

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125499Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

Individual Study Reviews

(Question-Based Review for PLEGRIDY™ is in DARRTS dated 01/24/2014)

BLA:	125499
Brand Name:	PLEGRIDY™ (BIIB017)
Generic Name:	PEGylated Interferon Beta-1a
Dosage Form & Strength:	Clear liquid solution containing [REDACTED] (b) (4) [REDACTED] of peginterferon beta-1a
Indication:	Treatment of patients with relapsing forms of Multiple Sclerosis (RMS)
Applicant:	Biogen Idec, Inc.
Submission:	505(b)(1), Standard
Submission Date:	5/15/2013
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewer:	Ta-Chen Wu, Ph.D.
Team Leader:	Angela Men, M.D., Ph.D.
Pharmacometrics Reviewers:	Xiaofeng Wang, Ph.D., Atul Bhattaram, Ph.D.

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4. Appendices

4.3 Individual Study Reviews

Study Report #	105HV101		
Title	A Phase 1, Single-Dose, Healthy Volunteer, Dose and Route Finding Study for PEGylated Interferon Beta-1a (BIIB017)		
Investigator/ Center	Royce Morrison, MD, Northwest Kinetics, Inc., Tacoma, WA 98418		
Study Dates	May 30, 2007 – September 30, 2007		
Objectives	<ul style="list-style-type: none"> • To identify the highest safe and tolerated dose of BIIB017 within the 31-188 µg dose range, IM or SC, in healthy subjects • To compare the pharmacokinetic (PK) and pharmacodynamic (PD) responses of BIIB017 when given via IM or SC administration to the response of the AVONEX® IM formulation • To determine the safety and tolerability of BIIB017 		
Formulation	Treatment	Lot #	
	BIIB017: 63 µg (6 MU), 125 µg (12 MU), and 188 µg (18 MU), IM and SC injection	06-013A	
	Avonex: 30 µg IM injection	06-013B	
	placebo/diluent	622077B	
Study Design	<ul style="list-style-type: none"> • Phase 1, randomized, blinded, single-dose (BIIB017 IM, BIIB017 SC, or Avonex), dose escalation, dose- and route-finding study of BIIB017 in 40 eligible healthy subjects, aged 18-45 years, with a BMI of 18-35 kg/m² and a BW ≥50 kg • 3 dosing cohorts (63 µg, 125 µg, and 188 µg BIIB017) of 20 subjects each – 8 subjects receiving BIIB017 SC, 8 subjects receiving BIIB017 IM, and 4 subjects receiving Avonex 30 µg IM • Subjects received treatment on Day 1 and were allowed to leave the clinic on Day 3 pending safety observations, and follow-up safety observations to Day 29. • Duration of study: in study for up to 29 days after screening 		
PK and PD Assessments	<ul style="list-style-type: none"> • Serum samples: PK profile of each dose of study treatment was assessed by determining the serum concentration-time curves of Avonex and BIIB017 from blood samples taken prior to and over a 4-week period following each dose of study treatment • PK time points: Predose and at 1, 2, 4, 6, 9, 12, 18, 24, 48, 72, 96, 120, 168, 336, 504, and 672h postdose, and at the early study withdrawal. • PD time points: Predose and at 6, 12, 24, 36, 48, 72, 96, 120, 168, 336, 504, and 672h postdose, and at the early study withdrawal. • BIIB017: C_{max}, T_{max}, AUC_{168h}, t_{1/2}, and t₅₀ (duration above ½ C_{max}) • Neopterin: E_{max} (maximum serum concentration), T_{max} (time to reach maximum serum concentration), E_{AUC-336h}, E_{AUC-dur} (area under the concentration-time curve above 1.5 ng/mL), E_{t-dur} (duration for concentrations above 1.5 ng/mL), E_{t-last} (time point for neopterin to drop below 1.5 ng/mL), and t_{1/2} 		

	<ul style="list-style-type: none"> • 2'5'-OAS: Emax, Tmax, EAUC-336h, and t1/2
Statistical Analysis	<ul style="list-style-type: none"> • PK parameters were calculated using WinNonlin Professional Version 5.2 software • Descriptive, tabular summary and plots for the medians/ranges and geometric means of serum Avonex and BIIB017, neopterin and whole blood 2', 5'-OAS expression
Bioanalytical Methods	<p>PK properties of Avonex and BIIB017:</p> <ul style="list-style-type: none"> • Enzyme-linked immunosorbent assay (ELISA) (by (b) (4)) and anti-viral Cytopathic effect (CPE) assay (by (b) (4)) • The LLQ of the ELISA was 15.6 pg/mL and 31.3 pg/mL for Avonex and BIIB017, respectively. The LLQ of the CPE assay was 10 U/mL and 7.5 U/mL for Avonex and BIIB017, respectively. <p>PD properties of BIIB017:</p> <ul style="list-style-type: none"> • Neopterin: a competitive binding enzyme immunoassay (Immuchem™) purchased as a kit from (b) (4) (by (b) (4)) • 2',5'-OAS: Relative expression of the three distinct forms of OAS (OAS1, OAS2, and OAS3) determined utilizing a Real-Time quantitative Polymerase Chain Reaction (qRT-PCR) assay procedure: detected down to 2-fold change in OAS gene expression (by (b) (4)) not detailed in this review. <p>These assays are considered validated assays.</p>

Table. Assay performance for BIIB017 and neopterin

Analyte	BIIB017 (serum)	Avonex (serum)	BIIB017 (serum)	Avonex (serum)	Neopterin (serum)
Method:	ELISA	ELISA	CPE	CPE	ELISA
Standard Range:	31.25-1500	15.625-1000	7.5-50 IU/mL	10-60	0.906-100.7
Curve:	pg/mL	pg/mL		IU/mL	ng/mL
Precision:	2.7-17.1%	0.9-10.2%	5.6-9.2%	6.0-13.6%	3.6-7.8%
Accuracy:	94.2-106.6%	80.2-103.3%	97.2-107.5%	95.9-107.9%	97.2-104.1%
LLOQ:	31.25 pg/mL	15.625 pg/mL	7.5 IU/mL	10 IU/mL	0.906 ng/mL
ULOQ:	1500 pg/mL	1000 pg/mL	50 IU/mL	60 IU/mL	100.656 ng/mL
LQC:	75 pg/mL	50 pg/mL	12.5 IU/mL	25 IU/mL	2 ng/mL
Precision:	11.6%	5.8%	14.9%	16.6%	12.7%
Accuracy:	99.6%	100.1%	91.3%	93.8%	92.4%
MQC:	400 pg/mL	200 pg/mL			15 ng/mL
Precision:	6.8%	4.1%			9.1%
Accuracy:	95.1%	98.4%			94.9%
HQC:	1100 pg/mL	750 pg/mL	27.5 IU/mL	42 IU/mL	75 ng/mL
Precision:	9.4%	7.4%	18.1%	20.8%	9.9%
Accuracy:	94.5%	99.1%	102.1%	95.9%	101.1%

Population/ Demographics	<ul style="list-style-type: none"> • 60 subjects enrolled and received treatment; 58 completed the study (2 subjects withdrew prematurely – 1 received Avonex and 1 received BIIB017) • Median age of 28.0 years (19-45 years); predominantly white (77%) and male (62%); median weight of 75.2 kg (55.2-118.2 kg); median BMI of 26.70 kg/m² • PK analysis population: all subjects who received at least 1 dose of study treatment and had sufficient samples with measurable drug concentration
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PK and PD Results

Figure 1. Medians of antiviral activity by treatment group (using CPE)

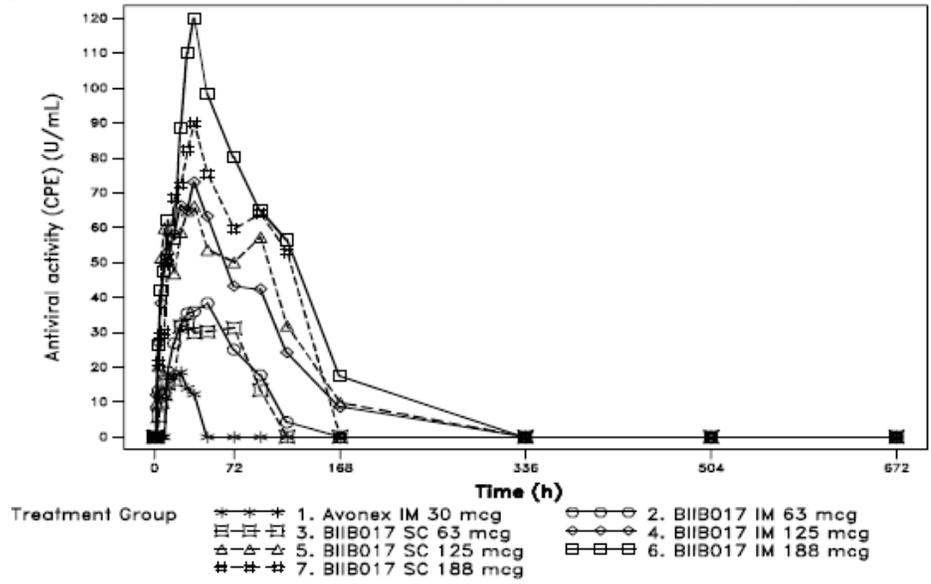


Figure 2. Serum Concentration-time profile of BIIB017 and INF β-1a by treatment (using ELISA)

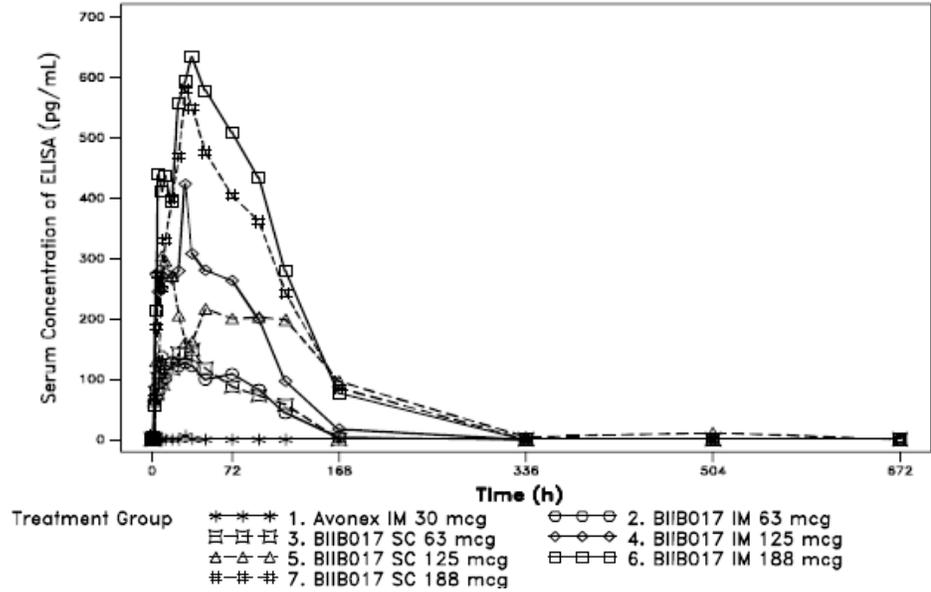


Figure 3. Median serum concentrations of neopterin by treatment group

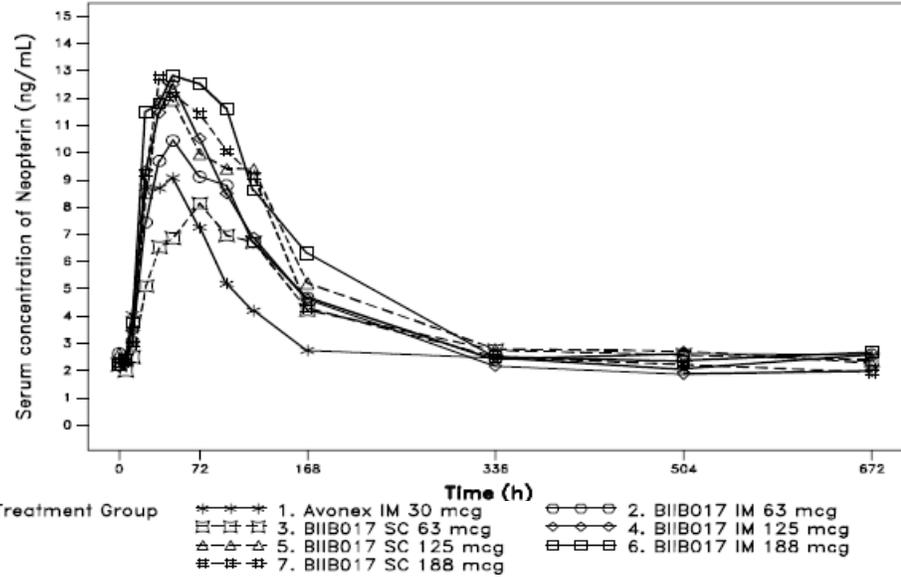
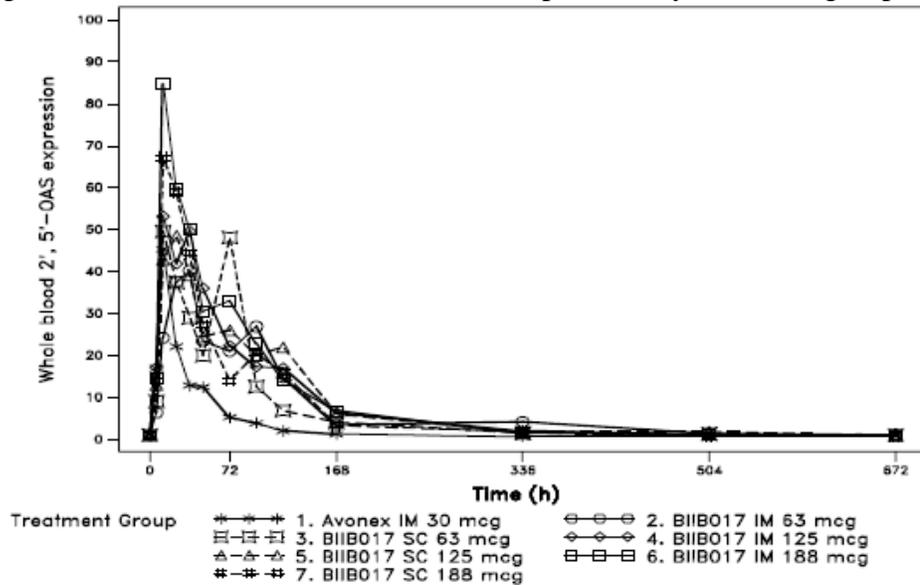


Figure 4. Median whole blood 2',5'-OAS expression by treatment group



- Detailed data are not presented.
- Similar BIIB017 induction in whole blood 2',5'-OAS expression between IM and SC routes, but in a less than dose-proportional manner.
- Greater BIIB017 induction than Avonex, with elevation lasting ~7 days longer.

Table 1. Summary of pharmacokinetic parameters for BIIB017 and INF β-1a

PK parameter	INF β-1a (n = 12)	BIIB017 (n = 8 per group)					
	IM Injection	IM Injection			SC Injection		
	30 μg (6 MIU)	63 μg (6 MIU)	125 μg (12 MIU)	188 μg (18 MIU)	63 μg (6 MIU)	125 μg (12 MIU)	188 μg (18 MIU)

AUC_{168h} ($\times 10^3$ h·IU/mL)	0.77 (0.05-1.99)	2.94 (0.00-5.05)	6.69 (2.19-14.6)	10.9 (4.31-17.9)	2.85 (0.87-4.59)	7.14 (2.52-21.9)	10.1 (2.15-19.9)
C_{max} (IU/mL)	20.8 (11.5-81.1)	41.6 (0.00-79.8)	80.7 (18.5-268)	136 (49.3-228)	38.9 (18.7-52.3)	70.1 (28.6-146)	98.0 (51.7-219)
t_{1/2} (h)	24.3 (12.6-1064)	45.4 (23.8-367)	33.3 (27.0-112)	38.7 (32.2-130)	48.4 (24.9-109)	39.2 (28.3-776)	66.3 (24.4-279)
T_{max} (h)	12.0 (9.00-48.0)	36.0 (0.00-119)	30.0 (12.0-72.0)	36.0 (18.0-96.0)	36.0 (12.0-72.0)	33.0 (30.0-96.0)	36.0 (18.0-96.0)

* Data presented based on CPE assay

- BIIB017 SC injection resulted in approximately 4-, 9-, and 13-fold higher AUC_{168h} at 63, 125 and 188 μ g doses, respectively, compare to INF β -1a 30 μ g IM.
- Terminal t_{1/2} of BIIB017 across doses was approximately 2-fold longer than INF β -1a 30 μ g IM.
- %CV of AUC_{168h} and C_{max} for BIIB017: 28-70% (CPE); 34-99% (ELISA)
- %CV of AUC_{168h} and C_{max} for INF β -1a: ~70% (CPE); 95-166% (ELISA)

Table 2. Summary of pharmacodynamic parameters for neopterin

PD parameter	IFN β -1a (n = 12)	BIIB017 (n = 8 per group)					
	IM Injection	IM Injection			SC Injection		
	30 μ g (6 MIU)	63 μ g (6 MIU)	125 μ g (12 MIU)	188 μ g (18 MIU)	63 μ g (6 MIU)	125 μ g (12 MIU)	188 μ g (18 MIU)
E_{AUC336h} (h ² ng/mL)	532 (312-1210)	977 (450-1650)	1150 (776-1890)	1460 (958-1880)	897 (148-1720)	1070 (806-2140)	1170 (632-2060)
E_{max} (ng/mL)	6.60 (4.70-13.5)	8.50 (4.00-16.8)	11.7 (6.40-15.9)	11.3 (8.80-18.6)	6.10 (3.80-16.0)	10.0 (6.20-16.2)	10.9 (7.20-21.0)
E_{Tmax} (h)	48.0 (24.0-72.0)	48.0 (36.0-95.0)	42.0 (36.0-72.0)	48.0 (24.0-96.0)	71.0 (36.0-72.0)	48.0 (36.0-120)	60.0 (36.0-96.0)

- %CV: 6-72% for neopterin; 18-76% for 2',5'-OAS
- BIIB017 induced neopterin elevation in a less than dose-proportional manner (E_{AUC-336h} and E_{max}) but for a longer period of time than for Avonex (7-10 days vs. 4-5 days).

Immunogenicity	<p>Antibody samples were collected at predose on Days 1, 15 and 29:</p> <ul style="list-style-type: none"> • No subject in this study developed antibodies against IFN β-1a. • Two of the 48 BIIB017-treated subjects tested positive for anti-PEG antibodies prior to treatment. • Five subjects who tested negative at baseline were positive for anti-PEG antibodies after BIIB017 cleared from the circulation. • The impact of anti-PEG antibodies on PK and PD was not assessed in this study.
Safety	<ul style="list-style-type: none"> • The occurrence of flu-like symptoms in BIIB017 treated subjects was dose-

	<p>dependent, regardless of the route of administration.</p> <ul style="list-style-type: none"> • Elevations in body temperature following BIIB017 treatment were not clinically significant, and resolved by 24 hours after treatment. • The risk of a reduction in absolute neutrophil concentration (ANC) and the duration of ANC reduction were both greater in BIIB017-treated subjects (no reported apparent dose-dependence) than in Avonex-treated subjects. • No associated serious infections were observed in this study. • The overall safety profile of single-dose BIIB017 in healthy subjects was reported to be comparable to that of Avonex.
Conclusion	<p><i>Pharmacokinetics:</i></p> <ul style="list-style-type: none"> • BIIB017 showed approximately dose-proportional increases in exposure (AUC_{168h} and C_{max}). • BIIB017 showed an approximately dose-independent t_{1/2}. • Following a single IM or SC administration, the BIIB017 concentration peaked at ~1.5 days post-dose, followed by a mono-phasic decline. • The PK parameters were comparable between the IM and SC routes. • Compared to Avonex at 6 MU, BIIB017 at 6 MU showed higher exposure (C_{max} and AUC_{168h}), longer t_{1/2} and later T_{max} following SC or IM administration at 6 MU. Higher doses at 12 MU and 18 MU provided further increase in exposure. <p><i>Pharmacodynamics:</i></p> <ul style="list-style-type: none"> • The pharmacological activity of BIIB017 in humans was confirmed by the elevation of serum neopterin concentration and whole blood 2',5'-OAS expression. • Both neopterin and 2',5'-OAS responses were less than dose-proportional in terms of EAUC-336h, EAUC-dur, E_{max} and induction ratio. • The PD parameters were comparable between the IM and SC routes at the same dose level. • Compared to Avonex treatment, BIIB017 treatment resulted in longer-lasting elevation of neopterin in terms of E_t-dur and E_t-last, and a higher magnitude of elevation in terms of EAUC-336h, EAUC-dur, E_{max} and induction ratio; BIIB017 also induced longer-lasting elevation of 2',5'-OAS as indicated by the raw data, and a higher magnitude of elevation of 2',5'-OAS in terms of EAUC-336h, EAUC-dur, E_{max} and induction ratio.

Study Report #	105HV102	
Title	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Dose-Ranging, Parallel-Group Study of PEGylated Interferon Beta-1a (BIIB017) in Healthy Volunteers	
Investigator/Center	Shawn Searle, MD. At Dedicated Phase 1 Inc. in Phoenix AZ.	
Study Dates	March 01, 2008 – May 25, 2008	
Objectives	<ul style="list-style-type: none"> To identify the highest safe and tolerated dose of BIIB017 SC within the 63-188 µg dose range, given SC Q2W or Q4W to healthy subjects To assess PK, PD, safety and tolerability of BIIB017 of multiple SC doses 	
Formulation	Treatment	Lot #
	BIIB017: 63 µg (6 MU), 125 µg (12 MU), and 188 µg (18 MU), IM and SC injection	Lot: 20702 Lot #: 06-013B
	Placebo SC Q2W as comparator	
Study Design	<ul style="list-style-type: none"> Single-center, randomized, double-blind, placebo-controlled, multiple-dose, dose-ranging, parallel-group study, in 68 eligible healthy subjects, aged 18-45 years, with a BMI of 18-35 kg/m² and a BW ≥50 kg N=10 randomized to placebo and N=59 subjects randomized to 1 of 3 BIIB017 doses administered either Q2W or Q4W Treatment period: SC Q2W (placebo or BIIB017) for up to 6 weeks, with injections scheduled to occur on Days 1, 15, 29, and 43. Follow-up period: on Days 50 and 71. Subjects were stratified into an intensive PK sampling group or a sparse PK sampling group. PK samples were obtained at various timepoints before and after dosing. PD samples were to be collected at the same time points as the sparse PK samples for all subjects participating in this study. 105HV102 Study Design: <pre> graph TD Screening[Screening] --> Randomization[Randomization 70 subjects planned (10 per group)] Randomization --> Treatment[6 week treatment + 4 week follow-up] Randomization --> Placebo[Placebo] Treatment --> Dose63[BIIB017 63 mcg, SC Q2W] Treatment --> Dose63Q4[BIIB017 63 mcg, SC Q4W] Treatment --> Dose125[BIIB017 125 mcg, SC Q2W] Treatment --> Dose125Q4[BIIB017 125 mcg, SC Q4W] Treatment --> Dose188[BIIB017 188 mcg, SC Q2W] Treatment --> Dose188Q4[BIIB017 188 mcg, SC Q4W] </pre>	
PK and PD Assessments	<ul style="list-style-type: none"> Serum samples: PK profile of each dose of study treatment was assessed by determining the serum concentration-time curves of Avonex and BIIB017 from blood samples taken prior to and over a 4-week period following each dose of study treatment. The PD effects of BIIB017 were evaluated via neopterin levels. Sparse PK group: <ul style="list-style-type: none"> Day 1: pre-dose, then 24, 72, and 168 h after the Day 1 dose. Day 15: pre-dose (i.e., 336 h after the Day 1 dose). Day 29: pre-dose, then 24, 72, and 168 h after the Day 29 dose. 	

	<ul style="list-style-type: none"> – Day 43: pre-dose (i.e., 336 h after the Day 29 dose). • Intense PK group: taken from approximately 14 subjects at the following additional time points relative to Day 1: 6, 28, 96, and 240 h after the Day 1 dose. • BIIB017: C_{max}, T_{max}, AUC_{168h}, t_{1/2}, and t₅₀ (duration above ½ C_{max}) • Neopterin: E_{max} (maximum serum concentration), T_{max} (time to reach maximum serum concentration), E_{AUC-336h}, E_{AUC-dur} (area under the concentration-time curve above 1.5 ng/mL), E_{t-dur} (duration for concentrations above 1.5 ng/mL), E_{t-last} (time point for neopterin to drop below 1.5 ng/mL), and t_{1/2} 																																																																				
Statistical Analysis	<ul style="list-style-type: none"> • PK and PD parameters were calculated using a non-compartmental analysis input model. PK/PD parameters were calculated following Day 1 and Day 29 doses. • Summary statistics (mean, standard deviation, median, and range), and categorical variables are presented with frequency distributions for each treatment group. No formal statistical testing was planned or performed for this study. 																																																																				
Bioanalytical Methods	<p>PK properties of Avonex and BIIB017:</p> <ul style="list-style-type: none"> • Enzyme-linked immunosorbent assay (ELISA) (at (b) (4) and anti-viral Cytopathic effect (CPE) assay (at (b) (4)) • The LLQ of the ELISA was 15.6 pg/mL and 31.3 pg/mL for Avonex and BIIB017, respectively. The LLQ of the CPE assay was 10 U/mL and 7.5 U/mL for Avonex and BIIB017, respectively. <p>PD properties of BIIB017:</p> <ul style="list-style-type: none"> • Neopterin: a competitive binding enzyme immunoassay (Immuchem™) purchased as a kit from (b) (4) (at (b) (4)) <p>Assays are validated and are acceptable.</p> <p>Table. Assay performance for BIIB017 and neopterin</p> <table border="1"> <thead> <tr> <th>Analyte</th> <th>BIIB017 (serum)</th> <th>BIIB017 (serum)</th> <th>Neopterin (serum)</th> </tr> </thead> <tbody> <tr> <td>Method:</td> <td>ELISA</td> <td>CPE</td> <td>ELISA</td> </tr> <tr> <td>Standard Range:</td> <td>31.3-1500 pg/mL</td> <td>7.5-50 IU/mL</td> <td>0.906-100.7 ng/mL</td> </tr> <tr> <td>Curve:</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Precision:</td> <td>0.9-4.2%</td> <td>2.5-6.0%</td> <td>3.8-7.2%</td> </tr> <tr> <td>Accuracy:</td> <td>98.3-103.9%</td> <td>98-108.3%</td> <td>95.7-104.8%</td> </tr> <tr> <td>LLOQ:</td> <td>31.3 pg/mL</td> <td>7.5 IU/mL</td> <td>0.906 ng/mL</td> </tr> <tr> <td>ULOQ:</td> <td>1500 pg/mL</td> <td>50 IU/mL</td> <td>100.656 ng/mL</td> </tr> <tr> <td>LQC:</td> <td>75 pg/mL</td> <td>12.5 IU/mL</td> <td>2 ng/mL</td> </tr> <tr> <td>Precision:</td> <td>6.4%</td> <td>10.8%</td> <td>13.3%</td> </tr> <tr> <td>Accuracy:</td> <td>100.1%</td> <td>104.7%</td> <td>87.9%</td> </tr> <tr> <td>MQC:</td> <td>400 pg/mL</td> <td></td> <td>15 ng/mL</td> </tr> <tr> <td>Precision:</td> <td>5.8%</td> <td></td> <td>8.4%</td> </tr> <tr> <td>Accuracy:</td> <td>98.7%</td> <td></td> <td>87.6%</td> </tr> <tr> <td>HQC:</td> <td>1100 pg/mL</td> <td>27.5 IU/mL</td> <td>75 ng/mL</td> </tr> <tr> <td>Precision:</td> <td>5.8%</td> <td>16.5%</td> <td>9.3%</td> </tr> <tr> <td>Accuracy:</td> <td>100%</td> <td>112.6%</td> <td>91.7%</td> </tr> </tbody> </table>	Analyte	BIIB017 (serum)	BIIB017 (serum)	Neopterin (serum)	Method:	ELISA	CPE	ELISA	Standard Range:	31.3-1500 pg/mL	7.5-50 IU/mL	0.906-100.7 ng/mL	Curve:				Precision:	0.9-4.2%	2.5-6.0%	3.8-7.2%	Accuracy:	98.3-103.9%	98-108.3%	95.7-104.8%	LLOQ:	31.3 pg/mL	7.5 IU/mL	0.906 ng/mL	ULOQ:	1500 pg/mL	50 IU/mL	100.656 ng/mL	LQC:	75 pg/mL	12.5 IU/mL	2 ng/mL	Precision:	6.4%	10.8%	13.3%	Accuracy:	100.1%	104.7%	87.9%	MQC:	400 pg/mL		15 ng/mL	Precision:	5.8%		8.4%	Accuracy:	98.7%		87.6%	HQC:	1100 pg/mL	27.5 IU/mL	75 ng/mL	Precision:	5.8%	16.5%	9.3%	Accuracy:	100%	112.6%	91.7%
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Accuracy:	100%	112.6%	91.7%																																																																		

Population/ Demographics

- 69 subjects were enrolled and randomized; 65 subjects completed the study; 68 subjects received at least 1 dose of study treatment and were included in the analysis.
- Median age of 33.2 years (18-46 years); predominantly white (77%); male (52%); median BMI of 26.36 kg/m²
- PK analysis population: all subjects who received at least 1 dose of study treatment and had sufficient samples with measurable drug concentration

PK and PD Results

PK results: The representative PK results obtained using ELISA assay were presented below (similar PK profile of BIIB017 using different assays).

