4).

Biogen considered only the actual titer in their analyses of BAbs. For NABs and anti-PEG, Biogen conducted additional analyses that categorized titers as low, medium or high. In the table below, I list the antibody levels that Biogen used as cutoffs in these analyses.

Antibody categories and their corresponding titers

Antibody test	Qualitative level	Titer
NABs	Low	<50
	Medium	>50-<=700
	High	>700
Anti-PEG	Low	<=100
	Medium	>100 and <800
	High	>=800

Summary of Clinical Safety, p.144

Biogen also classified all subjects with treatment emergent antibodies as either transient (single positive result or >1 positive result less than 74 days apart), or persistent (>1 positive result at least 74 days apart).

Baseline

Biogen found that the presence of antibodies at baseline was generally low among subjects. BAbs were noted in 3% (13/500) of placebo subjects compared to 2% (8/500) of BIIB017 every 4 weeks subjects and 3% (16/512) of BIIB017 every 2 week subjects. NABs were present at baseline in 1% (5/500) of placebo subjects compared to <1% (2/500) of BIIB017 every 4 weeks subjects and 2% (8/512) of BIIB017 every 2 week subjects (Clinical Study Report 105MS301, Table 403). Biogen attributed the positive anti-IFN antibody results to false positivity or prior INF exposure. Anti-PEG antibodies were present in 8% (39/500) of placebo subjects compared to 5% (27/500) of BIIB017 every 4 weeks subjects and 5% (25/512) of BIIB017 every 2 week subjects (Clinical Study Report 105MS301, Table 403). Biogen expected some patients to have anti-PEG antibodies at baseline given the presence of PEG in foods and medicines (Summary of Clinical Safety, p.144).

105MS301, Year 1

Among subjects negative for BAbs at baseline, by week 48 of 105MS301, 2% (12/482) of placebo subjects, 4% (20/485) of BIIB017 every 4 week subjects and 8% (38/480) of BIIB017 every 2 week subjects had BAbs (Clinical Study Report 105MS301, Table 397). Among the BIIB017 subjects with BAbs, 4 in the every 4 weeks group, and 18 in the every 2 weeks group met the definition for persistent antibodies.

Among subjects negative for NABs at baseline, by week 48 of 105MS301, <1% (2/490) of placebo subjects, <1% (2/491) of BIIB017 every 4 week subjects and <1% (4/488) of BIIB017 every 2 week subjects had NABs (Clinical Study Report 105MS301, Table

397). Among the BIIB017 subjects with NABs, 1 met the definition of persistent. Furthermore, the titer of 5 of the 6 patients with NABs was low (<50). The remaining subject had a transient titer that was medium (>50 - <=700).

Among subjects negative for anti-PEG antibodies at baseline, by week 48 of 105MS301, 5% (24/454) of placebo subjects, 9% (43/465) of BIIB017 every 4 week subjects and 7% (31/471) of BIIB017 every 2 week subjects had anti-PEG antibodies (Summary of Clinical Safety, p.145). 6 placebo subjects, 25 BIIB017 every 4 week subjects, and 10 BIIB017 every 2 week subjects met the definition of persistent anti PEG antibodies. Two subjects, both in the BIIB017 every 4 weeks group, had high titers (>800).

Overall BIIB017 experience (105MS301, 105MS302)

Biogen also summarized antibody status for the entire BIIB017 experience and there appeared to be few additional subjects who developed antibodies after the first year. In the following table, I summarize the antibody results for the entire BIIB017 experience.

Antibody status in BIIB017 exposed patients, Overall Phase III experience

	BIIB017		
	Every 4 weeks	Every 2 weeks	Total
BABs	4% (29/672)	7% (46/669)	6% (75/1341)
NABs	<1% (5/682)	<1% (5/678)	<1% (10/1360)
Anti-PEG antibodies	8% (51/644)	6% (41/646)	7% (92/1290)

Summary of Clinical Safety, Appendix Table 263

1 subject in the BIIB017 every 4 weeks group had persistent NAb reactivity compared to 4 subjects in the BIIB017 every 2 weeks group. The titer in 3 subjects in the BIIB017 every 4 weeks group was low (≤ 50) and 2 subjects showed a medium titer level (>50 and ≤ 700).

Of the anti-PEG-positive subjects, 5% (34/644) in the BIIB017 every 4 weeks group and 3% (17/646) in the BIIB017 every 2 weeks group had persistent anti-PEG reactivity. 4% of subjects in each group had low titers, and 1% and <1% had medium titer levels in the BIIB017 every 4 and every 2 weeks groups, respectively. Two subjects (<1%) and 1 subject (<1%) in the BIIB017 every 4 and every 2 weeks groups, respectively, had high titer levels (≥ 800) (Summary of Clinical Safety, pp. 145-6).

Biogen reported that 2-8.5% of subjects treated with Avonex during clinical trials developed NABs. In the Rebif Phase 3 clinical studies, NABs occurred in 12% to 46% of Rebif-treated subjects Biogen commented that AEs have not been associated with the development of NABs in subjects treated with IFN- β .

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In their submitted labeling, Biogen proposes titrating Plegridy to a dose of 125 µg every 2 weeks. In their Phase III trials, Biogen compared 2 dosing intervals for Plegridy, 125µg every 2 weeks or every 4 weeks. In their presentations of AEs, Biogen provided incidences for both dosing schedules and I included that information above, in the sections that discussed AEs.

Biogen did include a BIIB017 dose of 188 µg in Phase I studies 105HV101 and 105HV102. 105HV101 was a single dose trial and included 8 subjects exposed to BIIB017 188 µg SC and 8 subjects exposed to BIIB017 188 µg IM. Given the small number of exposed subjects, and the single dose design, the AE data do not allow for firm conclusions about safety at the 188µg dose.

In the Phase I trial 105HV102, Biogen exposed subjects to 188 µg every 2 weeks (a total of 4 doses) and 188µg every 4 weeks (a total of 2 doses). Based on these limited data, there did not appear to be meaningful differences in AE frequency when comparing the 125µg and 188µg dose groups. AEs appeared to be reported more commonly for subjects receiving 125µg and 188µg compared to subjects receiving 63 µg (Clinical Study Report 105HV102, Table 14-19).

7.5.2 Time Dependency for Adverse Events

I provided discussions of time related analyses for specific AEs in the relevant sections above.

7.5.3 Drug-Demographic Interactions

Age

There did not appear to be meaningful differences in AE risk when comparing BIIB017 patients <40 years old to those ≥40 years old.

The age range in the BIIB017 clinical trials was 18-65 years and therefore there are no safety data for pediatric or elderly populations. Biogen provided analyses that stratified AE risks by age (<40 years and ≥40 years). There appeared to be no meaningful differences in AE risk between these age groups. I provide age stratified risks for the following AEs that were common during the first year of trial 105MS301 and that occurred more frequently compared to placebo: injection site erythema, influenza like illness, pyrexia, myalgia, chills, injection site pain, injection site pruritus, body temperature increased, vomiting, pain, and ALT increased.

Common AEs that occurred more frequently among BIIB017 subjects compared to placebo subjects in 105MS301, stratified by age

AEs	Age	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Any AE	<40	83% (258)	95% (288)	93% (298)
	>=40	84% (159)	94% (184)	95% (183)
Injection site erythema	<40	6% (20)	55% (166)	59% (189)
	>=40	7% (13)	59% (116)	66% (126)
Influenza like illness	<40	12% (37)	47% (142)	48% (153)
	>=40	14% (26)	47% (92)	45% (86)
Pyrexia	<40	17% (54)	44% (133)	43% (137)
	>=40	12% (22)	43% (85)	47% (91)
Myalgia	<40	6% (20)	19% (59)	17% (55)
	>=40	5% (10)	19% (38)	22% (42)
Chills	<40	4% (11)	17% (52)	14% (44)
	>=40	6% (12)	20% (40)	23% (44)
Injection site pain	<40	3% (9)	13% (41)	16% (51)
	>=40	3% (6)	13% (26)	14% (26)
Injection site pruritus	<40	2% (5)	12% (36)	14% (45)
	>=40	<1% (1)	10% (20)	12% (23)
Body temperature increased	<40	3% (9)	7% (21)	7% (22)
	>=40	3% (5)	6% (12)	5% (9)
Vomiting	<40	2% (6)	8% (25)	5% (16)
	>=40	3% (5)	6% (12)	5% (10)
Pain	<40	3% (10)	6% (18)	5% (15)
	>=40	3% (6)	6% (11)	5% (10)
ALT increased	<40	2% (6)	5% (14)	5% (17)
	>=40	4% (7)	3% (5)	6% (12)