Figure 1: Median of BIIB017 serum concentration based on the ELISA assay by treatment group

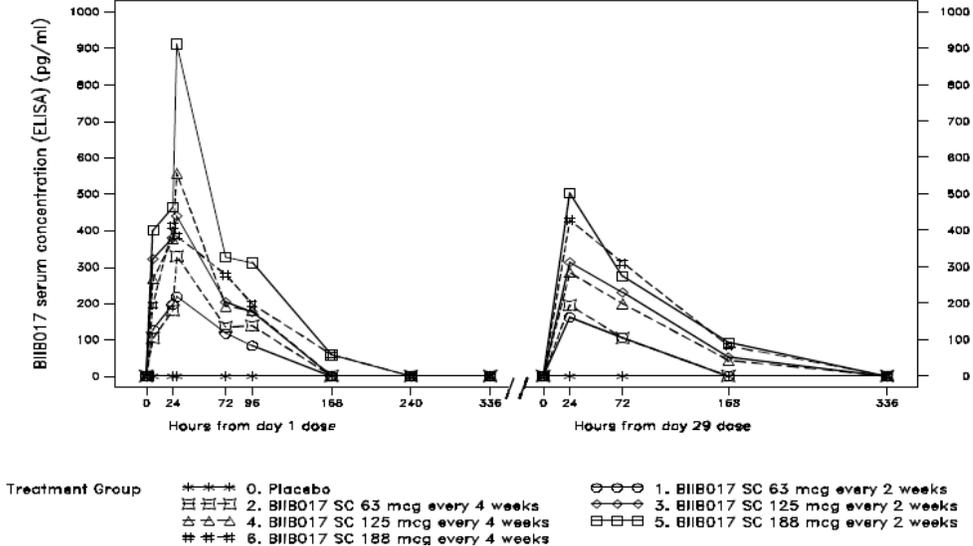


Figure 2. Pharmacokinetic profiles of BIIB017 following SC administration at a dose of 125 µg at a frequency of every 2 weeks (Q2W) or every 4 weeks (Q4W)

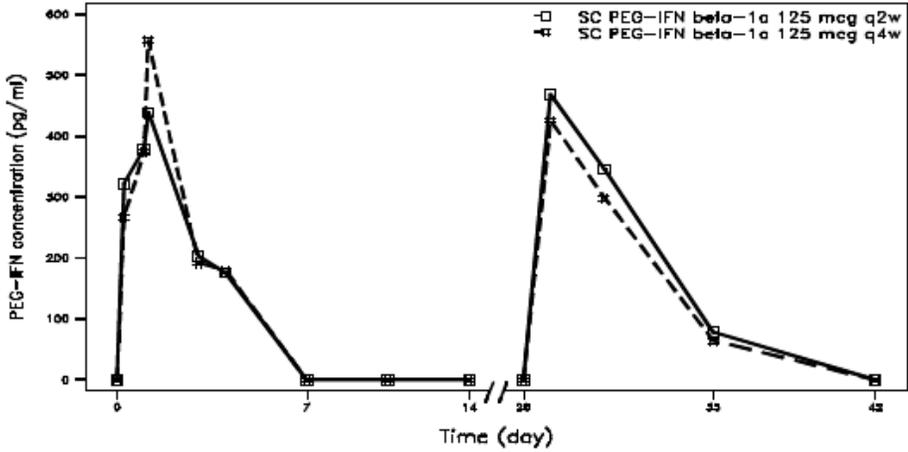


Table 1. Mean (SD) pharmacokinetic parameters of BIIB017 following a single and repeated SC dose administration every 2 weeks

PK Parameter	Day 1 (First Dose)		
	63 (µg)	125 (µg)	188 (µg)
AUC168 h (h*ng/mL)	14.9 (4.9)	37.1 (29.9)	42.7 (22.3)
Cmax (ng/mL)	0.19 (0.07)	0.51 (0.40)	0.55 (0.35)
Median Tmax (h)	24.0	24.0	24.0
t1/2 (h)	67 (50)	42 (2.2)	48 (16)
PK Parameter	Day 29 (Repeated Doses)		
	63 (µg)	125 (µg)	188 (µg)
AUC168 h (h*ng/mL)	12.7 (5.3)	33.4 (20.3)	46.6 (29.1)
Cmax (ng/mL)	0.15 (0.06)	0.35 (0.16)	0.53 (0.33)
Median Tmax (h)	24.0	24.0	24.0
t1/2 (h)	62 (7.4)	67.2 (22.2)	62.3(17.4)

+ Based on ELISA assay; values are presented as Mean (SD)

PD results:

Figure 3. Pharmacodynamic response profiles of neopterin following SC administration at a dose of 125 µg at a frequency of every 2 weeks (Q2W) or every 4 weeks (Q4W)

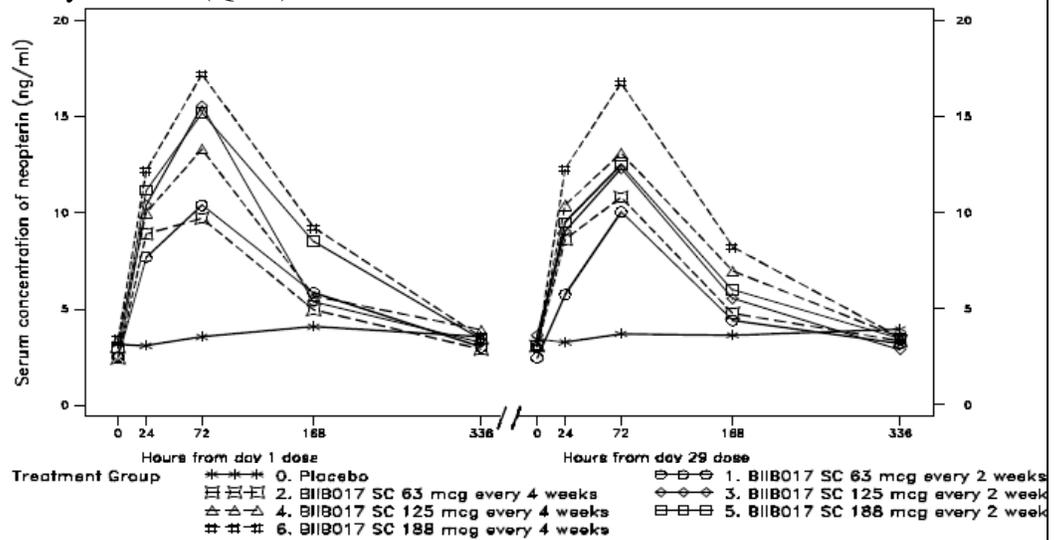


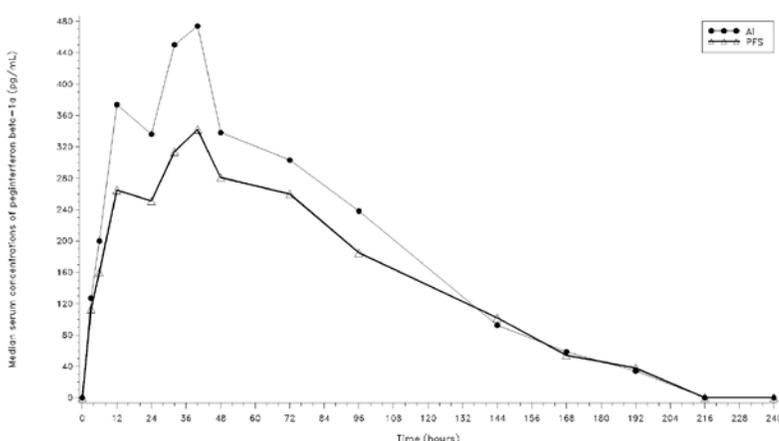
Table 2. Summary of neopterin PD parameters

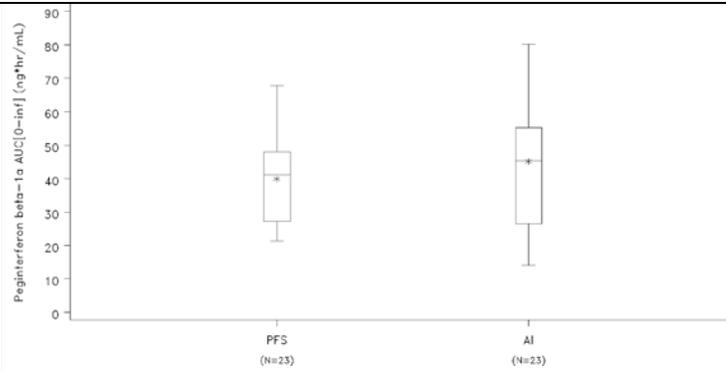
Dose (µg)	Study	Subjects	Route	No. of Dose		E _{AUCt} * (ng*hr/mL)	E _{max} (ng/mL)	E _{Tmax} (h)
63	105HV102	HV	SC	1 (Q2W)	Median	1190	8.40	72.0
					Mean	1150	8.80	71.9
					SD	461	3.50	0.30
125	105HV102	HV	SC	1 (Q2W)	Median	1375	12.7	72.0
					Mean	1370	11.6	67.1
					SD	512	4.90	15.1
188	105HV102	HV	SC	1 (Q2W)	Median	1895	12.4	72.0
					Mean	1830	12.5	72.0
					SD	468	2.70	0.00

		63	105HV102	HV	SC	1 (Q4W)	Median Mean SD	865 975 317	8.70 8.50 3.00	72.0 61.3 21.2
		125	105HV102	HV	SC	1 (Q4W)	Median Mean SD	1020 1310 786	9.80 9.70 4.00	71.0 50.6 25.2
		188	105HV102	HV	SC	1 (Q4W)	Median Mean SD	1845 1720 604	13.4 13.1 4.70	72.0 72.5 3.50
		63	105HV102	HV	SC	3 (Q2W)	Median Mean SD	919 1030 538	8.00 7.80 3.20	72.0 72.1 0.30
		125	105HV102	HV	SC	3 (Q2W)	Median Mean SD	1270 1390 738	9.70 10.1 5.50	72.0 67.2 15.2
		188	105HV102	HV	SC	3 (Q2W)	Median Mean SD	1410 1640 792	9.60 10.5 4.60	72.0 66.7 16.0
		63	105HV102	HV	SC	2 (Q4W)	Median Mean SD	1030 1090 492	8.10 8.20 2.20	72.0 66.6 16.0
		125	105HV102	HV	SC	2 (Q4W)	Median Mean SD	1145 1140 800	8.20 9.10 5.60	72.0 61.3 21.2
		188	105HV102	HV	SC	2 (Q4W)	Median Mean SD	1560 1630 768	12.7 12.8 5.30	71.0 52.6 24.6
Safety	<ul style="list-style-type: none"> • No discontinuations or withdrawals from the study due to AEs. • Overall, BIIB017 SC was reported to be generally well tolerated over a period of 2 months and up to 4 injections. • The most frequently reported AEs related to study treatment included headache, myalgia, chills, and pyrexia which were anticipated from the known profile of IFN β. Severe AEs were experienced by 1 or 2 subjects in each of the higher BIIB017 dose groups. • Flu-like symptoms: 63 μg and 125 μg BIIB017 dosed Q2W and Q4W resulted in a lower incidence of flu-like symptoms than the BIIB017 188 μg dose group. The overall incidence of flu-like symptoms increased with increasing BIIB017 dosing, and was greatest in the highest dose groups; most flu-like symptoms were of mild severity and were of short duration. The incidence of flu-like symptoms appeared to be attenuated more over time with repeat dosing every 2 weeks compared to dosing every 4 weeks. • 63 μg and 125 μg Q2W and Q4W resulted in a Low WBC, ANC, and platelets than the 188 μg dose group. • 63 μg and 125 μg dosed Q2W and Q4W resulted in a lower severity of injection site reactions than the 188 μg dose group. • Reported similar overall safety profile between dosing frequency groups (every 2 weeks and every 4 weeks) 									
Immunogenicity	<p>Antibody samples were collected pre-dose on Days 1, 29 and 71:</p> <ul style="list-style-type: none"> • No subjects in this study developed Anti-IFN β antibodies 									

	<ul style="list-style-type: none"> • Four out of 58 BIIB017- treated subjects tested positive for anti-PEG antibodies prior to Day 1 of dosing and the titer values of anti-PEG antibodies remained relatively constant following multiple administrations of BIIB017. • None of the subjects who tested negative at baseline developed anti-PEG antibodies after BIIB017 treatment. • Assessment for the potential impact of anti-PEG antibodies on PK and PD was not performed.
Conclusion	<p><i>Pharmacokinetics:</i></p> <ul style="list-style-type: none"> • The serum concentration of BIIB017 peaked at approximately 24h post-dose, followed by a mono-phasic decline. • The AUC_{168h} and C_{max} increased in an approximately dose-proportional manner. • There was a lack of accumulation for both dosing regimens • The t_{1/2} ranged from 36h to 67h across the different treatment groups. The t_{1/2} for the 125µg SC every 2 weeks or every 4 weeks regimen was 46.2h and 35.7h, respectively. • Drug concentrations were generally non-detectable by 14 days post-dose and no drug accumulation occurred for either dosing frequency. <p><i>Pharmacodynamics:</i></p> <ul style="list-style-type: none"> • Serum neopterin concentration peaked at approximately 72h post-dose and then returned to baseline level within 2 weeks post-dose. However, neopterin responses (EAUC-336h and E_{max}) did not reach plateau at the highest 188 µg dose. • Neopterin induction increased in a less than dose-proportional manner for both E_{max} and EAUC_{336h}. • The PD response profiles and parameters within treatment groups were similar on Days 1 (single dose) and 29 (repeat dose). <p><i>Overall:</i> BIIB017 125 mcg SC dosed Q2W or Q4W was reported to be the highest well-tolerated dose regimen assessed, based on safety and PK/PD results of this study.</p>

Study Report #	105HV103																																					
Title	A Randomized, Open-Label, Crossover Phase 1 Study to Evaluate the Pharmacokinetic Profile, Safety, and Tolerability of Peginterferon Beta-1a (BIIB017) Delivered by Pre-filled Syringe (PFS) or Autoinjector in Healthy Volunteers																																					
Investigator/Center	Mark Matson, MD, Prism Research, Saint Paul, Minnesota																																					
Study Dates	June 25, 2012 - October 25, 2012																																					
Objectives	To assess the PK profiles, safety and tolerability of peginterferon beta-1a delivered by the single-use autoinjector (AI) and PFS in healthy volunteers																																					
Formulation	Treatment	Item Code (Lot #)																																				
	125 µg BIIB017, SC, AI injection	I10049 (VVJK49 and VVKB14)																																				
	125 µg BIIB017, SC, PFS injection	I10049 (VVJK49) and I50249 (VVKA11)																																				
Study Design	<ul style="list-style-type: none"> Phase 1, randomized (1:1 ratio), open-label, 2-sequence, 2-period crossover study in 55 healthy males and females, aged 18-45 years, with a BMI of 18-35 kg/m² and a BW ≥50 kg Treatment period: eligible subjects were randomized in a 1:1 ratio to receive a single dose on Day 1 delivered by either PFS or autoinjector, followed by a single dose delivered by the other device on Day 22. PK serum samples were collected over 240-h postdose. Follow-up period: on Day 50 																																					
PK and PD Assessments	<ul style="list-style-type: none"> Serum samples for BIIB017: on Days 4, 5, 7, 8, 9, 10, and 11 and on Days 25, 26, 28, 29, 30, 31, and 32 (over 240-h postdose) PK parameters: C_{max}, T_{max}, AUC_{0-inf}, AUC_{0-240h}, AUC_{0-168h}, t_{1/2}, and CL/F 																																					
Statistical Analysis	<ul style="list-style-type: none"> Descriptive statistics/summary and Ln-transformed AUC_{0-inf}, AUC_{0-240h}, and C_{max} were calculated for comparison, and the mean, standard error, and 95% confidence interval for the mean were presented by injection type. 																																					
Bioanalytical Methods	<ul style="list-style-type: none"> Enzyme-linked immunosorbent assay (ELISA) for Avonex and BIIB017 (at (b) (4) which is validated. <p>Table. Assay performance</p> <table border="1"> <thead> <tr> <th colspan="2">Analyte</th> <th>BIIB017 (serum)</th> </tr> </thead> <tbody> <tr> <td colspan="3">Method: ELISA</td> </tr> <tr> <td>Standard Curve:</td> <td>Range:</td> <td>31.25–1500 pg/mL</td> </tr> <tr> <td></td> <td>Precision:</td> <td>0.9-2.8%</td> </tr> <tr> <td></td> <td>Accuracy:</td> <td>99.2-103.8%</td> </tr> <tr> <td>LLOQ:</td> <td></td> <td>31.3 pg/mL</td> </tr> <tr> <td>ULOQ:</td> <td></td> <td>1500 pg/mL</td> </tr> <tr> <td>LQC:</td> <td></td> <td>75 pg/mL</td> </tr> <tr> <td></td> <td>Precision:</td> <td>5.2%</td> </tr> <tr> <td></td> <td>Accuracy:</td> <td>96.7%</td> </tr> <tr> <td>MQC:</td> <td></td> <td>400 pg/mL</td> </tr> <tr> <td></td> <td>Precision:</td> <td>3.4%</td> </tr> </tbody> </table>		Analyte		BIIB017 (serum)	Method: ELISA			Standard Curve:	Range:	31.25–1500 pg/mL		Precision:	0.9-2.8%		Accuracy:	99.2-103.8%	LLOQ:		31.3 pg/mL	ULOQ:		1500 pg/mL	LQC:		75 pg/mL		Precision:	5.2%		Accuracy:	96.7%	MQC:		400 pg/mL		Precision:	3.4%
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<p>Population/ Demographics</p>	<ul style="list-style-type: none"> • N=55 enrolled and included in the safety population (N=26 in the PFS/autoinjector group and N=29 in the autoinjector/PFS group) • N=23 included in the PK population (N=12 in the PFS/autoinjector group and N=11 in the autoinjector/PFS group); 1 subject completed the study but was excluded from the PK population because of undetectable peginterferon beta-1a concentration after PFS treatment likely due to an unusually high anti-PEG antibody titer level of 3200 which could interfere with the assay. • Mean age of 28.4 years (19-44 years); mostly white (70%) and male (61%); mean BMI of 23.83 kg/m² (19.5-28.2 kg/m²) • PK analysis population: on all subjects who received a dose of study treatment but both devices and had sufficient concentrations through 240-h; additional PK analyses on subjects with negative anti-PEG antibody in both periods 								
<p>PK Results</p>	<p>Figure 1. (Top) Median Serum Concentrations of BIIB017 Following Single-Dose Administration of BIIB017 125 µg SC via PFS and PFP (AI); (Bottom) Box-Plots of BIIB017 Exposure comparison</p>  <p>Figure 2. Comparison (box-plots) of AUC_{0-inf} and C_{max} of BIIB017 125 µg SC via PFS and PFP (AI)</p> <p>AUC_{0-inf} (ng*h/mL):</p>								



Cmax (pg/mL):

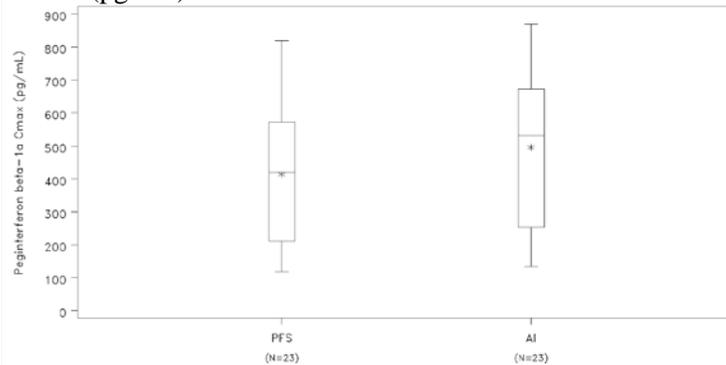


Table 1. Summary of Statistical Analysis for Relative Bioavailability of BIIB017 from Single Injection of PFS vs. PFP (AI)

Parameter	N	PFP (AI)	PFS	Geometric Mean Ratio (PFP/PFS)	90% CI
AUCinf (ng·h/mL)	23	41.040	38.304	1.07	(0.92, 1.24)
Cmax (pg/mL)	23	427.20	364.87	1.17	(0.90, 1.53)

* One subject was excluded in PK analysis due to non-detectable BIIB017 level.

* Exposure values expressed as geometric means

- The CL/F values from both devices were similar at 3.42 L/h, while t1/2 were 52.3 and 43.4 h for PFS and PFP/AI, respectively.
- Summary statistics for subjects with negative anti-PEG antibody at both periods showed similar PK parameters between PFS and autoinjector, consistent with the results observed in the PK population.
- The variability (%CV) was mostly in 32~68% for key PK parameters, which contributed to the 90% CI being outside of BE limits.

Immunogenicity

- Antibodies against the PEG moiety were measured prior to the injection on Days 1 and 22 using a validated ELISA.
- Five subjects (9% of the 55 subjects randomized and enrolled) tested positive for anti-PEG antibodies in the study; 4 subjects on Day 1 or Day 22 and 1 subject on both Days 1 and 22. Three of these subjects were included

	in the PK population.
Safety	<ul style="list-style-type: none"> • Similar incidence of treatment-emergent AEs was reported in subjects receiving study treatment delivered by PFS or autoinjector (100% and 98%, respectively). Most AEs were mild or moderate in severity. The incidence of severe AEs was similar between the 2 groups (PFS 24%, autoinjector 26%). There were no deaths or serious AEs reported in this study. Only 2 subjects discontinued study treatment due to an AE (1 subject in each injection type group), and one of these subjects was also withdrawn from the study due to an AE. • Most common reported AEs: neutropenia, influenza-like illness, lymphopenia, injection site erythema, leukopenia, headache, injection site pain, vessel puncture site hemorrhage, fatigue, dizziness, nausea, pain, and injection site induration • Single-dose 125 µg BIIB017 SC reported to be well-tolerated by both devices with similar safety profile and similar occurrence of injection site reactions.
Conclusion	<ul style="list-style-type: none"> • Similar PK parameter results were observed for the 2 injection types based on geometric means and on the percent difference in the geometric means. The percent difference in geometric means (autoinjector-PFS]/PFS) was 10.4% for AUC_{0-240h}, 7.1% for AUC_{0-inf}, 17.1% for C_{max}, and -13.3% for t_{1/2}. • Collectively, considering the high variability associated with PK parameters, sample size, overall similar exposure (AUC and C_{max}), and the similar safety and tolerability, the BIIB017 exposure from these two devices can be considered similar even though the 90% CIs are not strictly confined in the traditional BE limits.

Study Report #	105RI101																																					
Title	An Open-Label, Single-dose, Pharmacokinetic, Pharmacodynamic, and Safety Study of PEGylated Interferon Beta-1a (BIIB017) in Healthy Subjects and Subjects with Renal Impairment																																					
Investigator/Center	Mark A. Matson, MD at PRISM Research, St. Paul, MN, US																																					
Study Dates	May 04, 2010 – August 03, 2011																																					
Objectives	<ul style="list-style-type: none"> To evaluate the single-dose PK of BIIB017 SC in subjects with renal impairment and in subjects with normal renal function (healthy subjects). To determine the safety and tolerability and effect of renal impairment on PD of single-dose of BIIB017 SC. 																																					
Formulation	Treatment	Item Code (Lot #)																																				
	63 µg (0.13 mg/mL) BIIB017 (pre-filled syringe)	I41042 (45-09-095)																																				
	125 µg (0.25 mg/mL) BIIB017 (pre-filled syringe)	I41041 (45-09-094)																																				
Study Design	<ul style="list-style-type: none"> Phase 1, single-dose, open-label, multicenter, non-randomized, serial-group study of BIIB017 in 35 eligible subjects with normal, mild, moderate, severe renal impairment, and end stage renal disease (ESRD) renal function groups, aged 18-75 years, with a BMI of 18-35 kg/m² and a BW ≥50 kg Subjects: stratified by GFR (using Cockcroft-Gault formula) 																																					
	<table border="1"> <thead> <tr> <th>Group</th> <th>Description</th> <th>Estimated Creatinine Clearance (mL/min)¹</th> <th>Dose (SC)</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>Normal renal function (healthy subjects)</td> <td>>80</td> <td>125 mcg</td> <td>6</td> </tr> <tr> <td>2</td> <td>Mild renal impairment</td> <td>>50 to ≤80</td> <td>63 mcg 125 mcg</td> <td>3 6</td> </tr> <tr> <td>3</td> <td>Moderate renal impairment</td> <td>>30 to ≤50</td> <td>125 mcg</td> <td>6</td> </tr> <tr> <td>4</td> <td>Severe renal impairment</td> <td>≤30</td> <td>63 mcg 125 mcg</td> <td>2 6</td> </tr> <tr> <td>5</td> <td>ESRD</td> <td>Require hemodialysis 2 to 3 times a week</td> <td>125 mcg</td> <td>6</td> </tr> <tr> <td colspan="4" style="text-align: right;">Total:</td> <td>35</td> </tr> </tbody> </table> <p>* GFR: defined by estimation of creatinine clearance using the Cockcroft-Gault formula</p> <ul style="list-style-type: none"> Three subjects were enrolled and dosed with BIIB017 63 mcg SC in the mild renal function group and 2 subjects were enrolled and dosed with BIIB017 63 mcg SC in the severe renal function group. Six subjects each in the normal, mild, moderate, severe, and ESRD group were dosed with BIIB017 125 µg SC. Subjects received treatment on Day 1 and were allowed to leave the clinic on Day 3 pending safety observation, and follow-up safety observations to Day 29. Groups 1-4 were dosed on Day 1 with 72-h PK/PD sampling and returned to the clinic on Days 5, 8, 11, 15, 18, 22, 25, and 29 for outpatient visits Group 5 was dosed on Day 1 when hemodynamically stable (~2 hours post-hemodialysis) with 72-h PK/PD sampling taken within 2 h before and between 1-2 h after hemodialysis. Subjects in Group 5 remained in the clinic until the first post-hemodialysis PK/PD sampling time point was completed. Duration: 9 weeks, including 28-day screening, 28-day PK/PD assessment, 				Group	Description	Estimated Creatinine Clearance (mL/min) ¹	Dose (SC)	N	1	Normal renal function (healthy subjects)	>80	125 mcg	6	2	Mild renal impairment	>50 to ≤80	63 mcg 125 mcg	3 6	3	Moderate renal impairment	>30 to ≤50	125 mcg	6	4	Severe renal impairment	≤30	63 mcg 125 mcg	2 6	5	ESRD	Require hemodialysis 2 to 3 times a week	125 mcg	6	Total:			
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	and follow-up visit 1-week after the last PK/PD sampling visit.																																																
PK and PD Assessments	<ul style="list-style-type: none"> • Serum BIIB017 samples: predose and at 6, 12, 24, 36, 48, 72, 96, 168, 240, 336, 408, 504, 576, and 672 h postdose • Serum neopterin samples: predose and at 24, 36, 48, 72, 96, 168, 240, 336, 408, 504, 576, and 672 h postdose • Antibody samples (BABs and NABs to IFN β-1a, BABs to PE): predose and at 336 and 672 h postdose • BIIB017: C_{max}, T_{max}, AUC_t, AUC_{336h}, AUC_{inf}, t_{1/2}, V_d/F, and CL/F • Neopterin: baseline (pre-dose), E_{max} (maximum serum concentration), E_{Tmax} (time to reach maximum serum concentration), and E_{AUC672h}. 																																																
Statistical Analysis	<ul style="list-style-type: none"> • Summary statistics were provided by renal function group defined by estimated creatinine clearance (eCRCL) using the Cockcroft-Gault formula. The relationship between AUC and renal function was explored. • All PK and PD results using non-compartmental analysis methods were also summarized by renal function group defined by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) calculation. The area under the concentration-time curve was calculated using the trapezoidal rule with actual post-dose time. 																																																
Bioanalytical Methods	<ul style="list-style-type: none"> • BIIB017: Enzyme-linked immunosorbent assay (ELISA), with the LLOQ being 31.3 pg/mL and the ULOQ being 1500 pg/mL (at (b) (4)) • Neopterin: Competitive binding enzyme immunoassay (ImmucheM™, (b) (4)) (at (b) (4)) <p>Assays are validated and acceptable.</p> <p>Table. Assay performance for BIIB017 and neopterin</p> <table border="1"> <thead> <tr> <th>Analyte</th> <th>BIIB017 (serum)</th> <th>Neopterin (serum)</th> </tr> </thead> <tbody> <tr> <td>Method:</td> <td>ELISA</td> <td>Enzyme immunoassay</td> </tr> <tr> <td>Standard Curve:</td> <td>Range: 31.25–1500 pg/mL</td> <td>1.293–101.043 ng/mL</td> </tr> <tr> <td></td> <td>Precision: 1.6–10.4%</td> <td>3.4–6.3%</td> </tr> <tr> <td></td> <td>Accuracy: 93.62–103.0%</td> <td>94.7–106.0%</td> </tr> <tr> <td>LLOQ:</td> <td>31.3 pg/mL</td> <td>1.293 ng/mL</td> </tr> <tr> <td>ULOQ:</td> <td>1500 pg/mL</td> <td>101.043 ng/mL</td> </tr> <tr> <td>LQC:</td> <td>75 pg/mL</td> <td>2 ng/mL</td> </tr> <tr> <td></td> <td>Precision: 6.3%</td> <td>10.6%</td> </tr> <tr> <td></td> <td>Accuracy: 106.4%</td> <td>101.2%</td> </tr> <tr> <td>MQC:</td> <td>400 pg/mL</td> <td>15 ng/mL</td> </tr> <tr> <td></td> <td>Precision: 6.0%</td> <td>9.4%</td> </tr> <tr> <td></td> <td>Accuracy: 102.8%</td> <td>102.4%</td> </tr> <tr> <td>HQC:</td> <td>1100 pg/mL</td> <td>75 ng/mL</td> </tr> <tr> <td></td> <td>Precision: 5.1%</td> <td>9.6%</td> </tr> <tr> <td></td> <td>Accuracy: 100.4%</td> <td>99.9%</td> </tr> </tbody> </table>	Analyte	BIIB017 (serum)	Neopterin (serum)	Method:	ELISA	Enzyme immunoassay	Standard Curve:	Range: 31.25–1500 pg/mL	1.293–101.043 ng/mL		Precision: 1.6–10.4%	3.4–6.3%		Accuracy: 93.62–103.0%	94.7–106.0%	LLOQ:	31.3 pg/mL	1.293 ng/mL	ULOQ:	1500 pg/mL	101.043 ng/mL	LQC:	75 pg/mL	2 ng/mL		Precision: 6.3%	10.6%		Accuracy: 106.4%	101.2%	MQC:	400 pg/mL	15 ng/mL		Precision: 6.0%	9.4%		Accuracy: 102.8%	102.4%	HQC:	1100 pg/mL	75 ng/mL		Precision: 5.1%	9.6%		Accuracy: 100.4%	99.9%
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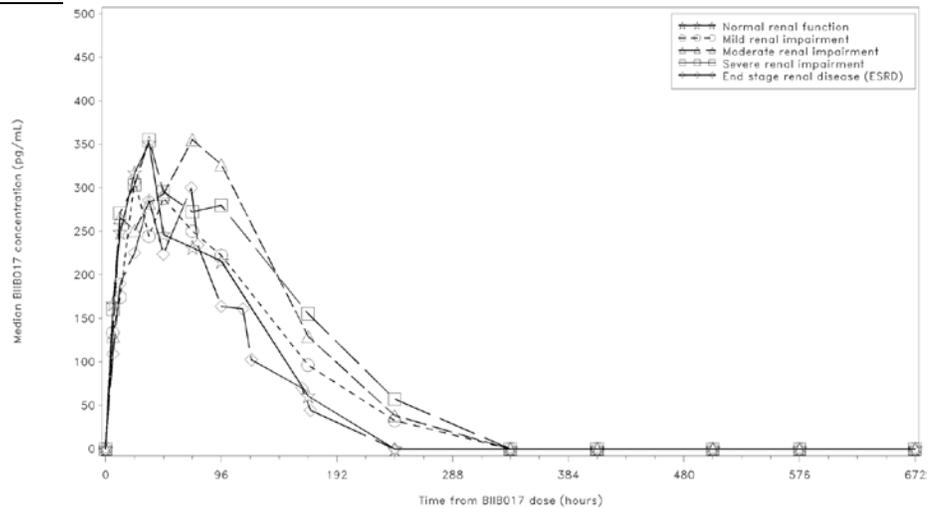
Population/
Demographics