From Summary of Clinical Safety Appendix Table 81

Sex

There appeared to be no meaningful differences in AE risk for males versus females. Biogen provided analyses that stratified AE risks by sex. I provide sex stratified risks for the following AEs that were common during the first year of trial 105MS301 and that occurred more frequently compared to placebo: injection site erythema, influenza like illness, pyrexia, myalgia, chills, injection site pain, injection site pruritus, body temperature increased, vomiting, pain, and ALT increased.

Common AEs that occurred more frequently among BIIB017 subjects compared to placebo subjects in 105MS301, stratified by sex

AEs	Age	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Any AE	Male	81% (115)	93% (138)	95% (144)
	Female	84% (302)	95% (334)	93% (337)
Injection site	Male	5% (7)	42% (62)	51% (77)

erythema	Female	7% (26)	63% (220)	66% (238)
Influenza like illness	Male	11% (15)	48% (71)	52% (78)
	Female	13% (48)	46% (163)	44% (160)
Pyrexia	Male	13% (19)	44% (65)	52% (78)
	Female	16% (57)	43% (153)	42% (150)
Myalgia	Male	4% (6)	11% (17)	12% (18)
	Female	7% (24)	23% (80)	22% (79)
Chills	Male	0	16% (23)	15% (22)
	Female	6% (23)	20% (69)	18% (66)
Injection site pain	Male	0	10% (15)	12% (18)
	Female	4% (15)	15% (52)	16% (59)
Injection site pruritus	Male	<1% (1)	5% (7)	10% (15)
	Female	1% (5)	14% (49)	15% (53)
Body temperature increased	Male	0	7% (10)	5% (7)
	Female	4% (14)	7% (23)	7% (24)
Vomiting	Male	2% (3)	6% (9)	5% (7)
	Female	2% (8)	8% (28)	5% (19)
Pain	Male	2% (3)	7% (11)	5% (7)
	Female	4% (13)	5% (18)	5% (18)
ALT increased	Male	4% (6)	5% (8)	4% (6)
	Female	2% (7)	3% (11)	6% (23)

From Summary of Clinical Safety Appendix Table 82

7.5.4 Drug-Disease Interactions

Biogen excluded patients with significant underlying diseases from participating in the BIIB017 clinical trials. Biogen did not provide analyses of AE risks stratified by underlying disease for enrolled patients.

7.5.5 Drug-Drug Interactions

Biogen did not conduct formal drug interaction studies with BIIB017. Biogen did provide analyses of AEs in patients who received concomitant IV corticosteroids. With the exception of MS relapse, Biogen found no notable differences in AEs when comparing patients who received IV corticosteroids to those who did not receive IV corticosteroids (Summary of Clinical Safety, p.151).

7.5.6 Adverse Events by Antibody Status

Biogen did not find evidence of increased AE risk among patients who developed antibodies to IFN or PEG.

Biogen examined whether AE incidence varied by presence/absence of BAbs, NABs, and anti-PEG Abs. Biogen explored this issue by comparing AE incidence among “ever

positive” and “never positive” subjects and, separately, by comparing AE incidence in those with any positive post baseline Ab test to the remaining subjects. Given the relatively small number of subjects who developed antibodies, AE analyses that stratify on antibody status generally result in strata with small numbers of events, which are difficult to interpret. Therefore, I will present the results for the following AEs that were common during the first year of trial 105MS301 and that occurred more frequently compared to placebo: injection site erythema, influenza like illness, pyrexia, myalgia, chills, injection site pain, injection site pruritus, body temperature increased, vomiting, pain, and ALT increased.

Ever Positive vs Never Positive

IFN BAbs

In general, the incidence of these commonly occurring AEs did not appear to vary when stratified by BAbs status. The following table summarizes the risks for the commonly occurring BIIB017-related AEs, stratified by BAbs (ever + vs never +).

Risks for the commonly occurring BIIB017-related AEs, stratified by BAbs (ever + vs never +) during 105MS301, year 1

AEs	BAbs	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Injection site erythema	Ever +	4% (1)	71% (20)	63% (34)
	Never +	7% (32)	56% (262)	61% (281)
Influenza like illness	Ever +	12% (3)	50% (14)	39% (21)
	Never +	13% (60)	47% (220)	48% (218)
Pyrexia	Ever +	20% (5)	50% (14)	41% (22)
	Never +	15% (71)	43% (204)	45% (206)
Myalgia	Ever +	4% (1)	25% (7)	11% (6)
	Never +	6% (29)	19% (90)	20% (91)
Chills	Ever +	4% (1)	25% (7)	19% (10)
	Never +	5% (22)	18% (85)	17% (78)
Injection site pain	Ever +	4% (1)	21% (6)	22% (12)
	Never +	3% (14)	13% (61)	14% (63)
Injection site pruritus	Ever +	8% (2)	7% (2)	17% (9)
	Never +	<1% (4)	11% (54)	13% (59)
Body temperature increased	Ever +	4% (1)	4% (1)	7% (4)
	Never +	3% (13)	7% (32)	6% (27)
Vomiting	Ever +	4% (1)	4% (1)	9% (5)
	Never +	2% (10)	8% (36)	5% (21)
Pain	Ever +	8% (2)	11% (3)	2% (1)
	Never +	3% (14)	6% (26)	5% (24)
ALT increased	Ever +	0	0	9% (5)
	Never +	3% (13)	4% (19)	5% (24)

From Summary of Clinical Safety Appendix Table 86

IFN NABs

The incidence of commonly occurring AEs did not appear to vary when stratified by NABs status, although the limited number of subjects with NABs limits this analysis. The following table summarizes the risks for the commonly occurring BIIB017-related AEs, stratified by NABs (ever + vs never +).

Risks for the commonly occurring BIIB017-related AEs, stratified by NABs (ever + vs never +) during 105MS301, year 1

AEs	NABs	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Injection site erythema	Ever +	14% (1)	100% (4)	42% (5)
	Never +	6% (32)	56% (278)	62% (310)
Influenza like illness	Ever +	0	25% (1)	17% (2)
	Never +	13% (63)	47% (233)	47% (237)
Pyrexia	Ever +	0	25% (1)	33% (4)
	Never +	15% (76)	44% (217)	45% (224)
Myalgia	Ever +	0	50% (2)	0
	Never +	6% (30)	19% (95)	19% (97)
Chills	Ever +	0	25% (1)	8% (1)
	Never +	5% (23)	18% (91)	17% (87)
Injection site pain	Ever +	14% (1)	50% (2)	25% (3)
	Never +	3% (14)	13% (65)	15% (74)
Injection site pruritus	Ever +	0	25% (1)	0
	Never +	1% (6)	11% (55)	14% (68)
Body temperature increased	Ever +	0	25% (1)	8% (1)
	Never +	3% (14)	6% (32)	6% (30)
Vomiting	Ever +	0	0	0
	Never +	2% (11)	7% (37)	5% (26)
Pain	Ever +	0	0	0
	Never +	3% (16)	6% (29)	5% (25)
ALT increased	Ever +	0	0	0
	Never +	3% (13)	4% (19)	6% (29)

From Summary of Clinical Safety Appendix Table 88

Anti-PEG Abs

In general, the incidence of these commonly occurring AEs did not appear to vary when stratified by Anti-PEG Abs status. The following table summarizes the risks for the commonly occurring BIIB017-related AEs, stratified by Anti-PEG Abs (ever + vs never +).