- All 35 subjects who were enrolled and dosed were included in the PK and PD analysis populations.
- Overall, the mean age of the safety population was 58.9 years (36-75 years).
- Overall, a greater proportion of subjects in the safety population were male (63%).
- Overall, the majority of subjects in the safety population were white (74%), and 23% of subjects in the overall safety population were black or African American.
- Mean BMI of the safety population was 27.94 kg/m² (20.9-35.9 kg/m²).

PK Results

Figure 1. Serum concentration-time profiles of BIIB017 and neopterin in patients with renal impairment vs. normal controls based on creatinine clearance using Cockcroft-Gault equation

BIIB017:



Neopterin:

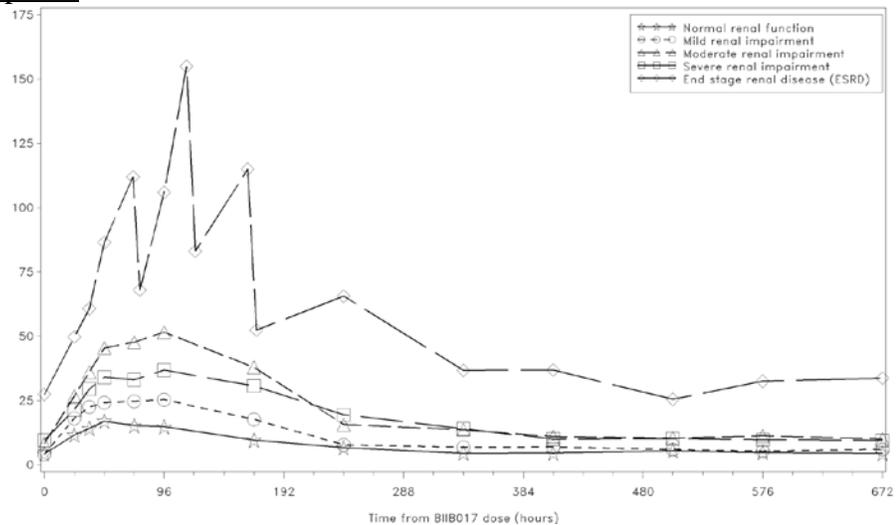
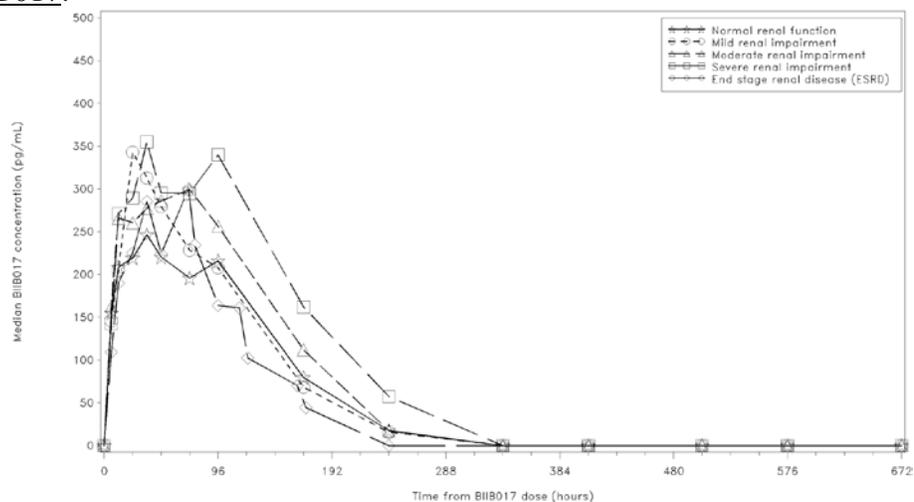


Figure 2. Serum concentration-time profiles of BIIB017 and neopterin in patients with renal impairment vs. normal controls based on eGFR using MDRD equation

BIIB017:



Neopterin:

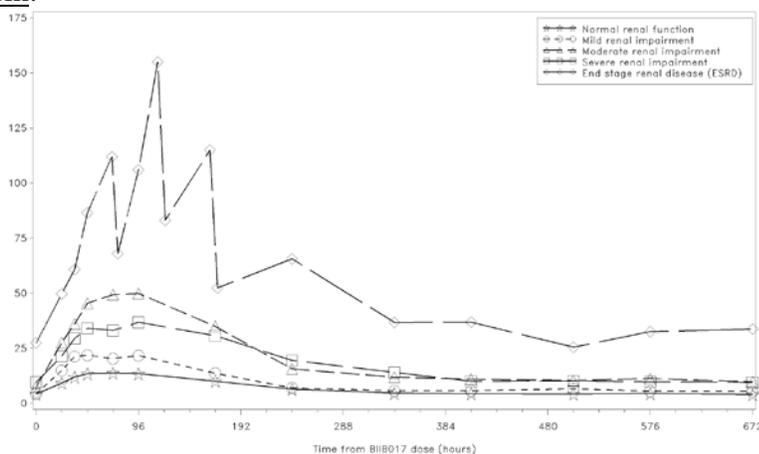


Table 1. Summary of key PK parameters of BIIB017 in subjects with renal impairment vs. normal controls

Subjects	AUC _{336h} (ng·h/mL)	AUC _∞ (ng·h/mL)	C _{max} (pg/mL)	T _{max} (h)	t _{1/2} (h)
Normal Controls	37.0 (13.6)	40.1 (13.1)	336 (139)	44.0 (28.1)	53.8 (14.3)
Mild RI	49.7 (24.9)	51.8 (24.5)	400 (96.7)	40.0 (18.1)	52.8 (16.6)
Moderate RI	51.1 (16.0)	52.9 (16.9)	460 (322)	52.0 (32.8)	48.8 (12.1)
Severe RI	55.3 (16.0)	64.9 (18.7)	492 (307)	34.0 (22.0)	82.4 (31.9)
ESRD (HD)	37.3 (26.4)	38.9 (25.9)	342 (224)	55.7 (20.1)	46.6 (19.2)

- Data presented as Mean (SD); T_{max} presented as Median (SD)

Table 2. Summary of key PK parameters of neopterin in subjects with renal impairment vs. normal controls

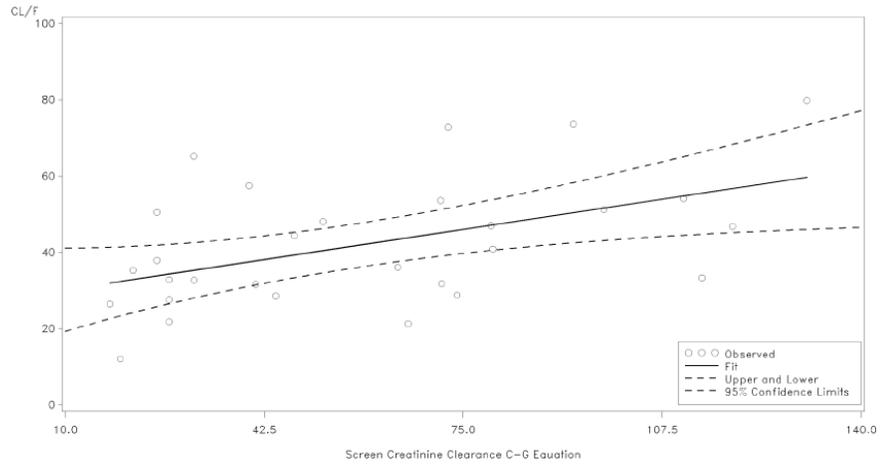
Subjects	EAUC _t (ng·h/mL)	E _{max} (ng/mL)	ET _{max} (h)
Normal Controls	2600 (1340)	15.2 (7.69)	48.0 (22.0)
Mild RI	5350 (3310)	31.3 (20.9)	72.0 (18.0)
Moderate RI	6670 (2710)	37.7 (14.5)	84.0 (28.0)
Severe RI	6090 (2590)	31.3 (7.65)	60.0 (48.6)

ESRD (HD)	22100 (7910)	115 (48.7)	117 (37.0)
-----------	--------------	------------	------------

- Data presented as Mean (SD); Tmax presented as Median (SD)

Relationships between renal function and PK parameters of BIIB017 renal function are presented in Figures below. Similar results were obtained for neopterin and thus are not presented.

Figure 3: BIIB017 CL/F vs. eCRCL



BIIB017 CL/F vs. eGFR

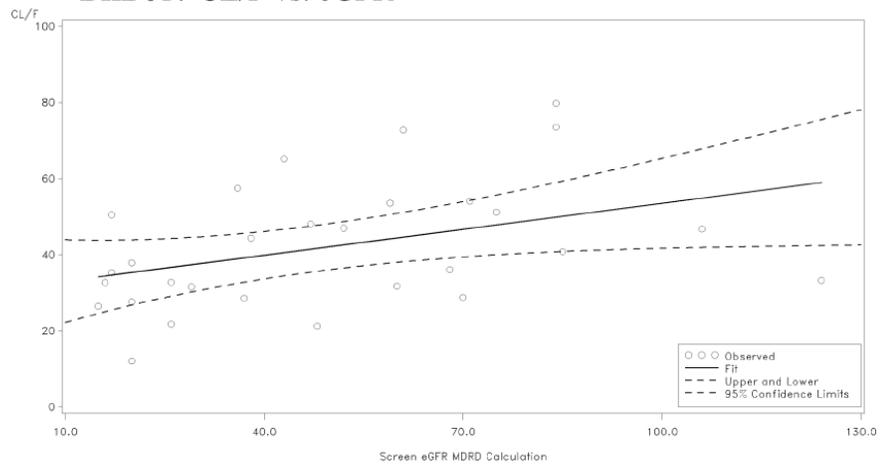


Table 3. Exposure comparisons for BIIB017 and neopterin in subjects with renal impairment vs. normal controls

BIIB017:

Classification Method	Parameter	Renal Impairment			
		Mild	Moderate	Severe	ESRD/HD
eCRCL (C-G):					
	AUC336h	1.30	1.40	1.53	0.88
	Cmax	1.27	1.26	1.42	0.93
eGFR (MDRD):					
	AUC336h	1.13	1.41	1.62	0.90
	Cmax	1.42	1.60	1.70	1.11

- Values represent geometric mean ratio (compared to normal control).
- Hemodialysis: 24% decrease in BIIB017 level
- Tmax ~doubled in ESRD

Neopterin:

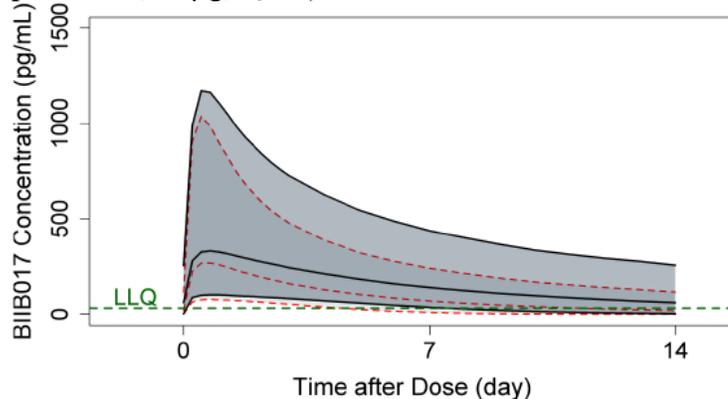
Classification Method	Parameter	Renal Impairment			
		Mild	Moderate	Severe	ESRD/HD
eCRCL (C-G):					
	EAUC672h	1.93	2.57	2.37	8.93
	Emax	1.92	2.54	2.20	7.60

- Values represent geometric mean ratio (compared to normal control).
- Baseline values were similar between methods.
- Hemodialysis: 46% decrease in neopterin level
- ETmax ~doubled in ESRD

Simulation by the Applicant: [verified by the Pharmacometrics review team, also see Consult Review in Section 4.1]

- Not part of the renal impairment study, but performed by the Applicant to support a proposed no dosage adjustment claim

Figure 4. Simulated steady-state PK profiles in normal vs. severe renal impairment (125µg, Q2W)



The red dashed lines from top to bottom represents the 95th, 50th, and 5th concentration percentiles in MS patients with normal renal function, respectively; the black solid lines represent the 95th, 50th and 5th concentration percentiles in MS patients with severe renal impairment, respectively.

Immunogenicity

Antibody samples were tested for predose on Day 1.

- Testing for IFN -1a antibodies was not conducted in this study.
- One ESRD subject was tested positive for anti-PEG antibodies at Baseline. However, testing for anti-PEG antibodies was not conducted for post-treatment samples.

Safety	<ul style="list-style-type: none"> • The incidences of AEs were similar across all study groups, with mild or moderate in severity. • The most common AEs were chills, headache, influenza-like illness, pyrexia, nausea, back pain, diarrhea, and dizziness. • No death or discontinuation from the study due to an treatment-related AE was reported. • No clinically significant changes were reported from baseline in safety laboratory results, vital signs, physical examinations, or ECG results and the degree of renal impairment. • Single dose of BIIB017 125 mcg SC was reported to be well-tolerated in subjects with normal renal function or with renal impairment.
Conclusion	<ul style="list-style-type: none"> • The progressive increases in BIIB017 exposure (C_{max} and AUC) were observed in increasing severity of renal impairment after single dose administration of BIIB017 125 µg. • In subjects with mild, moderate, and severe renal impairment, there was a 30%, 40%, and 53% increase in AUC_{336h} geometric means, respectively, and a 27%, 26%, and 42% increase in C_{max} geometric means, respectively, compared to normal controls. • The CL of BIIB017 was shown to be correlated with renal function. • The elimination t_{1/2} of BIIB017 was prolonged (77.8 h) in patients with severe renal function, compared to those among other renal function groups (44.2 ~52.4 h). • For the ESRD subjects, each hemodialysis reduced BIIB017 concentration by approximately 24% resulted in similar BIIB017 exposure to that of normal controls. • The PD responses (E_{AUC672h} and E_{max}) of neopterin also increased with increasing degrees of renal impairment, attributed to the reduced neopterin renal clearance and possibly the increased BIIB017 exposure. • It is noted that similar PK and PD results were reported when renal function was classified by estimated glomerular filtration rate (eGFR) calculated from the Modification of Diet in Renal Disease (MDRD) equation.
Comment	<p>For dosing consideration, although there is no indication of serious AE at the higher dose (small numbers and short duration), cautionary language may be used patients with severe renal impairment because of the following reasons:</p> <ul style="list-style-type: none"> • Similar C_{max} to those observed at 188 µg dose in Study 105HV102 • Dose-dependent AE (flu-like symptom) from 63 to 188 µg dose • Dose-dependent changes in hematology parameters (WBC count) from 63 to 188 µg dose • No indication of serious AE at the higher dose (small numbers and short duration)

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/s/

TA-CHEN WU
08/05/2014

YUXIN MEN
08/05/2014

CLINICAL PHARMACOLOGY REVIEW

BLA:	125499
Brand Name:	PLEGRIDY™ (BIIB017)
Generic Name:	PEGylated Interferon Beta-1a
Dosage Form & Strength:	Clear liquid solution containing [REDACTED] (b) (4) [REDACTED] of peginterferon beta-1a
Indication:	Treatment of patients with relapsing forms of Multiple Sclerosis (RMS)
Applicant:	Biogen Idec, Inc.
Submission:	505(b)(1), Standard
Submission Date:	5/15/2013
OND Division:	OND-1/Division of Neurology Drug Products
OCP Divisions:	Clinical Pharmacology DCP-1
Primary Reviewer:	Ta-Chen Wu, Ph.D.
Team Leader:	Angela Men, M.D., Ph.D.
Pharmacometrics Reviewers:	Xiaofeng Wang, Ph.D., Atul Bhattaram, Ph.D.

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1. Executive Summary

The sponsor is seeking approval of Plegridy (BIIB017, PEGylated Interferon Beta-1a or IFN β -1a) as a treatment for adult patients with relapsing forms of Multiple Sclerosis (RMS). BIIB017 belongs to the interferon beta class (e.g., Avonex[®] and Rebif[®]) that are among the commonly used first-line injectable multiple sclerosis (MS) therapies. The exact mechanism of action of IFN β -1a in MS is not fully understood, but it is thought to be similar to the unmodified IFN β -1a but binding to the Type 1 IFN receptors and trigger the associated immunomodulatory activity. The process of covalently conjugating a PEG moiety to a protein can decrease renal clearance and decrease rate of proteolysis, thus extending the terminal half-life (t/12).

The available strengths of Plegridy are (b) (4) in clear liquid solution. Both Prefilled Syringe (PFS) and Prefilled Pen (PFP, or single-use Autoinjector (AI)) are proposed for marketing. The proposed dosing regimen of Plegridy is 125 μ g injected subcutaneously (SC) every 2 weeks (Q2W). Dose titration at the initiation of treatment was proposed to ameliorate flu-like symptoms that can occur at treatment initiation with β -interferons.

To support the approval of the application, the sponsor conducted four Phase 1 clinical pharmacology studies to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of BIIB017, including three Phase 1 studies in healthy volunteers following single or repeated doses (Studies 105HV101, 105HV102, and 105HV103) and one study in renal impairment subjects (Study 105RI101). Study 105HV101 also evaluated the intramuscular (IM) route of administration for BIIB017, compared to SC administration. Among them, Study 105HV103 was designed to compare the PK profile of BIIB017 delivered by prefilled syringe (PFS) or prefilled pen (PFP or AI). Additional PK characterization was carried out in Phase 3 clinical trial with MS patients (Study 105MS301). BIIB017 serum concentration, PD marker concentrations (neopterin and 2',5'-OAS), anti-IFN antibody, and anti-PEG antibody were assessed for BIIB017 biological activity. The Phase 3 program included one pivotal study (Study 105MS301) and an uncontrolled extension study (Study 105MS302) to assess the clinical efficacy and safety in support of the approval. Population PK and PD analyses (PP-12-016-BIIB017) was performed using the data source from Study 105MS301 and Study 105HV102 to assess the potential impact of intrinsic factors and covariates. The relationship between BIIB017 concentrations and efficacy variables was not explored. However, the characteristics of dose-response relationships with respect to the efficacy endpoint (Annualized Relapse Rate (ARR)) and the incidence of flu-like symptoms were evaluated in Study 105MS301 in Subjects with RMS.

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 1 (OCP/DCP-1) has reviewed the submission and finds BLA 125499 acceptable from an OCP perspective provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

1.2 Phase IV Commitment

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics

Single and multiple dose:

- Similar PK profiles and exposure (AUC and C_{max}) between healthy volunteers and MS patients and between single-dose and multiple-dose across studies.
- Similar PK parameters between SC and IM routes of administration.
- Higher exposure and longer t_{1/2} at 63 µg to 188 µg (6 to 18 MIU), compared to a 30 µg IM IFN β-1a (Avonex[®]; 6 MIU) in healthy volunteers.
- Approximately dose-proportional exposure increase in the dose range of 63 to 188 µg in healthy volunteers.
- No accumulation was observed in BIIB017 exposure following multiple doses of 125 µg Q2W or Q4W in MS subjects.
- Disposition was characterized by a one-compartment linear model with a first-order absorption rate using a population PK analysis.
- Increases in AUC_{0-336h} (30%-53%) and C_{max} (26%-42%) were observed in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function.
- High inter-subject variability was observed in healthy volunteers for key PK parameters and in MS patients from Phase 3 trial, with the %CV for AUC_τ, C_{max} and t_{1/2} ranging 41-68%, 74-89% and 45-93%, respectively. The inter-subject variability of clearance and volume of distribution in patients, after accounting for effects of BMI, is 31% and 73%, respectively.

Absorption:

Following SC administration with BIIB017 to MS subjects, the peak concentration was reached between 1 and 1.5 days (i.e., T_{max}) post-dose. The C_{max} was approximately 280 pg/mL following repeat dosing with 125 µg BIIB017 Q2W.

Distribution:

Following repeated dosing with BIIB017 125 µg SC Q2W, BIIB017 was widely distributed with a volume of distribution of approximately 481 L which suggests wide distribution in the body.

Metabolism and Elimination:

BIIB017 is not extensively metabolized in liver. Clearance mechanisms of the protein include catabolism and excretion, with renal elimination being the major pathway.

The process of covalently conjugating a 20KDa PEG moiety extended the terminal t_{1/2} of BIIB017 to approximately 2-fold longer than non-PEGylated interferon beta-1a in

healthy volunteers and was approximately 78h in MS patients. The mean steady-state clearance of peginterferon beta-1a was 4.1 L/h.

Dose/Exposure-Response relationships:

The relationship between BIIB017 concentrations and efficacy variables was not explored. However, the characteristics of dose-response relationships with respect to the efficacy endpoint (Annualized Relapse Rate (ARR)) and side effect (the incidence of flu-like symptoms (FLS)) were evaluated in Study 105MS301 in Subjects with RMS.

BIIB017 125 µg SC administered every 4 weeks and every 2 weeks reduced the annualized relapse rate at Year 1 by 27.5% (p = 0.0114) and 35.6% (p = 0.0007), respectively, compared with placebo. The incidence of FLS was similar between BIIB017 dose frequency groups. Based on broad definition of FLS, the incidence of FLS followed the same pattern, with a higher incidence in both BIIB017 treatment groups (78% total BIIB017) compared with the placebo group (33%). These findings support the proposed dosing regimen with dose titration, which help reduce the incidence of FLS.

Intrinsic factors:

Age, gender, body weight, geographic region:

No significant differences in ARR are observed between male and female patients. The population PK analysis did not show significant effect of sex, body weight, age, geographic region, and other potential significant covariate (such as antibodies) on the PK of BIIB017. The analysis showed that the body mass index (BMI) influenced clearance, volume of distribution, and BIIB017 level. The findings do not warrant dose adjustments based on BMI or other intrinsic factors.

Renal impairment:

Results from a dedicated PK study show that in subjects with mild, moderate, and severe renal impairment, there was a 30%, 40%, and 53% increase in AUC_{336h}, respectively, and a 27%, 26%, and 42% increase in C_{max}, respectively, compared to normal controls. The elimination t_{1/2} of BIIB017 was prolonged (77.8 h) in patients with severe renal impairment. The PD responses (EAUC_{672h} and E_{max}) of neopterin also increased with increasing degrees of renal impairment. Simulation was carried out to compare the steady-state BIIB017 concentration between MS subjects with normal renal function and with severe renal impairment. Since there seems to be lacking in sufficient solid evidence to support a dose reduction in view of the exposure increases (per communication with Medical Officer), close monitoring of AEs (such as flu-like symptoms) in patients with severe renal impairment may be considered.

Immunogenicity:

The incidence of treatment-emergent antibodies to IFN β-1a or PEG was considered low in both healthy volunteers and MS subjects, with majority being transient responses.

PK Comparison between prefilled syringe (PFS) and prefilled pen (PFP):

Single-dose administration of BIIB017 125 µg SC via PFS and PFP (AI) resulted in generally similar PK profiles and comparable key PK parameters. The percent differences

between two injection devices were 10.40% for AUC0-240h, 7.143% for AUC0-inf, and 17.08% for Cmax. The median Tmax occurred at approximately 32 hours from both devices. Considering the high variability associated with PK parameters, sample size, overall similar exposure (AUC and Cmax), and the similar safety and tolerability, the BIIB017 exposure from these two devices can be considered similar in totality even though the 90% CIs are not strictly confined in the traditional BE limits.

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2. Question Based Review

2.1 General Attributes

2.1.1 What are therapeutic indication(s) and the proposed mechanisms of action of Plegridy?

Plegridy (BIIB017; PEGylated Interferon Beta-1a or IFN β -1a) is proposed as a treatment for patients with relapsing forms of Multiple Sclerosis (RMS). BIIB017 belongs to the interferon beta class (e.g., Avonex[®] and Rebif[®]) that are among the commonly used first-line injectable multiple sclerosis (MS) therapies.

The exact mechanism of action of IFN β -1a in MS is not fully understood, but it is thought to be similar to the unmodified IFN β -1a but binding to the Type 1 IFN receptors and trigger the associated immunomodulatory activity.

2.1.2 What are the highlights of physico-chemical properties of the drug substance?

Plegridy (BIIB017), a 166 amino acid glycoprotein with a molecular weight of (b) (4) KDa, is a pegylated form of interferon beta-1a (IFN β -1a) that is pegylated with a single 20kDa methoxypoly (ethyleneglycol)-O-2 methylpropionaldehyde (mPEG) moiety at the N-terminus. (b) (4)

Plegridy is a clear to slightly opalescent, colorless to slightly yellow solution containing approximately (b) (4) BIIB017 in (b) (4) sodium acetate, (b) (4) arginine.HCl, pH 4.8 (b) (4). Drug substance manufacturing process was changed from (b) (4) process (BIIB017-A; for Phase 1 Studies 105HV101 and 105HV102) to (b) (4) process (BIIB017-B; for Phase 3 and for commercialization) [referred to Section 2.5.1 for additional information]. As shown in the Table below, BIIB017-A and BIIB017-B were determined to be analytical comparable by CMC reviewers and no clinical study is warranted.

Table. Description of Drug Substance and Drug Product Used in the Development of BIIB017

Manufacturing Process	BIIB017-A	BIIB017-B
Material Use	Clinical	Clinical/Commercial
Cell Line (CHO)	(b) (4)	(b) (4)
Manufacturing Site	DS: Biogen Idec (Cambridge, MA, USA) DP: Biogen Idec (Cambridge, MA, USA)	DS: Biogen Idec (Cambridge, MA, USA) DP: (b) (4)
Number of Batches	2	8
Fermentation Scale	(b) (4)	(b) (4)

Culture		
Dosage Form	Refrigerated Liquid	Refrigerated Liquid
Formulation of Drug Product	(b) (4) acetic acid/sodium acetate pH 4.8, (b) (4) arginine.HCl (b) (4) Polysorbate 20	(b) (4) acetic acid/sodium acetate pH 4.8, (b) (4) arginine.HCl (b) (4) Polysorbate 20
Concentration of Drug Product	(b) (4)	(b) (4)
Clinical Studies Phase 1	105HV101, 105HV102	105HV103, 105RI101
Phase 3	NA	105MS301, 105MS302

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dosing regimen of Plegridy is 125 µg injected subcutaneously (SC) every 2 weeks (Q2W). Dose titration at the initiation of treatment was proposed to ameliorate flu-like symptoms (FLS) that can occur at treatment initiation with β-interferons. The sponsor proposed that the total daily dose of Plegridy should be administered via SC injection according to the following proposed dosing regimen:

Table. Proposed Dosing Regimen for Plegridy

Dose	Time*	Amount (µg)
Dose 1	Day 1	63 ^a
Dose 2	Week 2	94 ^a
Dose 3	Week 4 and every 2 weeks thereafter	125 (full dose)

* Dosed every 2 weeks

^a. Used in clinical trial for up-titration

2.1.4 What are the proposed strength(s) and dosage forms?

The available strengths of Plegridy are (b) (4) in clear liquid solution. Two delivery devices for marketing were proposed:

1. Prefilled Syringe (PFS):

- Injection: 125 µg of Plegridy per 0.5 mL solution in a single-use prefilled syringe
- Injection: Starter Pack containing 63 µg per 0.5 mL solution in a single-use prefilled syringe and 94 µg per 0.5 mL solution in a single-use prefilled syringe

2. Prefilled Pen (PFP, or single-use Autoinjector (AI)):

- Injection: 125 µg of Plegridy per 0.5 mL solution in a single-use prefilled pen
- Injection: Starter Pack containing 63 µg per 0.5 mL solution in a single-use prefilled pen and 94 µg per 0.5 mL solution in a single-use prefilled pen

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted four Phase 1 clinical pharmacology studies to characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of BIIB017, including three Phase 1 studies in healthy volunteers following single or repeated doses (Studies 105HV101, 105HV102, and 105HV103) and one study in renal impairment subjects (Study 105RI101). Study 105HV101 also evaluated the intramuscular (IM) route of administration for BIIB017, compared to SC administration. Among them, Study 105HV103 was designed to compare the PK profile of BIIB017 delivered by prefilled syringe (PFS) or prefilled pen (PFP). Additional PK characterization was carried out in Phase 3 clinical trial with MS patients (Study 105MS301). BIIB017 serum concentration, PD marker concentrations (neopterin and 2',5'-OAS), anti-IFN antibody, and anti-PEG antibody were assessed for BIIB017 biological activity. The Phase 3 program included one pivotal study (Study 105MS301) and an uncontrolled extension study (Study 105MS302) to assess the clinical efficacy and safety in support of the approval. A tabular summary of the clinical pharmacology and clinical studies used to support dosing or claims is presented below.

Table. Tabular Summary of Clinical Pharmacology and Clinical Studies

Study	Study Objective(s)	Study Design	Test Product; Dosage Regimen; Route of Administration	Treatment Period	Number of Subjects Enrolled; Completed
PK/PD Studies in Healthy Volunteers					
105HV101	To identify the maximum tolerated dose; To characterize PK and PD ; To evaluate safety and tolerability	Phase 1, single-dose, blinded, randomized, IM and SC dose escalation	30 µg/63, 125, and 188 µg; IM/IM and SC	Single-dose	37M/23F; 36M/22F
105HV102	To determine the optimal dose and frequency; To evaluate safety and tolerability; To characterize PK and PD in healthy volunteers	Phase 1, double-blind, randomized, placebo-controlled, multiple-dose, dose-ranging, parallel- group	63, 125, and 188 µg; 2 dosing frequencies (Q2W and Q4W); SC	Multiple dose-2 doses for Q4W and 4 doses for Q2W. Total treatment duration of 6 weeks	36M/33F; 35M/30F
105HV103	To characterize PK of BIIB017 delivered by an autoinjector (PFP) and a PFS in healthy volunteers; To evaluate safety and tolerability	Phase 1, open-label, 2-sequence, 2-period crossover	125 µg; SC	One injection per device with a 3-week washout in between	32M/23F; 14M/10F
PK and PD in Renal Impairment Subjects					
105RI101	To characterize PK and PD in healthy volunteers and subjects with various degrees of renal impairment; To evaluate safety and tolerability	Phase 1, single-dose, open-label, multicenter, serial group, non-randomized	63 and 125 µg; SC	Single-dose	22M/13F; 22M/13F
PK and PD Studies in MS Subjects					
105MS301	To determine efficacy and safety; To characterize PK and PD in subjects with relapsing MS	Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled	125 µg at 2 dosing frequencies (Q2W and Q4W); SC	2 years	441M/1071 F; Year 2 ongoing

105MS302	To evaluate the safety, tolerability, subject ease of use, and satisfaction with the single-use BIIB017 autoinjector (prefilled pen)	Phase 3, multicenter, parallel-group, dose-frequency blinded extension	125 µg at 2 dosing frequencies (Q2W or Q4W); SC	6 weeks	517 enrolled
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Population PK and PD analyses (PP-12-016-BIIB017) was performed using the data source from Study 105MS301 and Study 105HV102 to assess the potential impact of intrinsic factors and covariates.

2.2.2 What is the basis for selecting the clinical endpoints or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

In the pivotal Phase 3 Study 105MS301, the evaluation of the efficacy and safety of BIIB017 was based on standard measures used in registrational studies of MS therapies.

The key endpoints in Study 105MS301 that support the efficacy of BIIB017 on clinical and neuro-radiological measures used to assess MS disease activity are as follows:

- Primary endpoint: Annualized relapse rate (ARR)
- Secondary endpoint: Proportion of subjects relapsing, number of new or newly enlarging T2 hyperintense lesions, and disability progression measured by EDSS
- Tertiary endpoints: Number of gadolinium (Gd)-enhancing lesions and number of new T1hypointense lesions.

Other tertiary endpoints included clinical measures (such as relapses requiring steroid use, MS-related hospitalizations, Multiple Sclerosis Functional Composite), and MRI measures (including new active lesions, lesion volumes, brain atrophy, and magnetization transfer ratio).

The key study endpoint in Study 105MS302 is safety. The same efficacy endpoints evaluated in Study 105MS301 are also being evaluated in Study 105MS302 to provide additional efficacy information over another 2 years on BIIB017 treatment.

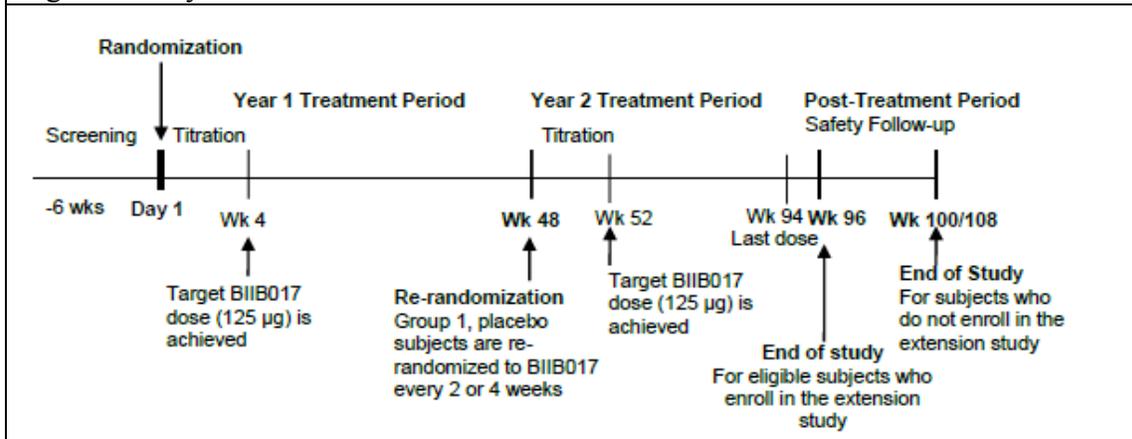
The pharmacological activity of BIIB017 was evaluated by monitoring the profiles of serum concentrations of neopterin (Studies 105HV101, 105HV102, and 105RI101) and whole blood 2',5'-oligoadenylate synthetase (2',5'-OAS) (Study 105HV101), two biological responders induced by IFN -1a in vivo.

2.2.3 Exposure-Response

2.2.3.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The characteristics of dose-response relationship was evaluated in Study 105MS301 (A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects with Relapsing Multiple Sclerosis. The study design and summary of ARR are shown in the Figures below.

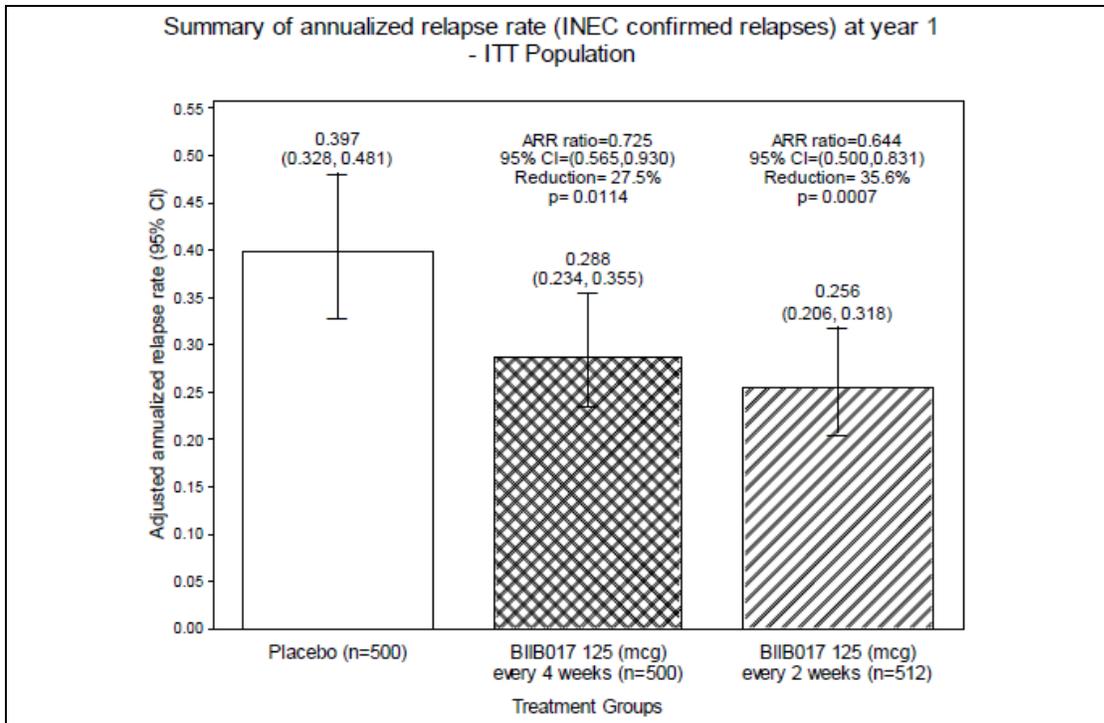
Figure. Study Scheme for 105MS301



At the beginning of the study, all subjects received (self-administered) an SC injection of study treatment (either BIIB017 or placebo) every 2 weeks. Subjects were randomized in a 1:1:1 ratio between the following treatment groups:

- Placebo group: 500 subjects received placebo every 2 weeks for 48 weeks
- BIIB017 every 4 weeks group: 500 subjects received 125 µg BIIB017 SC every 4 weeks for 96 weeks.
- BIIB017 every 2 weeks group: 500 subjects received 125 µg BIIB017 SC every 2 weeks for 96 weeks.

Figure. Summary of Annualized Relapse Rate (INEC-Confirmed Relapses) at Year 1 - ITT Population (INEC- Independent Neurology Evaluation Committee)



BIIB017 125 µg SC administered every 4 weeks and every 2 weeks reduced the annualized relapse rate at Year 1 by 27.5% (p = 0.0114) and 35.6% (p = 0.0007), respectively, compared with placebo.

The relationship between BIIB017 concentrations and efficacy variables was not explored.

For further details about the drug effects on primary and various other secondary endpoints [referred to the review by Medical Officer, Division of Neurology Products].

2.2.3.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Flu-like symptoms (FLS) are a known side effect of the IFN β therapies. The incidence of FLS was similar between BIIB017 dose frequency groups. Based on broad definition of FLS (including the preferred terms chills, hyperpyrexia, influenza-like illness, musculoskeletal pain, myalgia, pain, and pyrexia), the incidence of FLS followed the same pattern, with a higher incidence in both BIIB017 treatment groups (78% total BIIB017) compared with the placebo group (33%). The incidence of FLS for 12 week intervals in various treatment groups is shown in the Table below.

Table. Incidence of flu-like symptoms by 12-week intervals - Year 1

Treatment Group	0-12 weeks	>12-24 weeks	>24-36 weeks	>36-48 weeks
Placebo	9	5	4	3
125 ug every 4 weeks	36	30	29	29
125 ug every 2 weeks	39	34	29	27

2.2.3.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

Yes. The proposed dosing regimen, 125 µg injected subcutaneously every 2 weeks, has acceptable benefit-risk profile [referred to the review by Medical Officer, Division of Neurology Products]. The sponsor’s proposed dosing regimen is considered reasonable. Patients will start on 63 µg and will reach target dose by Week 4. The titration scheme is aimed to help reduce the incidence of FLS.

2.2.3.4 Does this drug prolong the QT or QTc interval?

The effect of BIIB017 on QT or QTc was not studied. As justified by the Sponsor, molecules with a MW 1,000 -25,000 Da rarely have been shown to inhibit the hERG channel function either directly; by binding to extracellular channel domains, or indirectly through other secondary mediators. Therefore, BIIB017 with a MW of approximately (b) (4) kDa has minimal to none potential for inducing QTc change.

2.2.4 What are the PK characteristics of the drug and its major metabolite?

The process of covalently conjugating a PEG moiety to a protein can decrease renal clearance and decrease rate of proteolysis, thus extending the terminal half-life ($t_{1/2}$). The PK characteristics of BIIB017 are summarized as follows:

- Similar PK profiles between healthy volunteers and MS patients and between single-dose and multiple-dose.
- Similar PK parameters between SC and IM routes of administration.
- Higher exposure and longer $t_{1/2}$ at 63 µg to 188 µg (6 to 18 MIU), compared to IFN β-1a 30 µg IM (Avonex[®]; 6 MIU) in healthy volunteers.
- Approximately dose-proportional exposure increase in the dose range of 63 to 188 µg in healthy volunteers.
- Serum BIIB017 concentration generally peaking between 1 to 1.5 days post-dosing, followed by a mono-phasic decline with a $t_{1/2}$ of approximately 2~3 days in MS patients.
- The terminal $t_{1/2}$ of peginterferon beta-1a was approximately 2-fold longer than non-PEGylated interferon beta-1a in healthy volunteers. In MS patients, the mean terminal $t_{1/2}$ of peginterferon beta-1a was approximately 78h at steady-state. The mean steady-state clearance of peginterferon beta-1a was 4.1 L/h.

- No accumulation was observed in BIIB017 exposure following multiple doses of 125 µg Q2W or Q4W in MS subjects.
- Disposition was characterized by a one-compartment linear model with a first-order absorption rate using a population PK analysis.
- Increases in AUC_{336h} (30%-53%) and C_{max} (26%-42%) were observed in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function.

2.2.4.1 What are the single and multiple dose PK parameters?

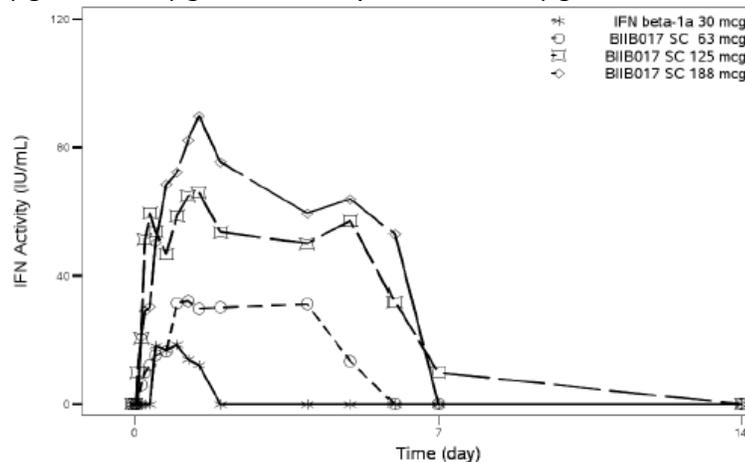
Single and multiple dose PK characteristics of BIIB017 were evaluated in Studies 105HV101 and 105HV102.

Study 105HV101 was a single-dose, ascending-dose-level, Phase 1 clinical study to establish the dose and route of administration for BIIB017. A single dose of BIIB017 63 (6 MIU), 125 (12 MIU), or 188 µg (18 MIU) was administered SC or IM (n=8 per group). For comparison, a single dose of IFN β-1a 30 µg (6 MIU) IM was administered to 12 subjects.

Pharmacokinetics:

Compared with IFN β-1a 30 µg IM, BIIB017 administered either IM or SC resulted in approximately 2-fold longer elimination t_{1/2} (approximately 2 days) at all dose levels tested. BIIB017 resulted in approximately a 4-, 9-, and 13-fold higher AUC_{168h} values following a dose of 63 µg, 125 µg, and 188 µg, respectively; compared with IFN β-1a 30 µg IM.

Figure. Pharmacokinetic Profiles of BIIB017 Following Single Doses of BIIB017 SC at 63 µg, 125 µg, and 188 µg and of IFN β-1a IM at 30 µg



The PK parameters within a dose level for BIIB017 were similar between the IM and SC routes of administration. The AUC_{168h} and C_{max} of BIIB017 increased in an approximately dose-proportional manner.

Table. Mean (SD) Pharmacokinetic Parameters of BIIB017 Following a Single SC Dose Administration (Study 105HV101)

PK parameter	IFN β -1a (n = 12)	BIIB017 (n = 8 per group)						
	IM Injection	IM Injection				SC Injection		
	30 μ g (6 MIU)	63 μ g (6 MIU)	125 μ g (12 MIU)	188 μ g (18 MIU)	63 μ g (6 MIU)	125 μ g (12 MIU)	188 μ g (18 MIU)	
AUC_{168h} ($\times 10^3$ h-IU/mL)	0.77 (0.05-1.99)	2.94 (0.00-5.05)	6.69 (2.19-14.6)	10.9 (4.31-17.9)	2.85 (0.87-4.59)	7.14 (2.52-21.9)	10.1 (2.15-19.9)	
C_{max} (IU/mL)	20.8 (11.5-81.1)	41.6 (0.00-79.8)	80.7 (18.5-268)	136 (49.3-228)	38.9 (18.7-52.3)	70.1 (28.6-146)	98.0 (51.7-219)	
$t_{1/2}$ (h)	24.3 (12.6-1064)	45.4 (23.8-367)	33.3 (27.0-112)	38.7 (32.2-130)	48.4 (24.9-109)	39.2 (28.3-776)	66.3 (24.4-279)	
T_{max} (h)	12.0 (9.00-48.0)	36.0 (0.00-119)	30.0 (12.0-72.0)	36.0 (18.0-96.0)	36.0 (12.0-72.0)	33.0 (30.0-96.0)	36.0 (18.0-96.0)	

• Based on CPE Assay

Pharmacodynamics:

The pharmacological activity of BIIB017 and IFN β -1a IM was characterized by the elevation of 2 biomarkers (serum neopterin concentration and whole blood 2',5'-OAS expression), which are induced by type I interferon exposure. The BIIB017 post-dose median neopterin concentration-time curve and the PD parameters are shown in Figure and Table below.

Figure. Pharmacodynamic Profiles of Neopterin Following SC Administration of BIIB017 or IM Administration of IFN β -1a

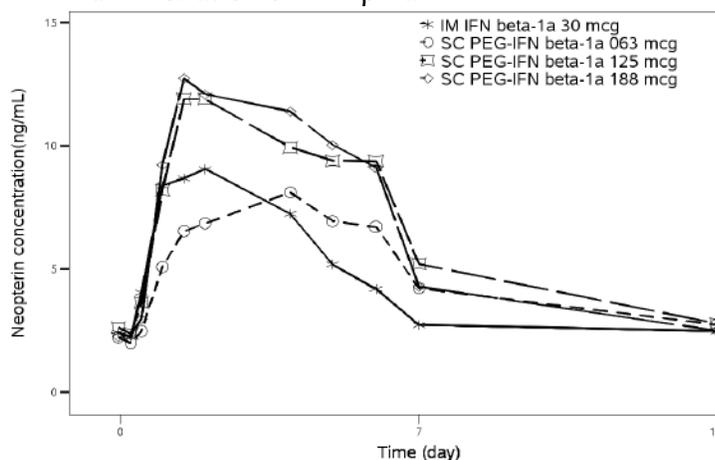


Table. Summary of Pharmacodynamics Parameters for Neopterin (Study 105HV101)

	IFN β -1a (n = 12)	BIIB017 (n = 8 per group)					
	IM Injection	IM Injection			SC Injection		
PD parameter	30 μ g (6 MIU)	63 μ g (6 MIU)	125 μ g (12 MIU)	188 μ g (18 MIU)	63 μ g (6 MIU)	125 μ g (12 MIU)	188 μ g (18 MIU)
$E_{AUC336h}$ (h ⁺ ng/mL)	532 (312-1210)	977 (450-1650)	1150 (776-1890)	1460 (958-1880)	897 (148-1720)	1070 (806-2140)	1170 (632-2060)
E_{max} (ng/mL)	6.60 (4.70-13.5)	8.50 (4.00-16.8)	11.7 (6.40-15.9)	11.3 (8.80-18.6)	6.10 (3.80-16.0)	10.0 (6.20-16.2)	10.9 (7.20-21.0)
E_{Tmax} (h)	48.0 (24.0-72.0)	48.0 (36.0-95.0)	42.0 (36.0-72.0)	48.0 (24.0-96.0)	71.0 (36.0-72.0)	48.0 (36.0-120)	60.0 (36.0-96.0)

Values presented as median (range); $E_{AUC336h}$: area under the concentration-time curve from time 0 to 336 h post-dose; E_{max} : maximum serum concentration; E_{Tmax} : time to reach E_{max} ; IM: intramuscular; MIU: million international units

Compared with IFN β -1a 30 μ g IM, BIIB017 generated higher magnitude and a longer duration of pharmacological response. The maximum neopterin concentration was higher in all BIIB017 treatment groups except for the BIIB017 63 μ g SC dose group. The neopterin elevation induced by BIIB017 was also more persistent in all treatment groups compared with IFN β -1a 30 μ g IM (10 days vs. 5 days). For the whole blood 2',5'-OAS expression, the E_{Tmax} occurred at approximately 12-24 h and 18-24 h following IM and SC administration, respectively. The elimination $t_{1/2}$ was 69-79 h and 55-90 h following IM and SC administration, respectively.

Study 105HV102 was a Phase 1, randomized, double-blind, placebo-controlled, multiple-dose, dose-ranging, parallel-group study to identify the optimal dose and frequency of BIIB017 administered by the SC route. Sixty-nine subjects were randomized (n=9 or 10 per group) to receive placebo or BIIB017 63, 125, or 188 μ g SC every once 2 weeks or once every 4 weeks. Subjects in the every 2 weeks group received 4 injections of BIIB017 and subjects in the every 4 weeks group received 2 injections of BIIB017.

Pharmacokinetics:

As shown in the Figure below, the serum concentration of BIIB017 peaked at approximately 24h post-dose, followed by a mono-phasic decline. The AUC_{168h} and C_{max} increased in an approximately dose-proportional manner. The $t_{1/2}$ ranged from 36h to 67h across the different treatment groups. The $t_{1/2}$ for the 125 μ g SC every 2 weeks or every 4 weeks regimen was 46.2h and 35.7h, respectively.

Drug concentrations were generally non-detectable by 14 days post-dose and no drug accumulation occurred for either dosing frequency.

Figure. Pharmacokinetic Profiles of BIIB017 Following SC Administration at a Dose of 125 μ g at a Frequency of Every 2 Weeks (Q2W) or Every 4 Weeks (Q4W) (Study 105HV102)

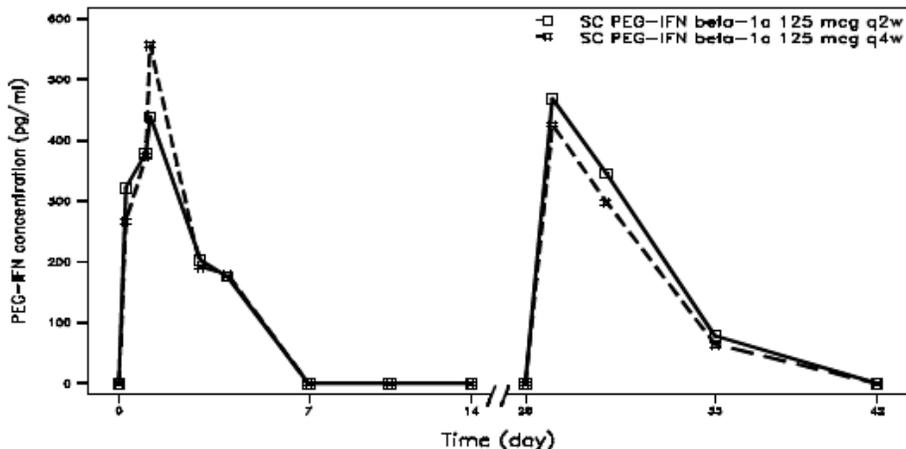


Table. Mean (SD) Pharmacokinetic Parameters of BIIB017 Following a Single and Repeated SC Dose Administration every 2 weeks (Study 105HV102)

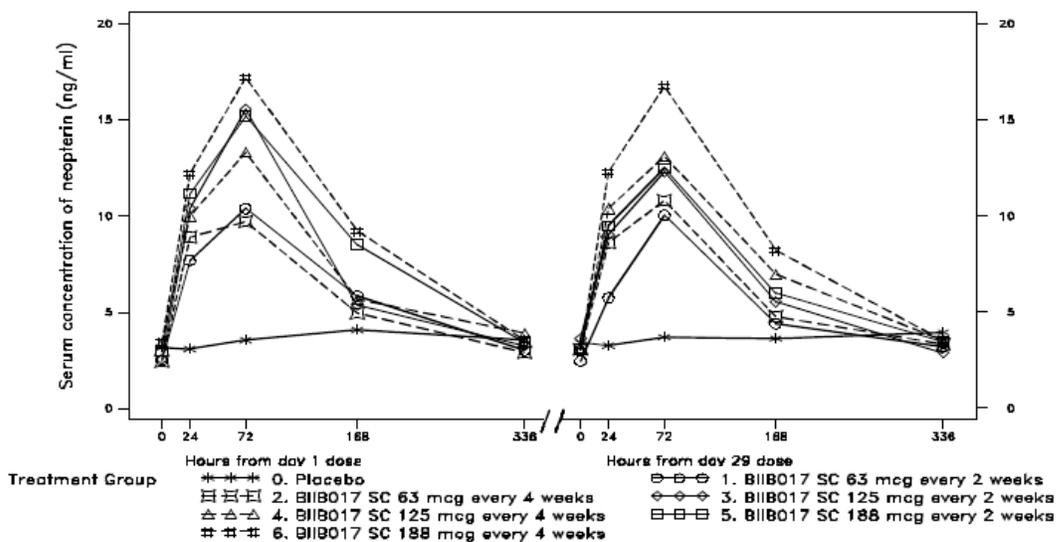
PK Parameter	Day 1 (First Dose)		
	63 (µg)	125 (µg)	188 (µg)
AUC168 h (h*ng/mL)	14.9 (4.9)	37.1 (29.9)	42.7 (22.3)
Cmax (ng/mL)	0.19 (0.07)	0.51 (0.40)	0.55 (0.35)
Median Tmax (h)	24.0	24.0	24.0
t1/2 (h)	67 (50)	42 (2.2)	48 (16)
PK Parameter	Day 29 (Repeated Doses)		
	63 (µg)	125 (µg)	188 (µg)
AUC168 h (h*ng/mL)	12.7 (5.3)	33.4 (20.3)	46.6 (29.1)
Cmax (ng/mL)	0.15 (0.06)	0.35 (0.16)	0.53 (0.33)
Median Tmax (h)	24.0	24.0	24.0
t1/2 (h)	62 (7.4)	67.2 (22.2)	62.3(17.4)

• Based on ELISA assay; values are presented as Mean (SD)

Pharmacodynamics:

Serum neopterin concentration peaked at approximately 72h post-dose and then returned to baseline level within 2 weeks post-dose. Neopterin induction increased in a less than dose-proportional manner for both Emax and EAUC336h. The PD response profiles and parameters within treatment groups were similar on Days 1 (single dose) and 29 (repeat dose). The PD response profiles are presented in the Figure below. The whole blood 2',5'-OAS expression was not measured in this study

Figure. Pharmacodynamic Response Profiles of Neopterin Following SC Administration at a Dose of 125 µg at a Frequency of Every 2 Weeks (Q2W) or Every 4 Weeks (Q4W)



2.2.4.2 What are the characteristics of drug absorption?

The PEGylated interferon β -1a (BIIB017) is believed to be absorbed through the lymphatic system and by blood capillary absorption after SC administration. Following SC administration with BIIB017 to MS subjects, the peak concentration was reached between 1 and 1.5 days (i.e., T_{max}) post-dose. The C_{max} was approximately 280 pg/mL following Q2W dosing with 125 μ g BIIB017.