Risks for the commonly occurring BIIB017-related AEs, stratified by anti-PEG Abs (ever + vs never +) during 105MS301, year 1

AEs	Anti-PEG Abs	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Injection site erythema	Ever +	11% (7)	59% (41)	61% (34)
	Never +	6% (26)	56% (241)	62% (281)
Influenza like illness	Ever +	8% (5)	41% (29)	48% (27)
	Never +	13% (58)	48% (205)	46% (212)
Pyrexia	Ever +	16% (10)	40% (28)	32% (18)
	Never +	15% (66)	44% (190)	46% (210)
Myalgia	Ever +	2% (1)	13% (9)	20% (11)
	Never +	7% (29)	20% (88)	19% (86)
Chills	Ever +	2% (1)	16% (11)	7% (4)
	Never +	5% (22)	19% (81)	18% (84)
Injection site pain	Ever +	3% (2)	10% (7)	5% (3)
	Never +	3% (13)	14% (60)	16% (74)
Injection site pruritus	Ever +	0	14% (10)	9% (5)
	Never +	1% (6)	11% (46)	14% (63)
Body temperature increased	Ever +	0	13% (9)	9% (5)
	Never +	3% (14)	6% (24)	6% (50)
Vomiting	Ever +	0	6% (4)	0
	Never +	3% (11)	8% (33)	6% (26)
Pain	Ever +	2% (1)	7% (5)	5% (3)
	Never +	3% (15)	6% (24)	5% (22)
ALT increased	Ever +	3% (2)	6% (4)	5% (3)
	Never +	3% (11)	3% (15)	6% (26)

From Summary of Clinical Safety Appendix Table 90

Any Post Baseline + vs Rest

As with the previous analyses, Biogen did not find evidence of increased AE risk when comparing subjects with any post baseline + result to those with no post baseline + test results. I provide the results for BAbs, NAbs, and anti-PEG Abs in the following tables.

IFN BAbs

The following table summarizes the risks for the commonly occurring BIIB017-related AEs, stratified by BAbs (any post baseline + vs rest).

Risks for the commonly occurring BIIB017-related AEs, stratified by BAbs (any post baseline + vs rest) during 105MS301, year 1

AEs	BAbs	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Injection site erythema	Any PB +	5% (1)	69% (18)	64% (34)
	Rest	7% (32)	56% (264)	61% (281)
Influenza like illness	Any PB +	14% (3)	46% (12)	40% (21)

	Rest	13% (60)	47% (222)	47% (218)
Pyrexia	Any PB +	10% (2)	54% (14)	40% (21)
	Rest	15% (74)	43% (204)	45% (207)
Myalgia	Any PB +	5% (1)	23% (6)	11% (6)
	Rest	6% (29)	19% (91)	20% (91)
Chills	Any PB +	5% (1)	23% (6)	19% (10)
	Rest	5% (22)	18% (86)	17% (78)
Injection site pain	Any PB +	1% (5)	19% (5)	23% (12)
	Rest	3% (14)	13% (62)	14% (65)
Injection site pruritus	Any PB +	10% (2)	8% (2)	15% (8)
	Rest	<1% (4)	11% (54)	13% (60)
Body temperature increased	Any PB +	5% (1)	4% (1)	8% (4)
	Rest	3% (13)	7% (32)	6% (27)
Vomiting	Any PB +	5% (1)	4% (1)	9% (5)
	Rest	2% (10)	8% (36)	5% (21)
Pain	Any PB +	5% (1)	12% (3)	2% (1)
	Rest	3% (15)	5% (26)	5% (24)
ALT increased	Any PB +	0	0	9% (5)
	Rest	3% (13)	4% (19)	5% (24)

From Summary of Clinical Safety Appendix Table 87

IFN NAbS

The following table summarizes the risks for the commonly occurring BIIB017-related AEs, stratified by NAbS (any post baseline + vs rest).