2.2.4.3 What are the characteristics of drug distribution?

Following repeated dosing with BIIB017 125 μ g SC Q2W, peginterferon β -1a was widely distributed with a volume of distribution of approximately 481 L which suggests wide distribution in the body.

Literature data has suggested that gastrointestinal organs, liver, and kidney were the major tissues in which the free PEG was distributed.

2.2.4.4 What are the characteristics of drug metabolism and elimination?

BIIB017 is not extensively metabolized in liver. Clearance mechanisms of the protein include catabolism and excretion, with renal elimination being the major pathway.

The process of covalently conjugating a 20KDa PEG moiety to a protein can alter the in vivo properties of the unmodified protein, including a reduction in renal clearance of the unmodified interferon and a reduced rate of proteolysis thus extending the terminal drug $t_{1/2}$ by approximately 2-fold longer than non-PEGylated interferon beta-1a in healthy volunteers and was approximately 78h in MS patients. The mean steady-state clearance of peginterferon beta-1a was 4.1 L/h.

The free PEG was reported to be predominantly eliminated via urinary clearance which could be rapid in humans, whereas the hepatic metabolism and biliary excretion serve as a minor route for clearance.

2.2.4.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Renal elimination is known to be a major route of elimination for BIIB017. Based on this information and its metabolism, a mass balance study for BIIB017 was deemed unnecessary and was not conducted in humans.

2.2.4.6 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

The AUC_{168h} and C_{max} of BIIB017 increased in an approximately dose-proportional manner following SC administration as either a single dose or repeated doses every 2 weeks or 4 weeks. Please refer to Section 2.2.4.1 for PK parameters in Tables following single and repeated doses from 63 µg to 188 µg. The variability was relatively high (%CV: 50%) after both single and repeated doses in healthy subjects..

2.2.4.7 How does the PK of the drug and its major metabolites in healthy subjects compare to that in patients?

The intensive PK was collected from the healthy subjects, whereas sparse PK and intense PK (subset) were obtained from Phase 3 study. The steady-state PK parameters of BIIB017 following 125 µg administered SC for every 2 weeks and 4 weeks in healthy volunteers (Study 105 HV102) and MS subjects (Study 105MS301) are presented in Table below. The mean data showed that both the every 2 weeks and every 4 weeks regimens were similar between healthy volunteers and MS subjects.

Table. Steady-state PK comparison between healthy subjects and MS patients following repeat doses

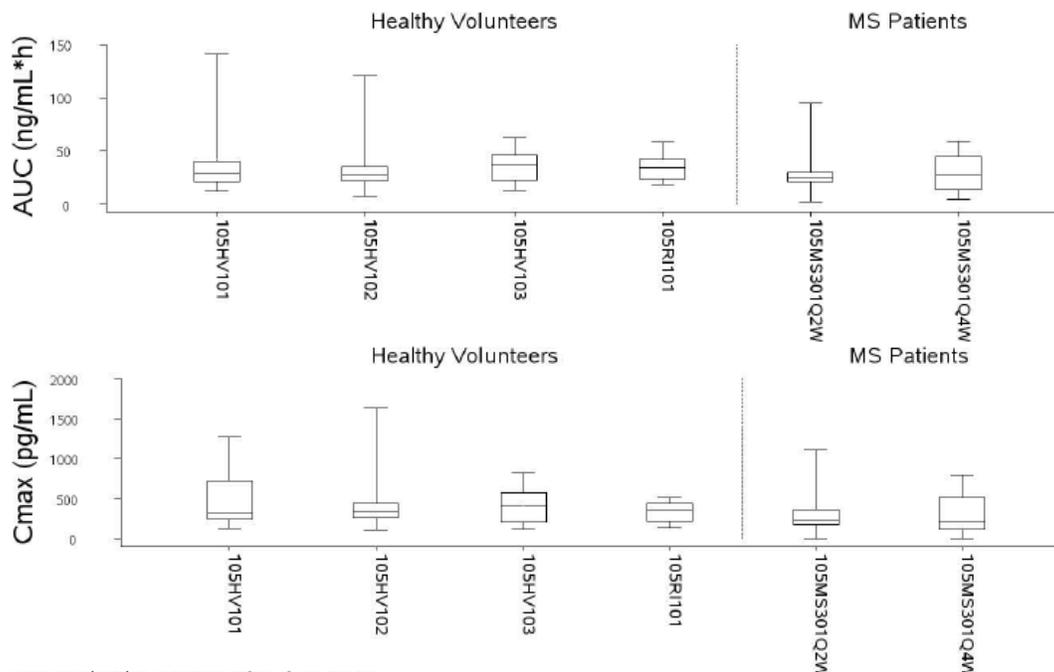
Dose (µg)	Study	Subjects	Route	No. of Dose	AUCt (ng·h/mL)	Cmax (pg/mL)	t1/2 (h)	Tmax (h)
125	105HV102	HV	SC	3 (Q2W)	33.4 (20.3)	346 (162)	67.2 (22.2)	24.0 (15.2)
125	105HV102	HV	SC	2 (Q4W)	26.3 (11.7)	326 (197)	54.9 (13.7)	24.0 (0.00)
125	105MS301	MS	SC	13 (Q2W)	29.9 (17.8)	279 (249)	77.6 (44.3)	35.9 (13.7)
125	105MS301	MS	SC	8 (Q4W)	29.5 (18.1)	305 (225)	67.7 (30.6)	35.0 (21.5)

- Data presented as Mean (SD); Tmax presented as Median (SD)

The Figure (box-plots) below for AUC and C_{max} comparison across Phase 1 and Phase 3 studies indicates an overall similar exposure between healthy volunteers and MS subjects. The median AUC ranged from 24.7 to 39.1 ng·hr/mL in healthy volunteers and 23.5 to

32.0 ng·hr/mL in MS patients. The median C_{max} ranged from 284 to 411 pg/mL in healthy volunteers and 202 to 264 pg/mL in MS patients.

Figure. AUC and C_{max} Comparison Between Healthy Volunteers vs. MS Patients



2.2.4.8 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

The inter-subject variability of clearance and volume of distribution in patients, after accounting for effects of BMI, is 31% and 73%, respectively.

The inter-subject variability in healthy volunteers for key PK parameters was relatively high (50%). High inter-subject variability was observed in MS patients from Phase 3 trial, with the %CV for AUC_τ, C_{max} and t_{1/2} ranging 41-68%, 74-89% and 45-93%, respectively.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, what is the impact of any differences in exposure on the pharmacodynamics, and what dosage regimen adjustments, if any, are recommended for each of these groups?

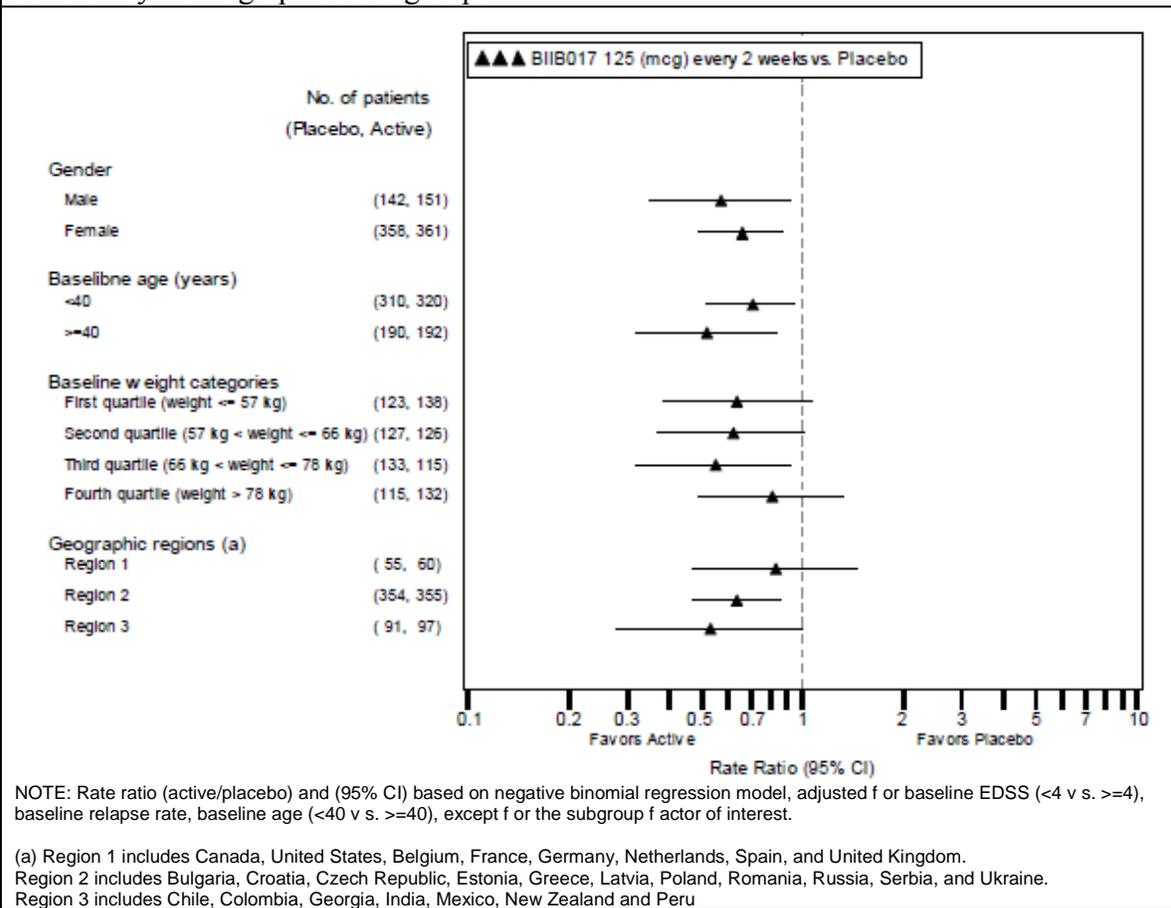
Intrinsic factors including age, gender, body weight, geographic region, renal impairment, and other potential significant covariate (such as anti-PEG antibodies) were studied in Phase 1 study or via population PK and PK analyses of PEGylated Interferon β-1a (BIIB017) in subjects with RMS from study 105MS301 [referred to the following

Sections and the Pharmacometrics Review in Section 4.2 of Appendices for additional details].

No dose adjustments were proposed for the specific populations. However, the result pertinent to the reduced renal function based on the population PK and PD analyses is not conclusive due to the limited numbers being included in the Phase 3 trial. Please refer to Section 2.3.1.2 for detail of findings from a study in subjects with various degrees of renal impairment.

Figure below shows the ARR ratio by gender, age and body weight. No significant differences in ARR are observed. These data do not suggest any need for dose adjustment for these intrinsic factors [See Section 2.2.3.1 for details on overall ARR ratio].

Figure. Annualized Relapse Rate (INEC Confirmed Relapses) at 1 Year - Rate Ratio and 95% CI by Demographics Subgroups



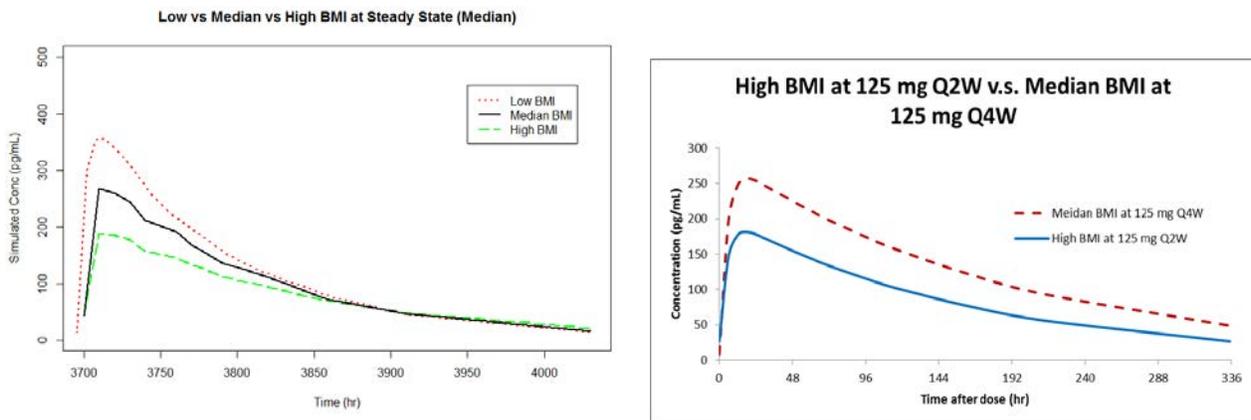
2.3.1.1 Age, Weight, Sex and Other Potential Significant Covariates

The population PK analysis did not show significant effect of sex, body weight, age, geographic region, and other potential significant covariate (such as anti-PEG antibodies) on the PK of BIIB017. A PK, efficacy, and safety study is planned in pediatrics ranging

from 10 to 17 years old. No studies are planned for subjects less than 10 years old since MS is exceedingly rare in this age group.

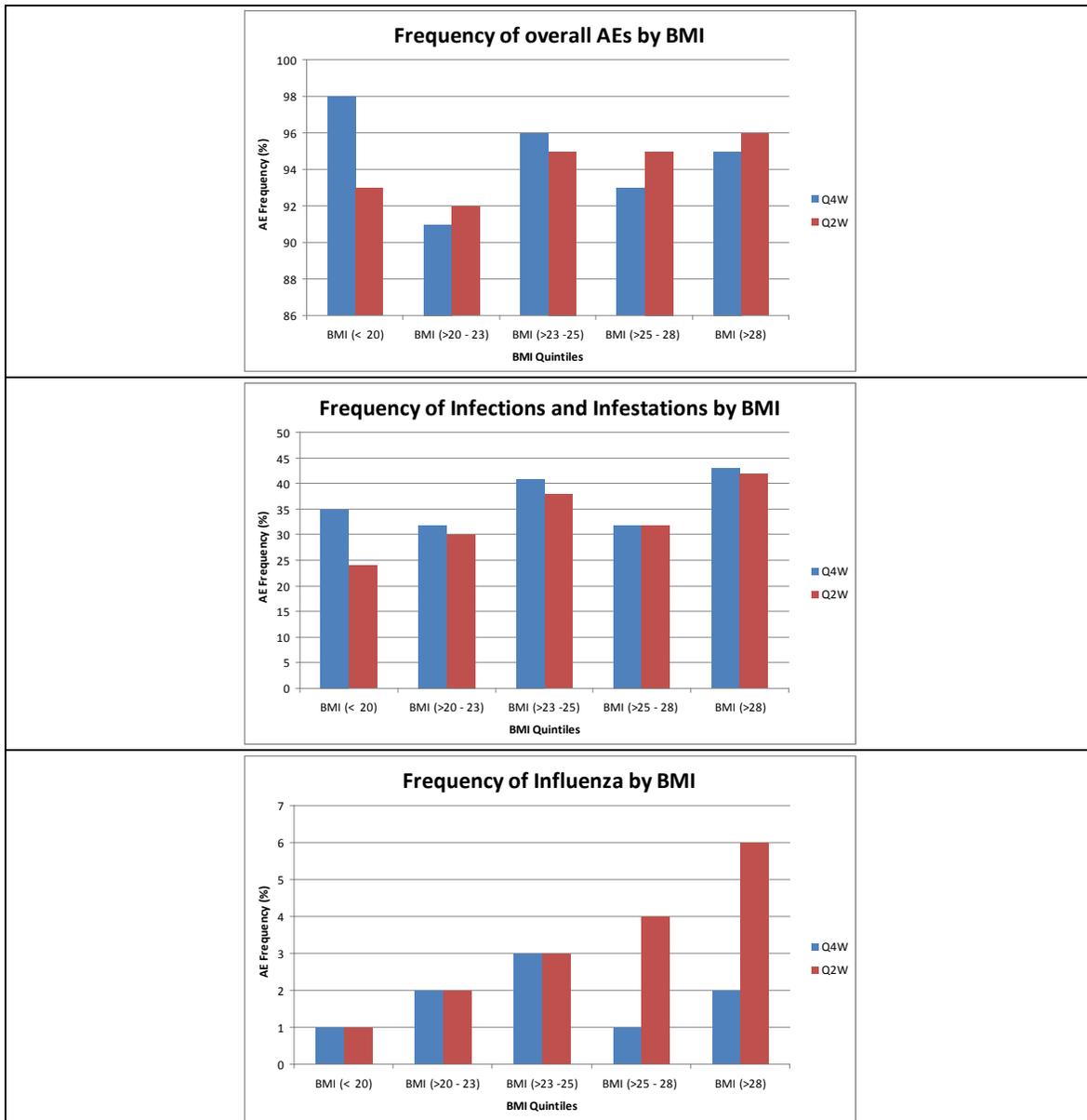
The population PK analysis of BIIB017 showed that the body mass index (BMI) influenced clearance and volume of distribution. The increase in clearance relative to BMI was less than proportional (e.g., a 50% increase in BMI corresponded to a 24% increase in clearance), whereas the increase in clearance relative to BMI was more than proportional. The Pharmacometrics reviewer (Dr. Xiaofeng Wang) conducted simulations in patients with various BMI with findings shown in Figure below which indicates that concentrations in a typical patient with high BMI treated with BIIB017 125 µg every 2 weeks is lower than a typical patient with median BMI treated with BIIB017 125 ug Every 4 Weeks.

Figure. (Left) BIIB017 Concentrations by BMI Category. Shown are the Mean Concentration Time Profiles after BIIB017 125 µg every 2 weeks in Patients Characterized Based on BMI (Low, Median, High). (Right) Shown is the Mean Concentration Time Profile in a Patient With Median BMI Treated With BIIB017 125 µg Every 4 Weeks and a Patient with High BMI Treated With BIIB017 125 µg Every 2 Weeks



The Figures below show the incidence of adverse events for various BMI quintiles in Study 105MS301. The findings from various subgroups show that the incidence of AEs does not increase with lower BMI, whereas patients with low BMI are likely to have higher BIIB017 concentrations. Overall, differences in concentrations are not considered clinically significant enough to warrant dosage adjustment based on BMI range known for MS patients [referred to Pharmacometrics Review in Section 4.2 of Appendices for details].

Figure. Incidence of Overall Adverse Events (AEs), Infections & Infestations, Influenza in Study 105MS301



2.3.1.2 Renal Impairment

The effect of renal impairment was assessed following administration of single doses of 125 µg or 63 µg BIIB017 in subjects with mild ($CL_{CR} >50$ to ≤ 80 mL/min; N=6), moderate ($CL_{CR} = >30$ to ≤ 50 mL/min; N=9), and severe ($CL_{CR} = \leq 30$ mL/min; N=6) renal impairment, as well as subjects with end stage renal disease (ESRD) requiring hemodialysis 2 to 3 times a week ($CL_{CR} = \leq 30$ mL/min; N=6), compared to normal control (N=6) (Study 105RI101). The ESRD patients were dosed at 2h post-hemodialysis with PK/PD sampling for 72h.

The PK profiles of BIIB017 in various groups are shown in the Figure and Table below. The progressive increases in BIIB017 exposure (C_{max} and AUC) were observed in

increasing severity of renal impairment after single dose administration of BIIB017 125 µg. In subjects with mild, moderate, and severe renal impairment, there was a 30%, 40%, and 53% increase in AUC_{336h} geometric means, respectively, and a 27%, 26%, and 42% increase in C_{max} geometric means, respectively, compared to normal controls. The CL of BIIB017 was shown to be correlated with renal function. The elimination t_{1/2} of BIIB017 was prolonged (77.8 h) in patients with severe renal function, compared to those among other renal function groups (44.2 ~52.4 h). For the ESRD subjects, each hemodialysis reduced BIIB017 concentration by approximately 24% resulted in similar BIIB017 exposure to that of normal controls. The PD responses (E_{AUC672h} and E_{max}) of neopterin also increased with increasing degrees of renal impairment, attributed to the reduced neopterin renal clearance and possibly the increased BIIB017 exposure. It is noted that similar PK and PD results were reported when renal function was classified by estimated glomerular filtration rate (eGFR) calculated from the Modification of Diet in Renal Disease (MDRD) equation.

Figure. Serum Concentration-Time Profiles of BIIB017 in Patients with Renal Impairment vs. Normal Controls

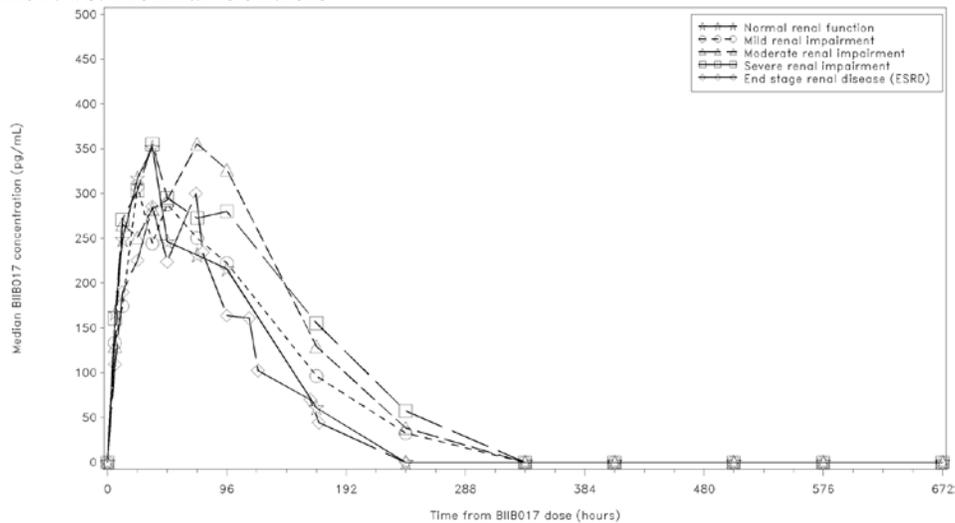


Table. Summary of Key PK Parameters in Subjects with Renal Impairment vs. Normal Controls

Subjects	AUC _{336h} (ng·h/mL)	AUC _∞ (ng·h/mL)	C _{max} (pg/mL)	T _{max} (h)	t _{1/2} (h)
Normal Controls	37.0 (13.6)	40.1 (13.1)	336 (139)	44.0 (28.1)	53.8 (14.3)
Mild RI	49.7 (24.9)	51.8 (24.5)	400 (96.7)	40.0 (18.1)	52.8 (16.6)
Moderate RI	51.1 (16.0)	52.9 (16.9)	460 (322)	52.0 (32.8)	48.8 (12.1)
Severe RI	55.3 (16.0)	64.9 (18.7)	492 (307)	34.0 (22.0)	82.4 (31.9)
ESRD (HD)	37.3 (26.4)	38.9 (25.9)	342 (224)	55.7 (20.1)	46.6 (19.2)

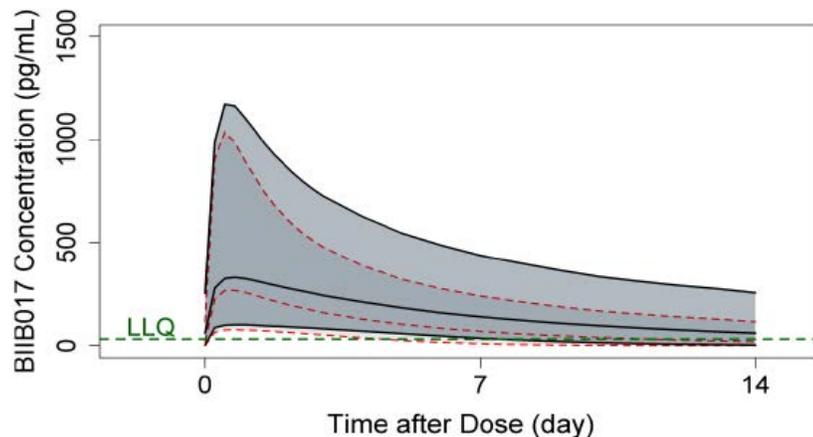
• Data presented as Mean (SD); T_{max} presented as Median (SD)

The Figure below shows the [5th, 95th] percentiles of the simulated concentrations by the Sponsor to compare the steady-state BIIB017 concentration between MS subjects with normal renal function (red dashed lines) and with severe renal impairment (black solid lines). The simulation showed minimal accumulation in both groups. Further, the high

inter-subject variability contributed to the overlapping of majority of the concentration intervals between the 2 groups. The Sponsor's simulation result was confirmed by the Pharmacometrics reviewer using population pharmacokinetic model [referred to Section 4.2 of the Appendices for details]. No change in dosing regimen based on renal function was proposed by the Sponsor.

The increases in exposure for some individuals with severe renal impairment to reach or potentially exceed the maximum exposure previously observed from the highest dose studied in Phase 1 studies is a concern from the safety standpoint. This safety concern and the consideration for a dose reduction were communicated with Medical Officer (Dr. Rodichok Lawrence). Gathering safety findings from Phase 1 studies, there seems to be a relationship between dose and AEs, though little evidence of dose-related AEs was observed in Phase 3 trial. Since there is a lack of solid evidence or sufficient data to support a stronger recommendation (i.e., dose reduction) in view of the exposure increases, a warning language via labeling may be considered for close monitoring of AEs (such as flu-like symptoms) in patients with severe renal impairment.

Figure. Simulated Steady State PK profiles of BIIB017 (125 µg; once every other week) for MS patients with normal renal function vs. MS patients with severe renal impairment.



Red dashed lines from top to bottom: the 95th, 50th, and 5th concentration percentiles in MS patients with normal renal function, respectively.
Black solid lines from top to bottom: the 95th, 50th and 5th concentration percentiles in MS patients with severe renal impairment, respectively.

2.3.1.3 Hepatic impairment

A dedicated hepatic impairment PK study was not conducted since the kidney is the primary clearance organ and the liver is likely one of many catabolism organs, hepatic impairment is not likely to have a significant effect on the elimination of BIIB017.

2.3.1.4 Immunogenicity

The incidence of treatment-emergent antibodies to IFN β -1a or PEG was considered low in both healthy volunteers and MS subjects, with majority being transient responses, as

summarized below [also referred to Section 4.2 of Appendices for additional information]:

- Incidence of treatment-emergent antibodies in Year 1 of pivotal Study 105MS301:
 - Binding Abs to IFN β -1a: 4% in Q4W and 8% in Q2W BIIB017 treatment groups
 - Neutralizing Abs (Nab) to IFN β -1a: less than 1% in both BIIB017 treatment groups, whereas 1 out of 6 NAb positive subjects had persistent NAb reactivity.
 - Anti-PEG Abs: 9% in Q4W and 7% in Q2W BIIB017 treatment groups, whereas 5% in Q4W and 2% in Q2W BIIB017 treatment groups overall showed the presence of persistent anti-PEG Abs, but did not affect BIIB017 serum concentrations or neopterin PD responses.
- The presence of non-neutralizing antibodies to IFN β -1a (BAbs) decreased the concentration of BIIB017 in serum as a result of possible assay interference, but did not impact the neopterin PD response.
- The evaluation of the influence of the anti-IFN NAbs on PK and neopterin parameters was not possible due to the low incidence of NAbs and visit time for PK and neopterin sample collection.

2.4 Extrinsic Factors

As a class, IFN (Avonex[®] IM, Rebif[®] SC, or Betaferon[®] SC) was reported to be a weak inhibitor of CYP1A2 but had no effects on other major CYP enzymes or transporters. Therefore, BIIB017 was not considered to have a significant risk on impacting the PK of concomitantly administered medications. Therefore, no additional studies were conducted to evaluate the drug-interaction potential.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation?

Not applicable

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

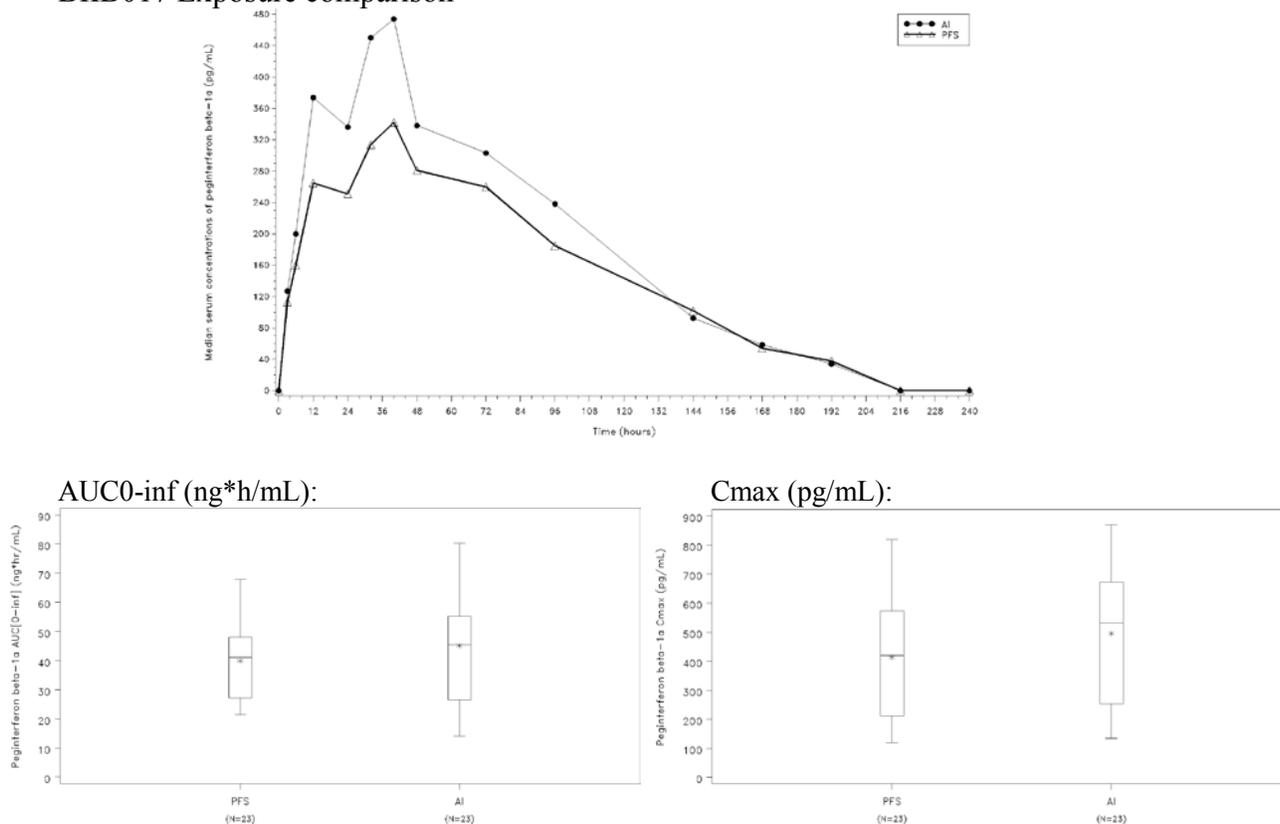
As described in the above Section 2.1.2, clinical formulation and TBM formulation are considered the same and thus a human BE bridging study is not needed.

BIIB017 was supplied as a liquid in vials in Studies 105HV101 and 105HV102 and as a liquid in pre-filled syringes (PFSs) for Studies 105RI101 and 105MS301. The Sponsor proposed two delivery devices of similar mechanism of needle penetration for marketing: Pre-filled syringe (PFS) and pre-filled pen (PFP or single-use autoinjector (AI)).

Study 105HV103 was a randomized, open-label, crossover, single-dose, Phase 1 study to characterize the PK profile, safety, and tolerability of BIIB017 (125 μ g) delivered by

these two devices in 24 healthy subjects. As shown in the Figures below, single-dose administration of BIIB017 125 µg SC via PFS and PFP (AI) resulted in generally similar PK profiles and key PK parameters.

Figure. (Top) Median Serum Concentrations of BIIB017 Following Single-Dose Administration of BIIB017 125 µg SC via PFS and PFP (AI); (Bottom) Box-Plots of BIIB017 Exposure comparison



The percent differences between two injection devices were 10.40% for AUC0-240h, 7.143% for AUC0-inf, and 17.08% for Cmax, based on geometric means. The median Tmax occurred at approximately 32 hours from both devices. The CL/F values from both devices were similar at 3.42 L/h, while t1/2 were 52.3 and 43.4 h for PFS and PFP/AI, respectively. The variability (%CV) was mostly in 32~68% for key PK parameters, which contributed to the 90% CI being outside of BE limits, as summarized in the Table below for AUCinf and Cmax. Collectively, considering the high variability associated with PK parameters, sample size, overall similar exposure (AUC and Cmax), and the similar safety and tolerability, the BIIB017 exposure from these two devices can be considered similar even though the 90% CIs are not strictly confined in the traditional BE limits.

Table. Summary of Statistical Analysis for Relative Bioavailability of BIIB017 from Single Injection of PFS vs. PFP (AI)

Parameter	N	PPF (AI)	PFS	Geometric Mean Ratio (PPF/PFS)	90% CI
AUCinf (ng·h/mL)	23	41.040	38.304	1.07	(0.92, 1.24)
Cmax (pg/mL)	23	427.20	364.87	1.17	(0.90, 1.53)

* One subject was excluded in PK analysis due to non-detectable BIIB017 level.

* Exposure values expressed as geometric means

2.5.3. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable

2.6 Analytical section

2.6.1 Were the active moieties identified and measured in the plasma in the clinical pharmacology study?

Yes. BIIB017 was measured in all studies, whereas neopterin was measured in Phase 1 studies (105HV101, 105HV102, 105RI101, and 105MS301) and 2',5'-OAS was measured in single ascending dose study (105HV101).

2.6.2 What analytical method was used to determine drug concentrations and was the analytical assay method adequately validated?

Validated enzyme-linked immunosorbent assay (ELISA) and cytopathic effect (CPE) bioassays were used to characterize the PK profile of BIIB017. For the initial PK comparison between BIIB017 and IFN-1a, conclusions were drawn based on results from the CPE assay. Both CPE and ELISA assays showed similar PK properties for BIIB017 in 2 studies (105HV101 and 105HV102), thus the ELISA assay (developed at Biogen Idec and validated at (b) (4)) was used in subsequent studies. The pharmacological activity of BIIB017 was evaluated by monitoring serum concentrations of neopterin by validated competitive ELISA (validated by (b) (4) and whole blood 2',5'-oligoadenylate synthetase (2',5'-OAS) mRNA by real-time PCR (qPCR). Only summaries of the bioanalytical assays for serum BIIB017 and neopterin are provided in the Tables below.

Table. Validation Summary for Determination of BIIB017 in Human Serum by ELISA

Parameter	ELISA	ELISA ((b) (4))	CPE	ELISA
Analytes	BIIB017	BIIB017	BIIB017	Neopterin
Matrix	Human serum			

Standard curve range	31.3 – 1500 pg/mL		7.5 to 50 IU/mL	0.25 – 100 ng/mL
Validation Samples (AP Runs):	31.3, 75.0, 400, 1100 and 1500 pg/mL		0.75, 1.0, 1.25, 2.75, 4.0, and 5 IU/mL	0.906, 2.000, 15.000, 75.000, and 100.656 ng/mL
Intra-Assay Accuracy (%Bias)	90.0 to 107%	86.4 to 106.0%	-12.00 to 36.19%	89.9 to 115%
Intra-Assay Precision (%CV)	≤ 6.2%	≤ 12.8%	1.31 to 18.79%	≤ 11.3%
Inter-Assay Accuracy (%Bias)	96.7 to 102%	92.7 to 103.9%	-2.06 to 21.31%	94.7 to 102%
Inter-Assay Precision (%CV)	≤ 7.4%	≤ 12.8%	10.48 to 13.72%	≤ 12.4%
Dilution Linearity and Prozone Evaluation	Met acceptance criteria at dilutions up to 1/12,800-fold within the range of the assay. A prozone effect was observed for BIIB017 in human serum at concentrations ≥125,000 pg/mL.	Met acceptance criteria for BIIB017 in NHS, MS, UC, and RI patient serum at 75.0 pg/mL and 1100 pg/mL by this modified method.	Met acceptance criteria for dilutional linearity at 4 IU/mL, 2 IU/mL, and 1 IU/mL in normal serum. Accuracy (%Bias): -15.9% to 34.4% Precision (%CV): 1.8% to 10.3 %	Met acceptance criteria for dilutions up to 1/1000-fold. Nonlinearity in dilution was observed for dilutions ≥ 1/2000. A prozone effect was not observed for neopterin in human serum.
Assay Selectivity	Met acceptance criteria for BIIB017 in NHS and MS sera at 75.0 pg/mL and 1100 pg/mL.		Unspiked samples were <LLOQ. For samples spiked with LLOQ concentration of BIIB017, the assay failed to demonstrate selectivity. There is a potential for matrix interference with structurally related compounds, such as other interferons. This is expected because of the presence of endogenous interferon in the assay.	Endogenous concentrations of neopterin were observed in all NHS, MS, UC, and RI patient serum samples. Assay selectivity met acceptance criteria for neopterin in NHS, MS, UC, and RI patient serum at 2.00 ng/mL and in NHS, MS, and UC patient serum 75.0 ng/mL after adjusting the concentrations with endogenous levels of neopterin in serum samples.
Heparin Interference		Met acceptance criteria for heparin at levels up to 10IU/mL; does not interfere with the accurate measurement of BIIB017 at a concentration as low as 75.0 pg/mL by this modified method.		Met acceptance criteria for heparin levels up to 10 IU/mL; does not interfere with the accurate measurement of neopterin at a concentration as low as 2.00 ng/mL.
Assay Specificity (Cross-Reactivity)	Met acceptance criteria for IFN α and IFN γ at		Failed as both IFNα and IFN γ are	

	<p>levels up to 38.5 pg/mL and 1.00 µg/mL, respectively, indicating that they do not significantly interfere with the accurate measurement of BIIB017 at concentrations as low as 400 pg/mL by this method.</p>		<p>measured in this activity assay and, if elevated, will contribute to the total measured interferon activity. This is expected because the activity readout does not discriminate between the different forms of interferon.</p>	
Stability	<p>F/T -70°C: Met acceptance criteria for up to 4 F/T cycles.</p> <p>Stability at Ambient Room Temperature (Bench Top Stability): Met acceptance criteria for up to 4 hours.</p> <p>Stability at 2 to 8°C: (Refrigerated Stability): A gradual decline of the measured concentrations was observed in stability samples stored 1, 7, and 14 days at 2 to 8°C. Refrigerated storage not recommended.</p> <p>Long-Term Stability at -60 to -80 °C: Met acceptance criteria for up to 12 months.</p>	<p>Short-Term Stability at -15° to -30°C: Met acceptance criteria for up to 6 months.</p> <p>Long-Term Stability at -60 to -80 °C: Met acceptance criteria for up to 30 months.</p>	<p>F/T -70°C: Met acceptance criteria for up to 5 F/T cycles.</p> <p>Stability at Ambient Room Temperature (Bench Top Stability): Met acceptance criteria for up to 20 hours.</p> <p>Stability at 1 to 8°C (Refrigerated Stability): Met acceptance criteria for up to 14 days at 1 to 8°C.</p> <p>Long-Term Stability at -20 and -70 °C: Met acceptance criteria for up to 180 days at -20 °C and -70 °C</p>	<p>F/T -70°C: Met acceptance criteria for up to 3 F/T cycles.</p> <p>Short-Term Stability at Ambient Room Temperature (Bench Top Stability): Met acceptance criteria for up to 16 hours.</p> <p>Short-Term Stability at 2° to 8°C (Refrigerated Stability): Met acceptance criteria for up to 14 days.</p> <p>Short-Term Stability at -15° to -30°C: Met acceptance criteria for up to 6 months.</p> <p>Long-Term Stability at -60° to -80°C: Met acceptance criteria for up to 24 months.</p>

3. Labeling Recommendations

The Office of Clinical Pharmacology has reviewed the proposed labeling for PLEGRIDY™ (BIIB017) and found it acceptable provided that an agreement is reached between the Sponsor and the Agency regarding the revised labeling language.

4. Appendices

4.1 Consult Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

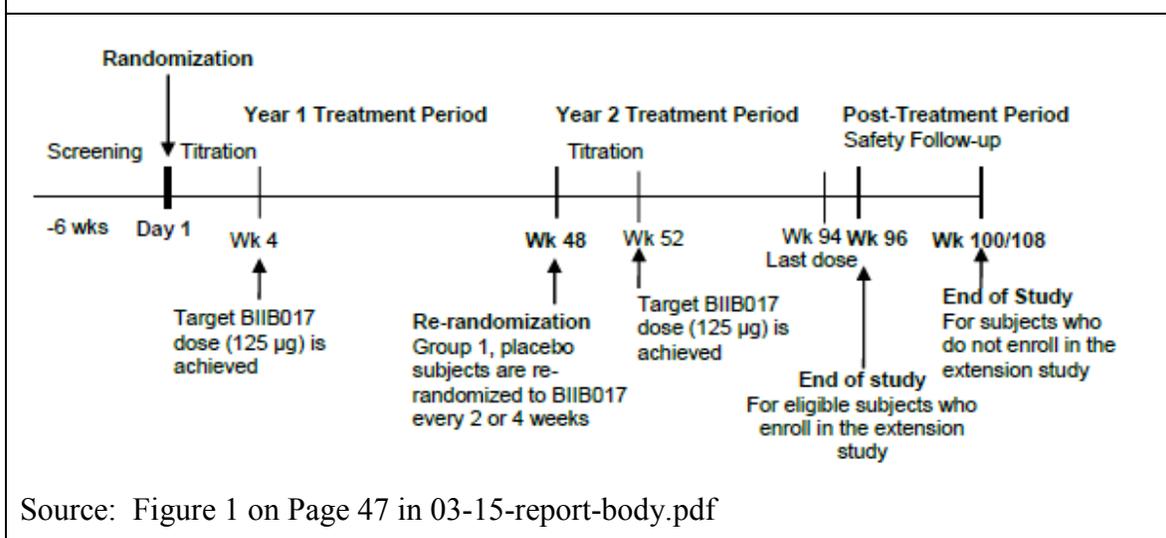
2 KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions.

2.1.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The characteristics of dose-response relationship was evaluated in Study 105MS301 (A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of PEGylated Interferon Beta-1a (BIIB017) in Subjects with Relapsing Multiple Sclerosis). The study design is shown in Figure 1.

Figure 1. Study Scheme for 105MS301

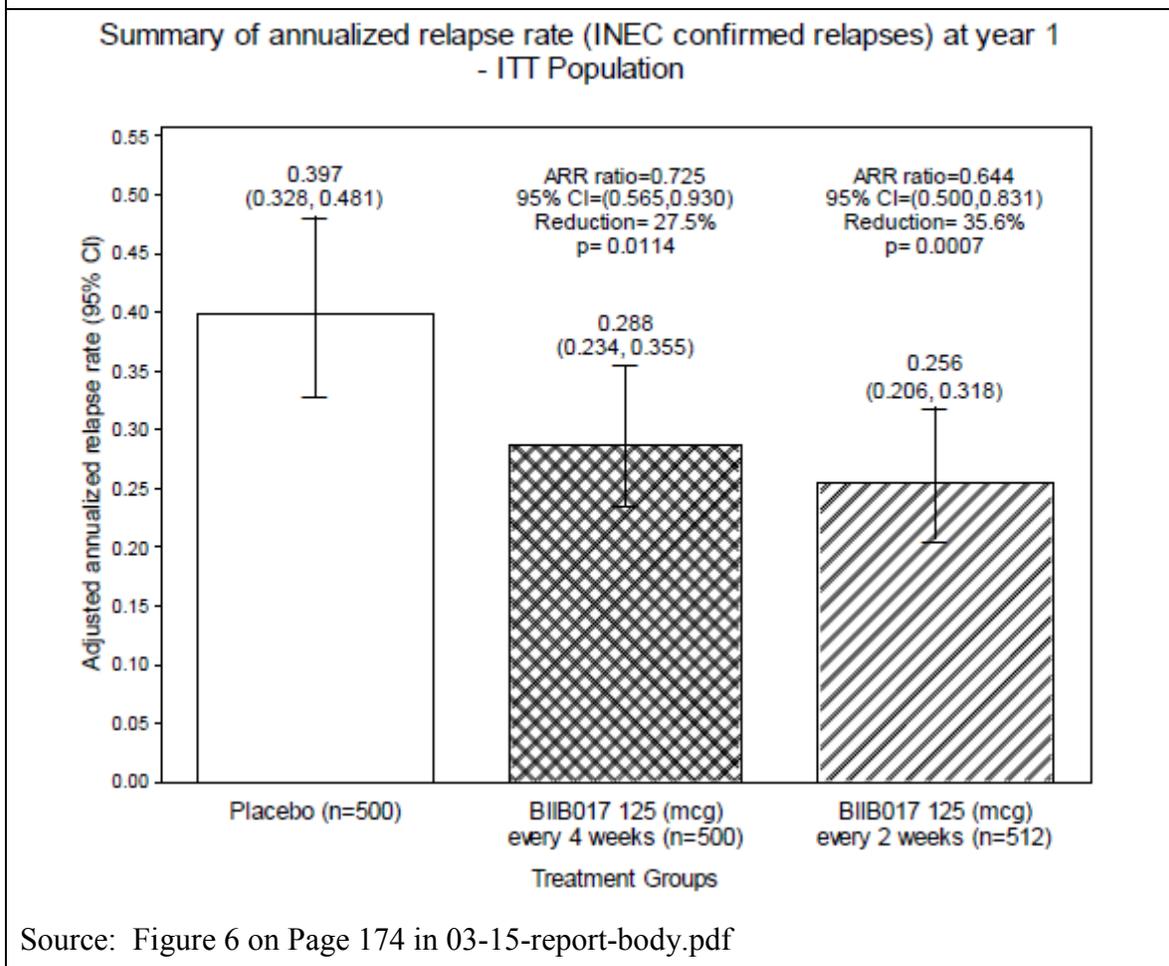


Source: Figure 1 on Page 47 in 03-15-report-body.pdf

At the beginning of the study, all subjects received (self-administered) an SC injection of study treatment (either BIIB017 or placebo) every 2 weeks. Subjects were randomized in a 1:1:1 ratio between the following treatment groups:

- Placebo group: 500 subjects received placebo every 2 weeks for 48 weeks
- BIIB017 every 4 weeks group: 500 subjects received 125 µg BIIB017 SC every 4 weeks for 96 weeks.
- BIIB017 every 2 weeks group: 500 subjects received 125 µg BIIB017 SC every 2 weeks for 96 weeks.

Figure 2. Summary of Annualized Relapse Rate (INEC-Confirmed Relapses) at Year 1 - ITT Population (INEC- Independent Neurology Evaluation Committee)



BIIB017 125 µg SC administered every 4 weeks and every 2 weeks reduced the annualized relapse rate at Year 1 by 27.5% (p = 0.0114) and 35.6% (p = 0.0007), respectively, compared with placebo.

The relationship between BIIB017 concentrations and efficacy variables was not explored.

For further details about the drug effects on primary and various other secondary endpoints, please refer to the review by Dr John Marler (Medical Officer, Division of Neurology Products).

2.1.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

Flu-like symptoms (FLS) are a known side effect of the IFN β therapies. The incidence of FLS was similar between BIIB017 dose frequency groups. Based on broad definition of FLS (including the preferred terms chills, hyperpyrexia, influenza-like illness, musculoskeletal pain, myalgia, pain, and pyrexia), the incidence of FLS followed the same pattern, with a higher incidence in both BIIB017 treatment groups (78% total BIIB017) compared with the placebo group (33%). The incidence of flu-like symptoms for 12 week intervals in various treatment groups is shown in Table 1.

Table 1. Incidence of flu-like symptoms by 12-week intervals - Year 1				
Treatment Group	0-12 weeks	>12-24 weeks	>24-36 weeks	>36-48 weeks
Placebo	9	5	4	3
125 ug every 4 weeks	36	30	29	29
125 ug every 2 weeks	39	34	29	27

Source: Table 51 on Page 286 in 03-15-report-body.pdf

2.1.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The proposed dosing regimen, 125 micrograms injected subcutaneously every 2 weeks, has acceptable benefit-risk profile (Please refer to the review by Dr John Marler, Medical Officer, Division of Neurology Products). Patients will start on 63 ug and will reach target dose by Week 4. The titration scheme is aimed to help with flu-like symptoms.

Table 2. Proposed Dosing Regimen for BIIB017.		
Dose	Time*	Amount (micrograms)
Dose 1	Day 1	63
Dose 2	Week 2	94
Dose 3	Week 4 and every 2 weeks thereafter	125 (full dose)

*Dosed every 2 weeks

Source: Proposed label

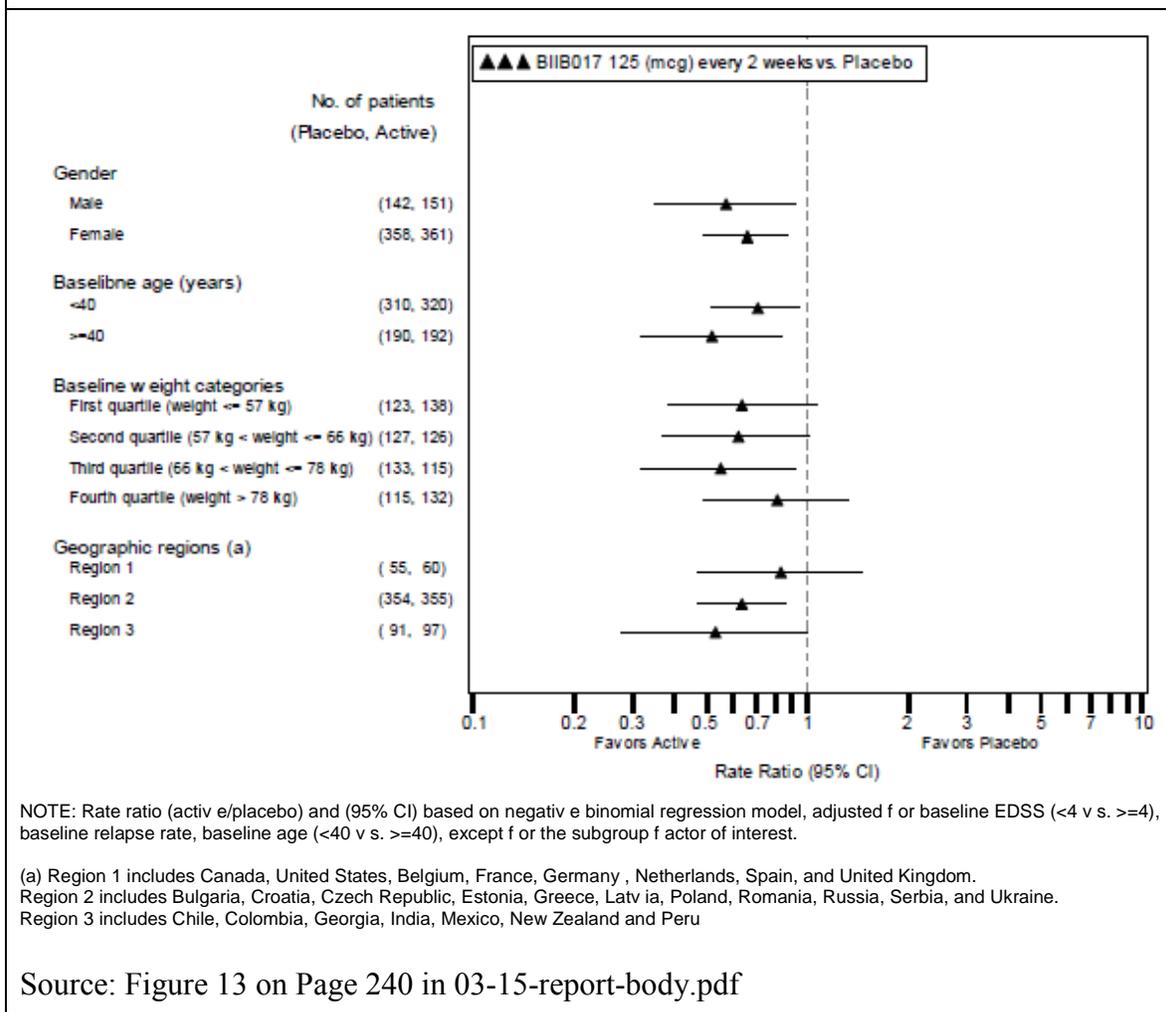
2.1.4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability of clearance and volume of distribution in patients, after accounting for effects of BMI, is 31% and 73% respectively.

2.1.5 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Figure 3 show the annual relapse rate ratio by gender, age and body weight. The data do not suggest any need for dose adjustment for these intrinsic factors.

Figure 3. Annualized relapse rate (INEC confirmed relapses) at 1 year - rate ratio and 95% CI by demographics subgroups



2.1.6 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dose adjustments are proposed for specific populations.

2.1.7 Gender (see Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, <http://www.fda.gov/cder/guidance/old036fn.pdf>)

No significant differences in annualized relapse rate are observed between male and female patients (Figure 3)

3 RECOMMENDATIONS

None

4 LABEL STATEMENTS

No changes to the proposed label.

5 PERTINENT REGULATORY BACKGROUND

BIIB017, a polyethylene glycol (PEG)-conjugated form of interferon beta-1a (IFN β -1a), was developed to provide a longer circulating half-life than current first-line injectable therapies (including recombinant IFN β), aiming to provide multiple sclerosis (MS) patients with an efficacious treatment option with less frequent dosing. The clinical development program consists of a pivotal Phase 3 study in subjects with relapsing remitting MS (RRMS) ([Study 105MS301], referred to as Study 301), and its 2-year extension (Study 105MS302, referred to as Study 302). BIIB017 has also been studied in 3 Phase 1 studies in healthy subjects and a Phase 1 study in subjects with renal impairment. The Phase 1 studies demonstrated the prolonged half-life of BIIB017 and informed the selection of the dose and dosing regimen assessed in the Phase 3 program.

Population pharmacokinetic and pharmacodynamic analyses of PEGylated Interferon Beta-1a (BIIB017) was conducted in subjects with relapsing multiple sclerosis from study 105MS301.

Study 105MS301 was a multicenter, randomized, double-blind, parallel-group, placebo controlled study to determine the efficacy and safety of BIIB017 in RMS patients. In this study, 1512 patients were randomized with a ratio of approximately 1:1:1 into 3 treatment groups: placebo, 125 μ g BIIB017 every two weeks (Q2W), and 125 μ g BIIB017 every four weeks (Q4W). BIIB017 or placebo was administered subcutaneously (SC). Intensive PK and PD samples were taken using an intensive sampling schedule at Week 4 and Week 24 from 25 BIIB017 treated subjects. Sparse PK/PD samples from all subjects in Weeks 4, 12, 24, 56 and 84. PK model was developed using 105MS301 data only. In order to stabilize the PD model, PK and neopterin data from a multiple-dose study in healthy volunteers (105HV102) were combined with the Phase 3 data. In study 105HV102, 68 subjects were randomized into 7 groups with approximately 10 subjects each to receive 8-week treatment: 63 μ g, 125 μ g, or 188 μ g BIIB017 SC Q2W; 63 μ g, 125 μ g, or 188 μ g BIIB017 SC Q4W; or placebo once every 2 weeks. PK and neopterin samples were collected from all subjects.