Risks for the commonly occurring BIIB017-related AEs, stratified by NAbS (any post baseline + vs rest) during 105MS301, year 1

AEs	NAbS	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Injection site erythema	Any PB +	20% (1)	100% (2)	42% (5)
	Rest	6% (32)	56% (280)	62% (310)
Influenza like illness	Any PB +	0	0	17% (2)
	Rest	13% (63)	47% (234)	47% (237)
Pyrexia	Any PB +	0	50% (1)	33% (4)
	Rest	15% (76)	44% (217)	45% (224)
Myalgia	Any PB +	0	50% (1)	0
	Rest	6% (30)	19% (96)	19% (97)
Chills	Any PB +	0	0	8% (1)
	Rest	5% (23)	18% (92)	17% (87)
Injection site pain	Any PB +	20% (1)	50% (1)	25% (3)
	Rest	3% (14)	13% (66)	15% (74)
Injection site pruritus	Any PB +	0	50% (1)	0
	Rest	1% (6)	11% (55)	14% (68)
Body temperature increased	Any PB +	0	0	8% (1)
	Rest	3% (14)	7% (33)	6% (30)
Vomiting	Any PB +	0	0	0

Safety Review
Gerard Boehm, MD, MPH
BLA 125499
PLEGRIDY, PEGylated interferon beta-1a

	Rest	2% (11)	7% (37)	5% (26)
Pain	Any PB +	0	0	0
	Rest	3% (16)	6% (29)	5% (25)
ALT increased	Any PB +	0	0	0
	Rest	3% (13)	4% (19)	6% (29)

From Summary of Clinical Safety Appendix Table 89
Anti-PEG Abs

The following table summarizes the risks for the commonly occurring BIIB017-related AEs, stratified by Anti-PEG (any post baseline + vs rest).

Risks for the commonly occurring BIIB017-related AEs, stratified by anti-PEG Abs (any post baseline + vs rest) during 105MS301, year 1

AEs	Anti-PEG Abs	Placebo	BIIB017	
			Every 4 weeks	Every 2 weeks
Injection site erythema	Any PB +	9% (5)	56% (35)	57% (28)
	Rest	6% (28)	57% (47)	62% (287)
Influenza like illness	Any PB +	7% (4)	41% (26)	47% (23)
	Rest	13% (59)	48% (208)	47% (216)
Pyrexia	Any PB +	16% (9)	41% (26)	47% (23)
	Rest	15% (67)	44% (192)	46% (213)
Myalgia	Any PB +	2% (1)	14% (9)	16% (8)
	Rest	7% (29)	20% (88)	19% (89)
Chills	Any PB +	2% (1)	17% (11)	6% (3)
	Rest	5% (22)	19% (81)	18% (85)
Injection site pain	Any PB +	4% (2)	11% (7)	4% (2)
	Rest	3% (13)	14% (60)	16% (75)
Injection site pruritus	Any PB +	0	14% (9)	8% (4)
	Rest	1% (6)	11% (47)	14% (64)
Body temperature increased	Any PB +	0	13% (8)	8% (4)
	Rest	3% (14)	6% (25)	6% (27)
Vomiting	Any PB +	0	5% (3)	0
	Rest	2% (11)	8% (34)	6% (26)
Pain	Any PB +	2% (1)	5% (3)	6% (3)
	Rest	3% (15)	6% (26)	5% (22)
ALT increased	Any PB +	2% (1)	6% (4)	6% (3)
	Rest	3% (12)	3% (15)	6% (26)

From Summary of Clinical Safety Appendix Table 91

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

I summarized information about malignancies diagnosed during the BIIB017 trials above, with the AEs of Special Interest.