Table 3. PK/PD Sample Collection Schedule in 105MS301

Subgroup	Tests	Year 1: Treatment																	Year 2: Treatment					
Intensive	Visit Week	Baseline (Day 1)	Week 4										Wk 12	Week 24						Wk 56	Wk 84			
	Visit Window												+10 Days							+10 Days	+10 Days			
	Time of collection	Pre-dose	Pre-dose	6 hr	24 hr	28 hr	36 hr	72 hr	120 hr	168 hr	240 hr		Pre-dose	6 hr	24 hr	28 hr	36 hr	72 hr	120 hr	168 hr	240 hr			
	PK	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
	PD	•	•						•	•	•	•	•						•	•	•	•	•	•
Sparse	Visit Week	Baseline (Day 1)	Week 4										Wk 12	Week 24						Wk 56	Wk 84			
	Visit Window		at least 1 hour after the last dose administered										+10 Days	+10 Days						+10 Days	+10 Days			
	PK	•	•											•	•							•	•	
	PD	•	•											•	•							•	•	

Source: Table 2 on Page 17 in study-report-cpp-12-016-biib017.pdf

For the PK model, the inter-compartment change was assumed first-order linear kinetics as described by Equation below.

$$\frac{dA_i}{dt} = -K_{ij} * A_i + K_{ji} * A_j$$

where:

A_i represents the amount of drug in the ith compartment; A_j represents the amount of drug in the jth compartment; K_{ij} represents the rate constant for drug to transfer from compartment i to compartment j; K_{ji} represents the rate constant for drug to transfer from compartment j to compartment i.

For the compartments where absorption or elimination occurred, the K_{ji} (constant to entering the compartment) was zero. The K_{ij} and K_{ji} were estimated by re-parameterized using volume of distribution and clearance.

NONMEM ((b) (4) version 7.1.2, and 7.2) was used for population PK analysis with Intel Fortran compiler (Intel Corporation, Santa Clara, California, version 11.1.048 and version 12.1).

6 RESULTS OF SPONSOR'S ANALYSIS

Figure 4 shows the media n and range of BIIB017 concentrations by treatment group and time in a subgroup of patients from whom intensive PK samples were obtained.

Figure 4 Median and Range of BIIB017 Concentrations by Treatment Group and Time. Evaluable Subjects in Intensive PK Population.

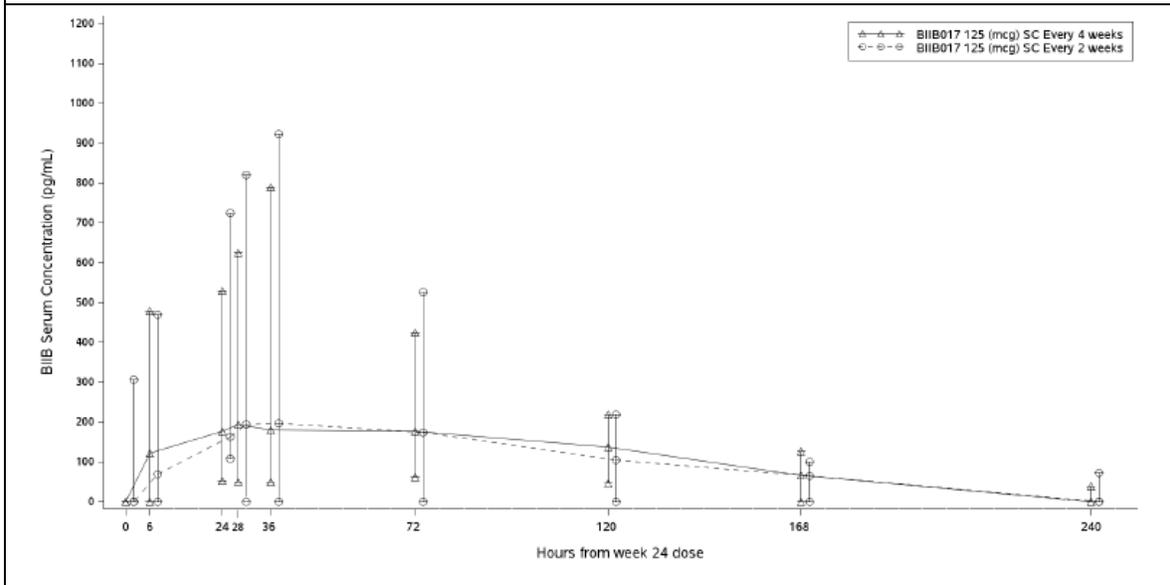
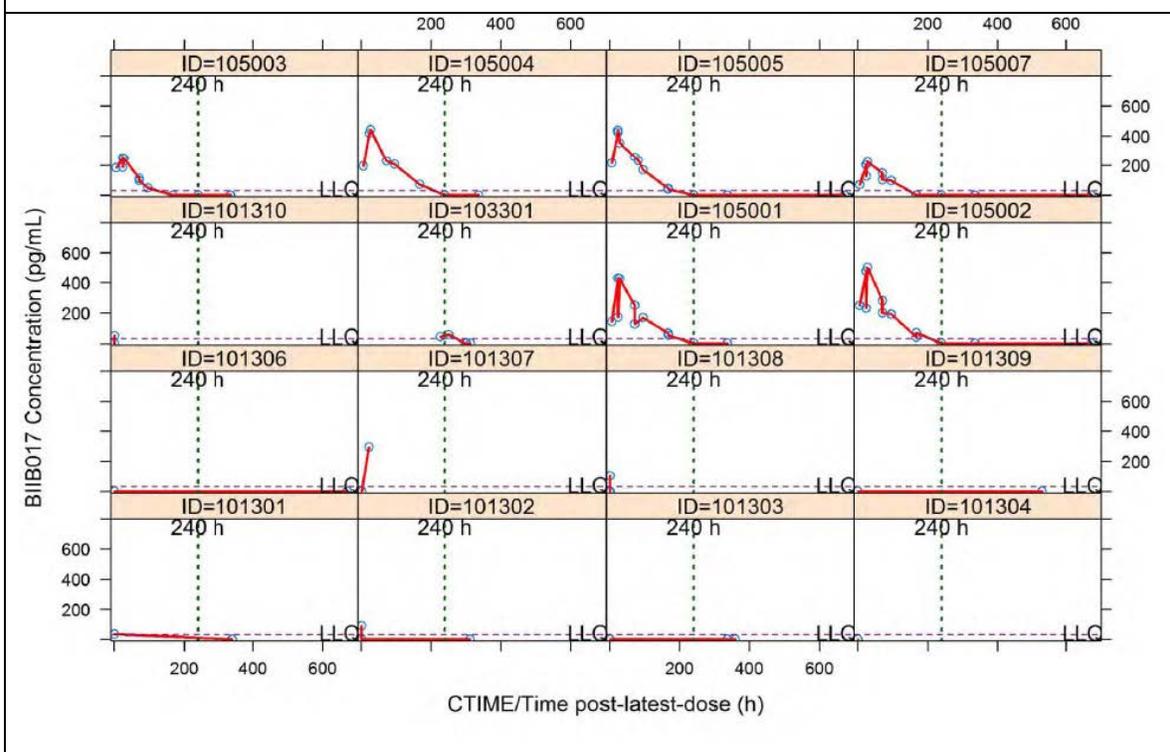


Figure 5 shows the individual concentration time profile in few patients. The graph shows the lower limit of quantitation(LLQ).

Figure 5. Individual Concentration vs Time



Source: Page 152 in study-report-cpp-12-016-biib017.pdf

The baseline categorical demographic histograms for datasets included in the analysis are shown in Figure 6 and the summary of the continuous demographics at baseline are listed in Table 4.

Figure 6. Histograms of race and sex.

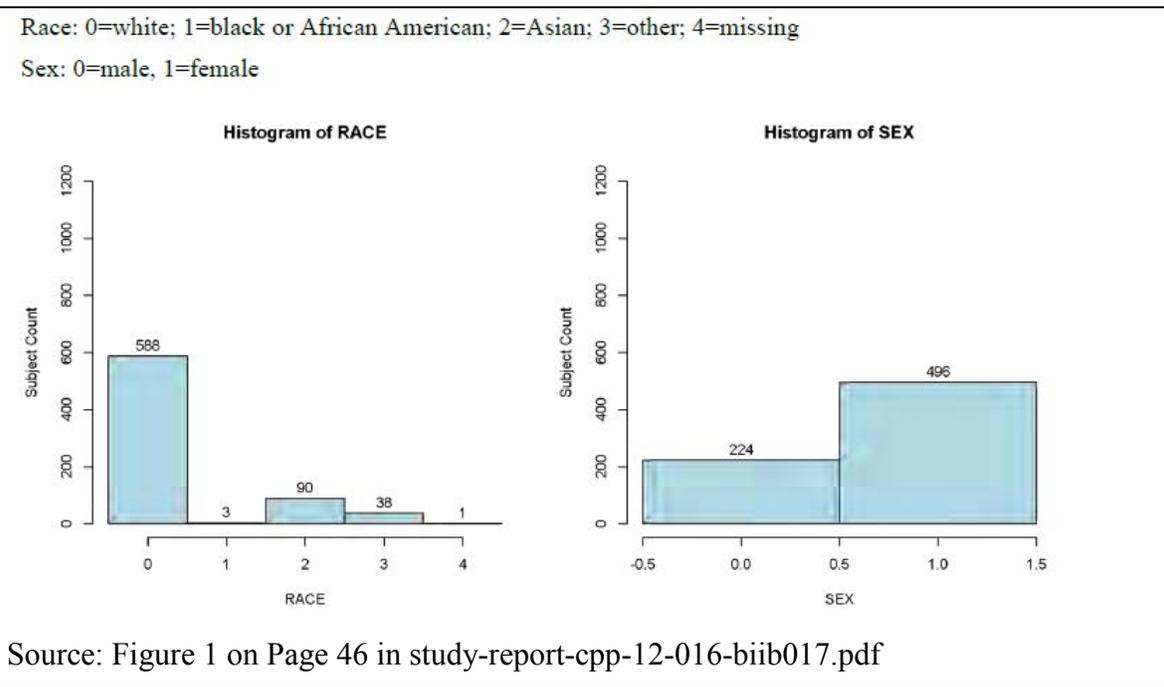


Table 4. Summary of continuous covariates

Covariate	Mean	SD	Median	10 th Percentile	90 th Percentile	5 th Percentile	95 th Percentile	Minimum	Maximum
Age (year)	36.8	9.90	36.1	21.7	52.4	20.4	54.2	18.4	61.1
ALT (IU/L)	21.6	12.5	18.0	10.0	44.3	9.00	53.0	7.00	134
AST (IU/L)	20.7	6.80	19.0	13.0	32.0	12.0	37.0	9.00	88.0
bilirubin (mg/dL)	8.60	4.60	7.00	3.40	17.0	3.00	22.0	3.00	33.0
body mass index (kg/m ²)	24.0	4.70	23.3	18.0	32.2	17.4	34.4	14.8	57.6
body surface area (m ²)	1.80	0.20	1.70	1.40	2.20	1.40	2.30	1.20	2.80
BUN (mg/dL)	4.60	1.30	4.40	2.80	6.80	2.50	7.30	1.70	11.3
creatinine clearance (mL/min)	110	28.1	107	74.0	160	68.5	170	32.7	279
estimated glomerular filtration rate (mL/min)	92.9	16.9	92.0	68.1	121	64.2	127	34.4	180
Height (m)	1.70	0.100	1.70	1.50	1.90	1.50	1.90	1.40	2.00
ideal body weight (kg)	60.6	10.1	59.6	46.0	79.5	44.2	81.4	34.3	94.0
lean body weight (kg)	49.3	9.50	46.9	37.1	67.7	36.2	70.9	30.6	91.0
serum creatinine concentration (μmol/L)	70.5	12.7	69.0	53.0	93.0	50.0	97.7	34.0	141
Weight (kg)	67.5	15.7	65.0	48.0	98.0	45.4	103	36.0	147

Source: Table 3 on Page 37 in study-report-cpp-12-016-biib017.pdf

The estimates of pharmacokinetic parameters using the final model is shown in Table 5.

Table 5. PK Parameter Estimates for the Final Covariate Model (run 203 problem 5) for Study 105MS301

Parameter	Definition	Estimated value	Relative standard error (%)	Shrinkage (%)
CL (L/h)	Clearance	3.60	3.30	NA
V (L)	Volume of distribution	460	7.00	NA
DKa (h ⁻¹)	Absorption rate	0.200	6.90	NA
CLARM	Coefficient of ARM (Q4W) for CL	-0.330	12.0	NA
CLBMI	Exponent of BMI for CL	0.540	28.0	NA
VBMI	Exponent of BMI for V	1.27	20.0	NA
ω^2_{CL}	Intersubject variance of CL	0.100	25.0	55.0
ω^2_v	Intersubject variance of V	0.540	14.0	35.0
COV _{V_CL}	Covariance of V and CL	0.055	60.0	NA
SD1	Coefficient of random error for drug concentration	0.560	2.50	NA
σ^2	Additive random error for log-transformed data	1 Fixed	NA	14

NA, not applicable.

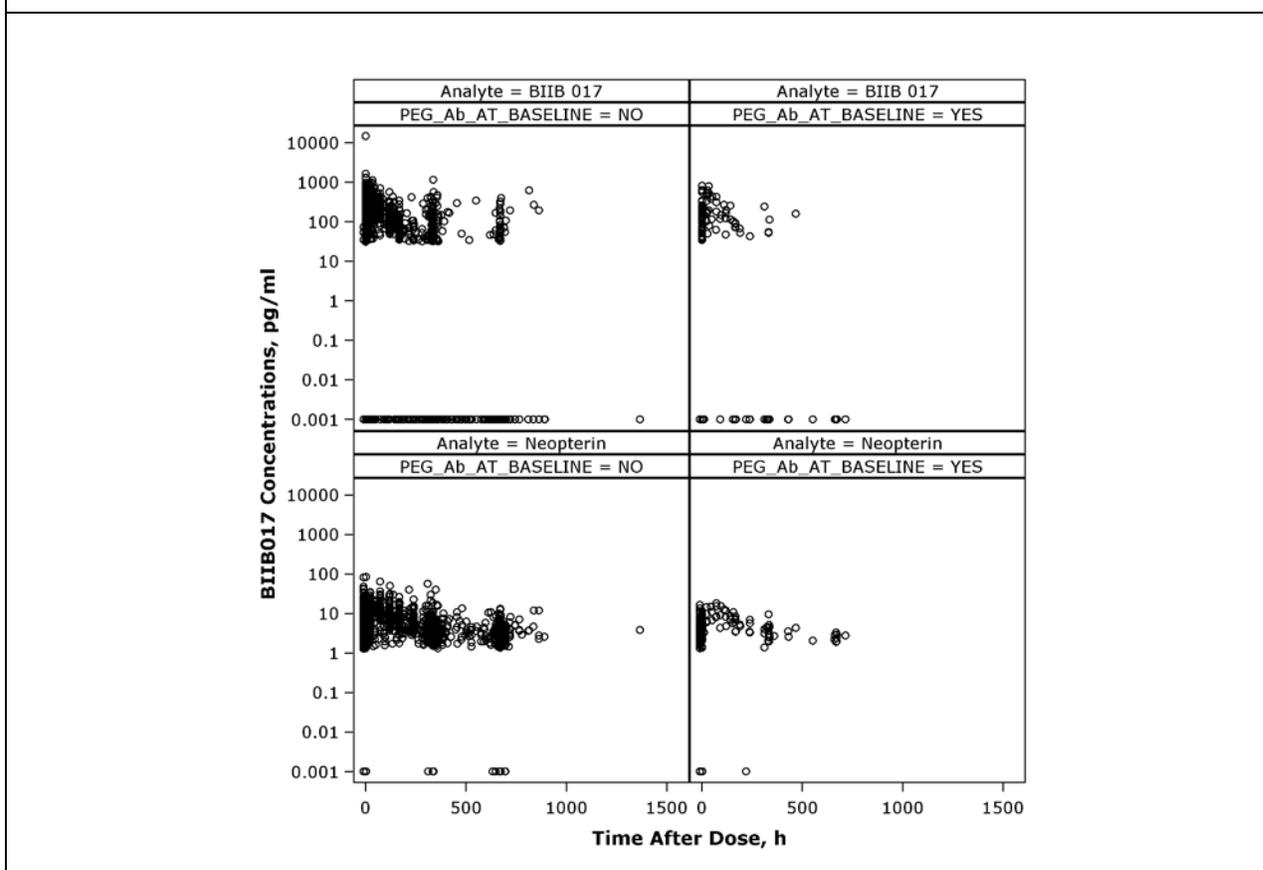
Source: Table 6 on Page 40 in study-report-cpp-12-016-biib017.pdf

Influence of anti-PEG Abs, anti-IFN and anti-IFN NAbs on BIIB017 concentration

Influence of Anti-PEG Abs

Figure 7 show the BIIB017 (PK) and neopterin (PD) concentrations obtained at various visits by anti-PEG Abs presence (positive) or absent (negative) status. In the Phase III study (105MS301), about 6% of the patients had anti-PEG Abs at baseline. The influence of anti-PEG Abs was evaluated because the common use of PEG in cosmetics and drugs which results in pre-existing anti-PEG Abs in patients. The analysis showed no influence on BIIB017 clearance by anti-PEG Abs status or titer values.

Figure 7. (Top) BIIB017 and Neopterin concentrations by anti-PEG Abs status at baseline (YES- refers to presence of anti-PEG Abs at baseline, NO- refers to absence of anti-PEG Abs at baseline).

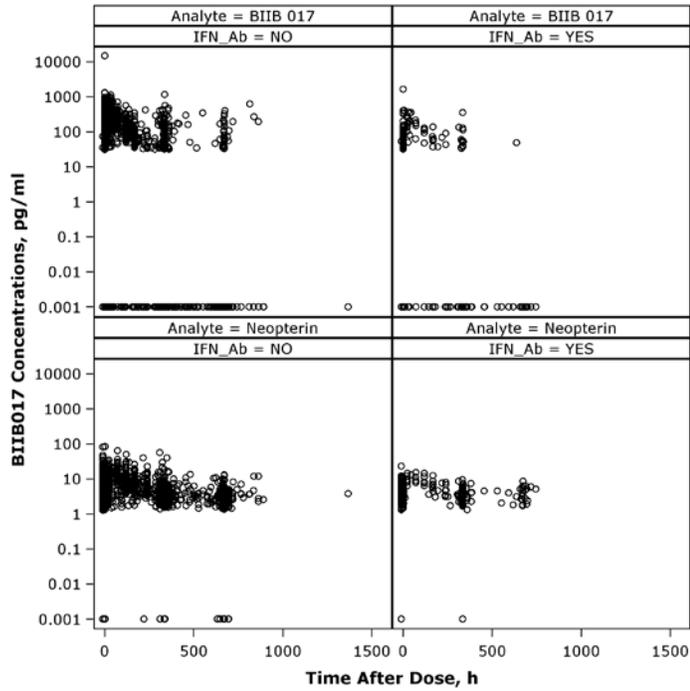


Influence of Anti-IFN Abs (Binding Anti-IFN B-1A Antibody)

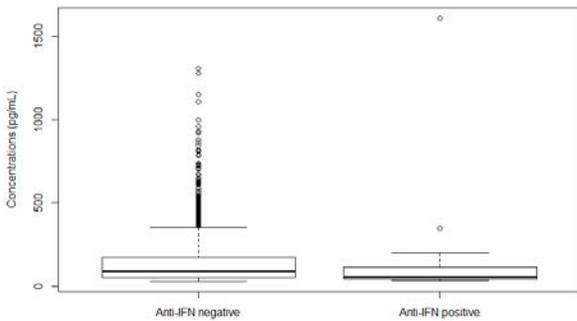
Figure 8 shows the BIIB017(PK) and neopterin (PD) concentrations obtained at various visits by anti-IFN Abs presence (positive) or absent (negative) status. In the Phase III study (105MS301), about 6% of the patients had anti-IFN Abs either at baseline or at a

later visit during the study. The samples from these subjects were taken either within 2 hours or after 10 days post-dose. The concentrations were generally expected to be BLQ or close to be BLQ at these time points (Figure 9).

Figure 8. (Top) BIIB017 and Neopterin concentrations by anti-IFN Abs status at baseline or at later visit during the study (YES- refers to presence of anti-IFN Abs NO- refers to absence of anti-IFN Abs). (Bottom Left) Box plots showing BIIB017 concentrations by anti-IFN Abs status (Bottom Right) Summary statistics of BIIB017 concentrations by anti-IFN Abs status.

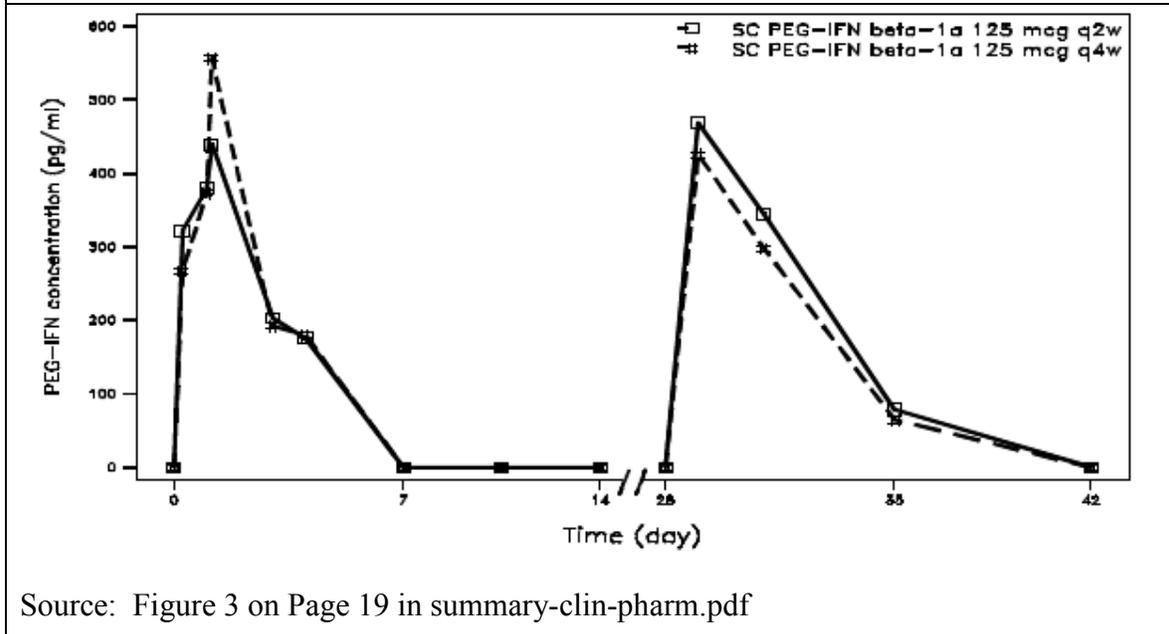


Boxplots comparing concentrations for anti-IFN antibody negative and positive points



	Anti-IFN antibody negative	Anti-IFN antibody positive
Mean	145.6	125.7
Median	89.65	56.9
Standard Error	3.87	41.53
1 st quantile	50.68	43.25
3 rd quantile	174.0	115.2

Figure 9. Pharmacokinetic Profiles of BIIB017 Following SC Administration at a Dose of 125 µg at a Frequency of Every 2 Weeks (Q2W) or Every 4 Weeks (Q4W) (Study 105HV102)

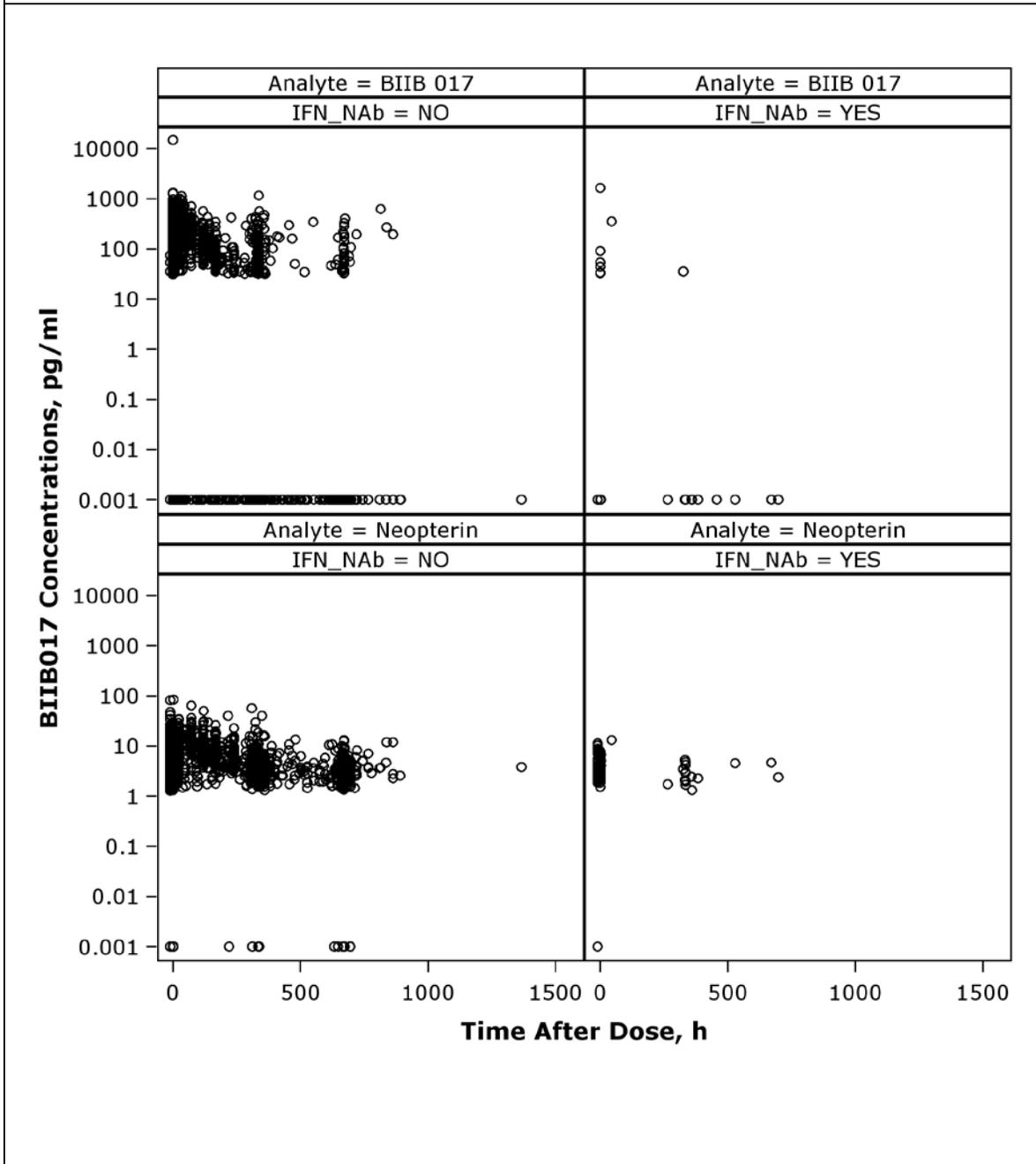


Source: Figure 3 on Page 19 in summary-clin-pharm.pdf

Influence of Anti-IFN N Abs(Neutralizing Anti-IFNB)

Figure 10 shows the BIIB017 (PK) and neopterin (PD) concentrations obtained at various visits by anti-IFN N Abs presence (positive) or absent (negative) status. In the Phase III study (105MS301), about 1.5% of the patients had anti-IFN Abs either at baseline or at a later visit during the study. The samples from these subjects were taken either within 2 hours or after 10 days post-dose. The concentrations were generally expected to be BLQ or close to be BLQ at these time points (Figure 9).

Figure 10. BIIB017 concentrations by anti-IFN NAb status



Influence of renal function on BIIB017 concentration

Interferons are known to be catabolized in the kidney, and both moderate and severe degrees of renal impairment have been shown to have an impact on the PK of other PEGylated interferons. Thus, the potential requirement to dose-adjust BIIB017 in subjects with impaired renal function was assessed. Table 6 shows the sample size and renal function categories.