7.6.2 Human Reproduction and Pregnancy Data

Biogen did not study the use of BIIB017 in pregnant women. The BIIB017 development program clinical trials required that women have a negative pregnancy test prior to enrollment and required that women participating in clinical trials use contraception. Despite these requirements, Biogen identified 14 pregnancies during BIIB017 clinical trials, with 12 in BIIB017 exposed women. For the pregnancies in BIIB017 exposed women, 2 ended in spontaneous abortion, 5 in elective abortion, 3 in live birth, and for 2, the outcome was pending at the time of data cutoff. The spontaneous abortions occurred at 6 weeks and 4 weeks of pregnancy. For the elective abortions, Biogen noted that none were reported to have occurred due to identification of a fetal anomaly. For the 3 live births, the outcome is not known for the first, and for the second and third, the births were without complications and no defects were noted (120 Day Safety Update, pp.120-1).

7.6.3 Pediatrics and Assessment of Effects on Growth

Biogen did not include patients under the age of 18 years in BIIB017 trials.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Biogen identified no reports of BIIB017 overdose. Biogen concluded that the safety profile of BIIB017 did not suggest rewarding effects or abuse related behaviors. An analysis of AE terms potentially suggestive of abuse (mood elevation, euphoria, hallucination, sedation, somnolence, insomnia, cognitive disorder, and anxiety) demonstrated that these events occurred infrequently, and were balanced across treatment groups (120 Day Safety Update, p.122).

Biogen concluded that BIIB017 is not associated with withdrawal or rebound. Biogen's conclusion was based on similarity in the percentages of patients by treatment that discontinued from study treatment (BIIB017 or placebo) and then subsequently experienced an AE. Biogen reported that after discontinuing study treatment, 11% of the patients who had received placebo experienced an AE compared to 11% of patients who received BIIB017 every 4 weeks and 12% of patients who had received BIIB017 every 2 weeks (Summary of Clinical Safety p.157). The types of AEs reported by these

patients were similar across treatment groups (Summary of Clinical Safety, Appendix Table 282).

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

N/A

9 Appendices

9.1 Literature Review/References

Biogen's submitted literature references appeared appropriate to support this application. I did not identify any important references regarding safety of PEGylated interferon B-1a for the treatment of MS that were omitted from this application submission.

9.2 Labeling Recommendations

Labeling recommendations to be presented and discussed during review team meetings.

9.3 Advisory Committee Meeting

N/A

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

/s/

GERARD A BOEHM
01/13/2014

SALLY U YASUDA
01/13/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: **125499**

Applicant: **Biogen-Idec** Stamp Date: **5-17-2013**

Drug Name: **PEG-interferon-β-1a**

BLA Type: **351a**

Clinical Review

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Since there is only one clinical trial the ISE is the CSR for that trial
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Clinical Overview pp. 39 - 46 of 60
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(1)			The application is a BLA for a new standalone biologic with clinical data
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			The single large trial compared two dose regimens: once every two weeks every 4 weeks
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			There is one well-controlled trial presented in the application as discussed with the applicant at the pre-BLA meeting
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Yes, to the extent agreed to previously in a pre-BLA meeting with the Division of Neurological Products.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			The endpoints conform to an SPA agreement issued on May 3, 2010.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Not found in the application. Only 3% of subjects were from the USA.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?			X	This document pertains only to the clinical review of efficacy.
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	See above.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	See above.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	See above.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	See above.
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	See above.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	See above.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	See above.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			The applicant has submitted all efficacy data requested during the pre-BLA discussions.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		Could not locate in application
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?			X	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			The statement appears in each clinical trial report.

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

The application is fileable with regard to the clinical review of efficacy.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

This review could not find a statement of applicability of foreign data to the US population in the application. The applicant should provide the information or direct us to its location in the submission.

The sponsor should conduct a sensitivity analysis to be sure that the payments to clinical investigators at 26 sites did not determine the outcome of the 105MS301 year one trial.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

John Marler, M.D.

22-June-2013

Reviewing Medical Officer

Date

Billy Dunn, M.D.

Clinical Team Leader

Date

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

/s/

JOHN R MARLER
07/09/2013

WILLIAM H Dunn
10/24/2013