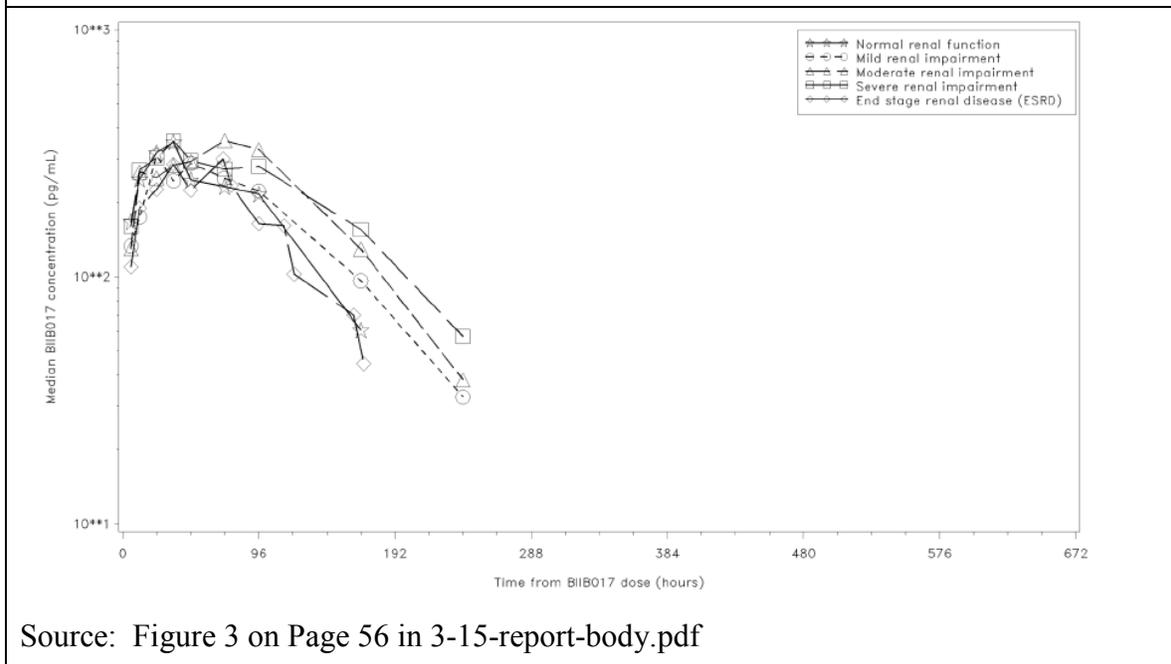
Table 6. Estimated Creatinine Clearance (mL/min) and Number of Subjects by Group

Group	Description	Estimated Creatinine Clearance (mL/min) ¹	Dose (SC)	N
1	Normal renal function (healthy subjects)	>80	125 mcg	6
2	Mild renal impairment	>50 to ≤80	63 mcg 125 mcg	3 6
3	Moderate renal impairment	>30 to ≤50	125 mcg	6
4	Severe renal impairment	≤30	63 mcg 125 mcg	2 6
5	ESRD	Require hemodialysis 2 to 3 times a week	125 mcg	6
Total:				35

¹Estimated Creatinine Clearance (CRCL) classification according to [Committee for Medicinal Products for Human Use (CHMP) 2004].

Figure 11 shows the time course of BIIB017 concentrations in healthy subjects and subjects with renal impairment.

Figure 11. Median Serum Concentration of BIIB017 Over Time on a Logarithmic Scale

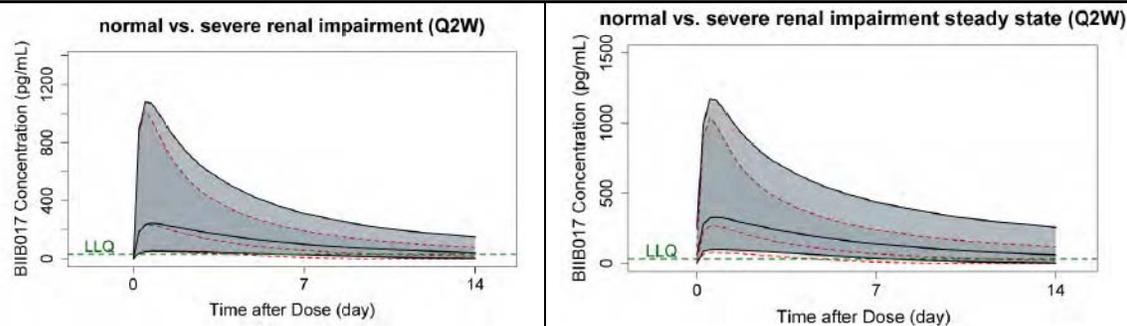


The geometric mean AUC_{336h} was 35.01, 45.65, 48.85, 53.53, and 30.96 ng*hr/mL for subjects in the normal, mild, moderate, severe, and ESRD renal function groups, respectively, as defined by eCRCL (Estimated Creatinine Clearance).

The CL of BIIB017 was shown to be correlated with renal function and up to 53.0% increase in AUC_{336h} and up to 42.0% increase C_{max} was observed. The geometric mean CL decreased 3.25 L/h in healthy subjects to 1.99 L/h in subjects with severe renal impairment. Assuming the same magnitude of clearance decrease comparing MS patients with severe renal impairment to patients with normal renal function, a simulation was carried out to compare the steady state BIIB017 concentration between MS subjects with normal renal function and with severe renal impairment. The [5th, 95th] percentiles of the simulated concentrations in the 2 groups following an initial dose with no prior treatment as well as a steady state dose are displayed in .

The simulation showed minimal accumulation comparing the PK profiles at steady state to those following the initial dose in both groups. Additionally, the majority of the 90.0% concentration intervals overlapped between the 2 groups because of high inter-subject variability.

Figure 12. Simulated Steady State PK profiles of BIIB017 (125 µg; once every other week) for MS patients with normal renal function vs. MS patients with severe renal impairment.



Source: Figure 9 on Page 60 in 3-15-report-body.pdf

Sponsor's Overall Conclusions

The disposition of BIIB017 was well described by a one-compartment linear model with a first-order absorption rate.

- Body mass index were identified as significant covariates in the final PK model.
- The clearance increased with BMI in a less than proportional manner. A 50% increase in BMI corresponded to a 24% increase in clearance
- The volume of distribution increase with BMI in a greater than proportional manner. A 50% increase in BMI corresponded to a 67% increase in volume of distribution

- The non-neutralizing anti-IFN binding antibodies appeared to interfere with BIIB017 measurement by ELISA, thereby influencing PK parameters. However, the effect could not be quantified because of consequent BLQs in some subjects
- Covariates tested but not significant included concomitant medications commonly used in 105MS301, anti-PEG antibodies, as well as other demographic characters

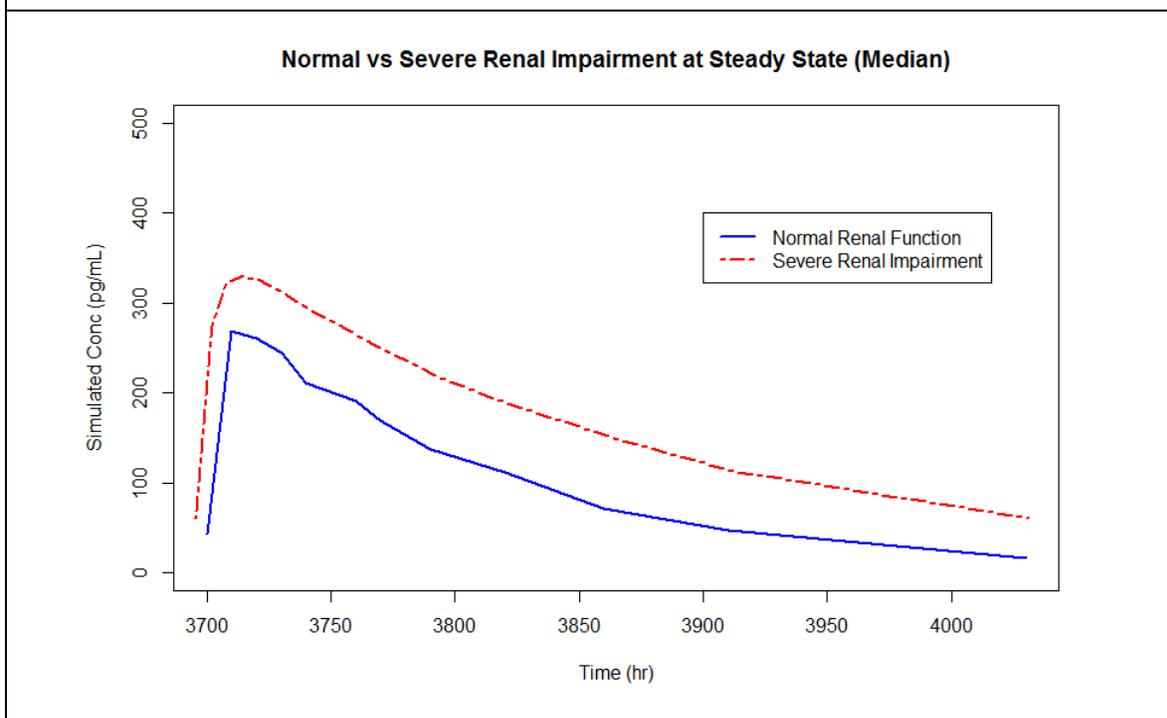
Reviewer's Comments: The reviewer (Dr Xiaofeng Wang) was able to run the population pharmacokinetic model and confirm sponsor's findings.

Is there a need for dose adjustment based on renal function?

Interferons are known to be catabolized in the kidney. Increasing degrees of renal impairment resulted in increased BIIB017 exposures. Overall, subjects with mild, moderate, and severe renal impairment had a 30%, 40%, and 53% increase in AUC_{336h} and a 27%, 26%, and 42% increase in C_{max}, respectively, compared with subjects with normal renal function. The reviewer conducted simulations in patients with renal impairment to evaluate alternate dosing regimens that would improve benefit-risk ratio.

Simulations show that the concentrations of BIIB017 are higher in patients with severe renal impairment in comparison to control population (Figure 13).

Figure 13. BIIB017 Concentrations by Renal Function Category. Shown are the Mean Concentration Time Profiles after BIIB017 125 ug every 2 weeks in Patients with Normal or Severe Renal Impairment.



There is inadequate data on safety findings in patients with renal impairment from the registration trial. The options for addressing this issue:

(A) Change the dosing regimen from 125 mcg once every 2 weeks to 125 mcg once every 4 weeks after completion of initial titration.

The dose (125 mcg every 4 weeks) administered with this option, in patients with severe renal impairment, would be equivalent to 188 mcg every 4 weeks in patients with normal renal function. Based on the findings from Study 105MS301, it is likely that the new dosing regimen (125 mcg every 4 weeks in patients with severe renal impairment) will not show lower benefit when compared to 125 mcg every 4 weeks in patients with normal renal function.

(B) Include language in the label that would inform physicians of need for close monitoring of adverse events such as flchangu like symptoms in patients with severe renal impairment.

Is there a need for dose adjustment based on BMI?

The reviewer conducted simulations in patients with various BMI administered fixed doses of BIIB017. The findings are shown in Figure 15, which indicates that concentrations in a typical patient with high BMI treated with BIIB017 125 mcg every 2 weeks are lower than a typical patient with median BMI treated with BIIB017 125 mcg Every 4 Weeks.

Figure 14 shows the incidence of adverse events for various BMI quintiles (Source Table 84 from iss.pdf report) in Study 105MS301. The findings from various subgroups show that the incidence of AEs does not increase with lower BMI (Patients with low BMI are likely to have higher BIIB017 concentrations). Overall, the findings do not warrant dose adjustments based on BMI.

Figure 14. Incidence of Overall Adverse Events (AEs), Infections & Infestations, Influenza in Study 105MS301

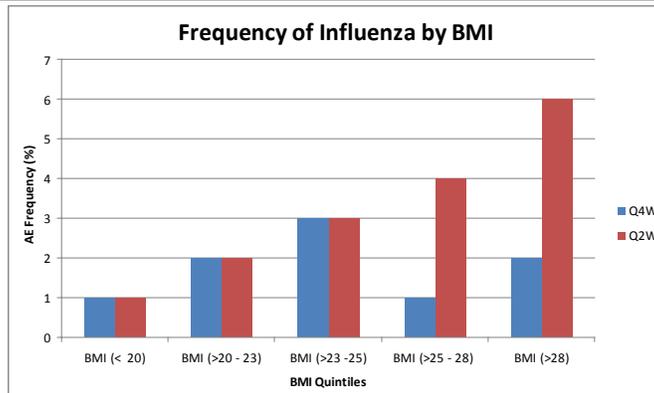
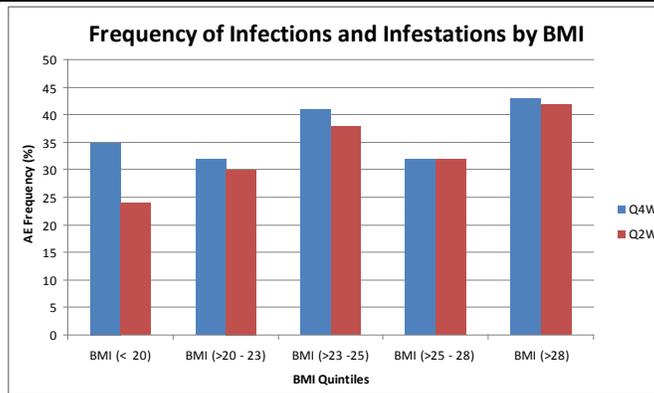
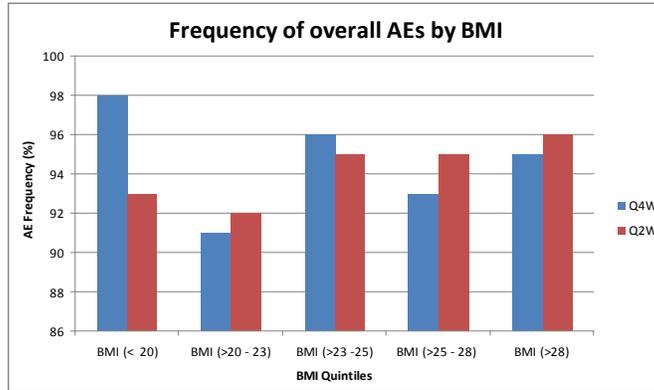
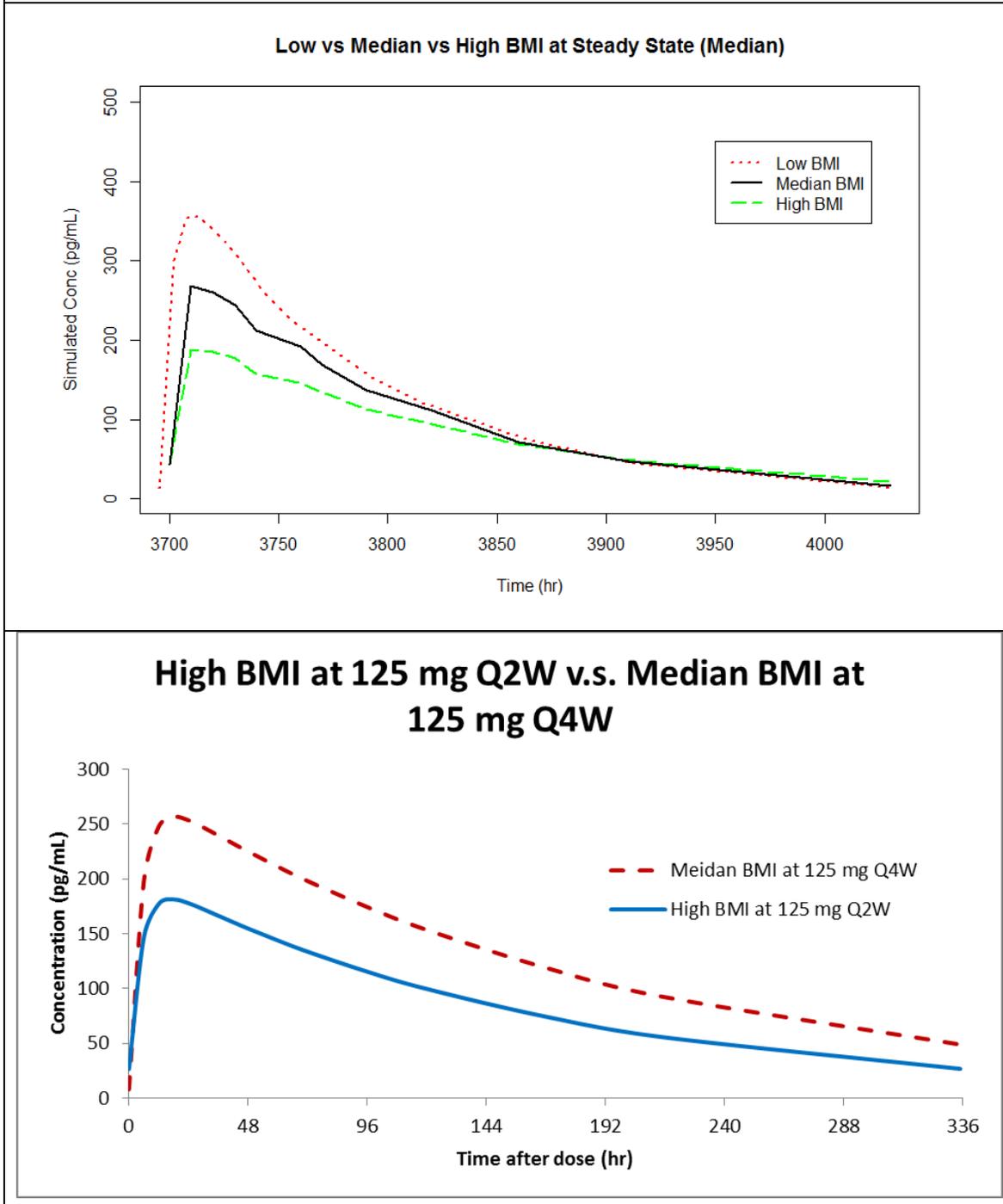


Figure 15. (Top) BIIB017 Concentrations by BMI Category. Shown are the Mean Concentration Time Profiles after BIIB017 125 ug every 2 weeks in Patients Characterized Based on BMI (Low, Median, High). (Bottom) Shown is the Mean Concentration Time Profile in a Patient With Median BMI Treated With BIIB017 125 ug Every 4 Weeks and a Patient with High BMI Treated With BIIB017 125 ug Every 2 Weeks .



7 REVIEWER'S ANALYSIS

8 INTRODUCTION

NA

9 OBJECTIVES

Analysis objectives are:

1. To confirm sponsor's population pharmacokinetic analysis.
2. To evaluate the impact of various intrinsic/extrinsic factors and the need for dose adjustment.

10 METHODS

10.1.1 Data Sets

Data sets used are summarized in Table 7.

Table 7. Analysis Data Sets

Study Number	Name	Link to EDR
105MS301	poppk.csv	

10.1.2 Software

NONMEM 7.2 (b)(4), R 3.0.2 (R Foundation for Statistical Computing)

10.1.3 Models

Base PK model: one-compartment linear model with first order absorption

Covariate model: BMI on CL and V

(b)(4)

11 RESULTS

12 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\

4.2 OCP Filing/Review Form

6 Pages Have Been Withheld As A Duplicate Copy Of The "OCP Filing Review Form" signature dated July 16, 2013 Located In This Review Section Of The NDA Approval Package



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

/s/

TA-CHEN WU
01/23/2014

XIAOFENG WANG
01/23/2014

VENKATESH A BHATTARAM
01/24/2014

YUXIN MEN
01/24/2014

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	125499	Brand Name	Plegridy (BIIB017)
OCP Division (I, II, III, IV, V)	DCP-1	Generic Name	PEGylated Interferon Beta-1a
Medical Division	HFD-120	Drug Class	Interferon beta-1a (IFN β-1a)
OCP Reviewer	Ta-Chen Wu, Ph.D.	Indication(s)	Treatment of patients with relapsing forms of MS (RMS)
OCP Team Leader	Angela Men, M.D., Ph.D.	Dosage Form	Refrigerated Liquid (b)(4)
Pharmacometrics Reviewer	Joo-Yeon Lee, Ph.D.	Dosing Regimen	<ul style="list-style-type: none"> • 125 µg every 2 weeks • 63 µg and 94 µg doses only used during the titration phase of the clinical study
Pharmacometrics Team Leader (Acting)	Atul Bhattaram, Ph.D.		
Date of Submission	05/15/2013	Route of Administration	Subcutaneous (SC) Injection
Estimated Due Date of OCP Review	01/16/2014	Sponsor	Biogen Idec, Inc.
Medical Division Due Date	1/23/2014	Priority Classification	S (Original BLA)
PDUFA Due Date	05/16/2014		

Clin. Pharm. and Biopharm. Information

Summary:

The Sponsor submits an original Biologics License Application to seek approval of Plegridy (BIIB017) for the treatment of multiple sclerosis. BIIB017, a 166 amino acid glycoprotein, is a pegylated form of interferon beta-1a (IFN β-1a) that is pegylated with a single 20kDA methoxypoly (ethyleneglycol)-O-2 methylpropionaldehyde (mPEG) moiety at the N-terminus. BIIB017 belongs within the interferon beta class (Avonex, Rebif) that are among the commonly used first-line injectable multiple sclerosis (MS) therapies. (According to the Sponsor, BIIB017 provides a more optimized and less-frequent dosing regimen, and has efficacy and safety profiles comparable with currently approved first-line injectable therapies.)

The mechanism of action of IFN β-1a in MS is not fully understood, but it is thought to be similar to the unmodified IFN β-1a but binding to the Type 1 IFN receptors and trigger the associated immunomodulatory activity.

Drug Substance and Formulations:

- A clear to slightly opalescent, colorless to slightly yellow solution containing approximately (b)(4) BIIB017 in (b)(4) sodium acetate, (b)(4) arginine.HCl, pH 4.8 (b)(4)
- Drug substance manufacturing process changed from (b)(4) process (BIIB017-A; for Phase 1 Studies 105HV101 and 105HV102) to a (b)(4) process (BIIB017-B; for Phase 3 and commercial) – considered analytical comparable; human BE study is not needed; clinical formulation and TBM formulation

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are the same

- Studies 105HV101 and 105HV102: liquid in vials
- Two delivery devices for marketing:
 - Pre-filled syringe (PFS) and pre-filled pen (PFP or single-use autoinjector (AI))
 - Studies 105RI101 and 105MS301: PFS
 - Study 105HV103: compared PFS and PFP (0.25 mg/mL strength)
 - Study 105MS302 (Phase 3 extension study): PFS for 96 weeks; PFS and PFP in AI sub-study

Clinical Program: [see **Appendix 1** for listing of clinical studies]

It consists of one pivotal Phase 3 study ([Study 105MS301](#)) to support the approval. The key study endpoint in extension [Study 105MS302](#) is safety, with the same efficacy endpoints to provide additional 2-year efficacy information. Efficacy endpoints included:

- Primary: Annualized relapse rate
- Secondary: Proportion of subjects relapsing, number of new or newly enlarging T2 hyperintense lesions, and disability progression measured by EDSS
- Tertiary: Number of gadolinium (Gd)-enhancing lesions and number of new T1 hypointense lesions.

Clinical pharmacology program:

It characterized PK and PD of BIIB017 in 3 Phase 1 clinical studies in healthy volunteers following single or repeated doses ([Studies 105HV101](#), [105HV102](#), and [105HV103](#)). Additionally, the PK was characterized in renal impairment subjects ([Study 105RI101](#)) and in MS subjects ([Study 105MS301](#)). BIIB017 serum concentration, PD marker concentrations (neopterin and 2',5'-OAS), anti-IFN antibody, and anti-PEG antibody were assessed for BIIB017 biological activity. [see **Appendix 1** and Critical Comments in Table below for respective study for additional information.]

Population PK and PD analysis ([PP-12-016-BIIB017](#)): Data source from Study 105MS301 and Study 105HV102; intrinsic factors (but not on extrinsic or renal impairment) and covariates

- Due to the limited full PK profiles obtained from few patients (N=13 in the Q4W group and N=12 in the Q2W group) in Study 105MS301, a robust and conclusive analysis was not feasible for establishing an exposure-effectiveness relationship. Therefore, an exposure/response analysis relating to effectiveness or safety was not performed for BIIB017.
- PK, PD and PK/PD in pivotal Phase 3: PK parameters were assessed by determining the serum concentration of BIIB017 vs. time curves. PD parameters included, but were not limited to, determining the serum neopterin concentration vs. time curves. For the intensive PK/PD analysis, samples were to be taken with an intensive sampling schedule at Week 4 and Week 24 from 5% of the overall population. PK/PD samples were collected from all subjects in the study, with a sparse sampling schedule for use in a population PK/PD analysis.

Renal impairment ([105RI101](#)): Full study design + simulation for MS patients with normal renal function vs. severe renal impairment at steady state (Q2W)

Immunogenicity: Evaluation of the influence of the anti-IFN NAbs on PK and neopterin parameters was not possible due to the low incidence of NAbs. The presence of antibodies to PEG did not have a discernible impact on BIIB017 serum concentrations or neopterin PD effect at the titers observed in the pivotal Study 105MS301.

Bioanalytical reports:

- ELISA for Measuring BIIB017 Levels in Serum: Serum BIIB017 was determined by sandwich ELISA [validation report CST017-010VR, CST017-010VR-R.1, CST017-010VR-R.2, CST017-010VR-R.3].
- Neopterin Assay: Serum neopterin was determined by competitive ELISA [validation report CST017-011VR, CST017-011VR-R.1, CST017-011VR-R.2].
- CPE Assay for Measuring BIIB017 Levels in Serum: A cell-based activity assay was validated at (b) (4) to detect and quantify BIIB017 in the serum of healthy volunteers from Phase 1 studies (Study 105HV101, Study 105HV102) [validation report CST017-004VR-R.1].
- Anti-IFN -1a BAb Assays: An ELISA was developed at Biogen Idec and validated at (b) (4)

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(b) (4) to determine the presence of BAbs specific for IFN -1a in serum. Sample analysis was performed at Focus using an earlier form of this assay for Study 105HV101 and Study 105HV102 and at (b) (4) for Study 105MS301 and Study 105MS302 [validation report CST18-342VR, CST18-342VR-R.1].

- Detection of NABs in the Cell-Based MxA Induction Assay: A cell-based activity assay was developed and validated at (b) (4) to detect and determine the titer of anti-BIIB017 NABs in the serum. Sample analysis was performed using a different cellular readout at Biogen Idec for Study 105HV101 and Study 105HV102; and at (b) (4) in Study 105MS301 and Study 105MS302 [validation report CST017-036VR, CST017-036VR-R.1].
- Anti-PEG Binding Antibody Assay: A sandwich ELISA was developed at Biogen Idec and validated at (b) (4) to detect and determine the titer of antibodies directed against the PEG moiety of BIIB017 in the serum of subjects with MS. Sample analysis was performed at Biogen Idec for Study 105HV101 and Study 105HV102; and at (b) (4) for Study 105MS301, Study 105MS302, Study 105RI101, and Study 105HV103 [validation report CST017-037VR, CST017-037VR-R.1].

Pediatric waiver request: A waiver in children aged <10 years for BIIB017 delivered via the SC route of administration for the treatment of RMS - because necessary studies are impractical due to the extremely low prevalence of MS in this specified age group in the pediatric population.

Pediatric deferral request: A deferral in children aged 10-17 years for BIIB017 delivered via the SC route of administration for the treatment of RMS - to allow for the evaluation and assessment of Phase 3 adult data and the preparation for pediatric study.

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			Clin Pharm Summary and Review Aid provided
Labeling	X			<ul style="list-style-type: none"> • Annotated labeling in PDF • Word and PDF labelings.
Reference Bioanalytical and Analytical Methods	X			<ul style="list-style-type: none"> • Method validations are provided. • In-study validation and QC performance are provided.
I. Clinical Pharmacology				
Mass balance:	-			
Isozyme characterization:	-			
Blood/plasma ratio:	-			
Plasma protein binding:	-			
Pharmacokinetics (e.g., Phase I) -	-			
Healthy Volunteers-				
single dose:	X			105HV101, 105HV103
multiple dose:	X			105HV102
Patients-				
single dose:	-			
multiple dose:	-			
Dose proportionality -				
fasting / non-fasting single dose:	X			105HV101, 105HV102
fasting / non-fasting multiple dose:	X			105HV102
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-			
In-vivo effects of primary drug:	-			
In-vitro:	-			
Subpopulation studies -				

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ethnicity:	-			
gender:	-			
pediatrics:	-			
geriatrics:	-			
renal impairment:	X			<ul style="list-style-type: none"> • 105RI101 (normal, mild, moderate, severe, ESRD); • Simulation for MS patients (normal vs. severe renal impairment at steady state (Q2W))
hepatic impairment:	-			
PD -				
Phase 2:	-			
Phase 3:	X			105MS301
PK/PD -				
Phase 1 and/or 2, proof of concept:	X			105HV101, 105HV102, 105HV103
Phase 3 clinical trial:	X			105MS301 (intensive PK sampling from 5% patients for PK profile; PK/PD samples from all subjects, with a sparse sampling schedule for use in a population PK/PD analysis)
Population Analyses -				
Data rich:	X			105HV102 (used to stabilize the neopterin model (Emax model))
Data sparse:	X			105MS301
II. Biopharmaceutics				
Absolute bioavailability	-			
Relative bioavailability -				
solution as reference:	-			
alternate formulation as reference:	X			Study 105HV103 (delivery devices PFS vs. PFP)
Bioequivalence studies -				
traditional design; single / multi dose:	X			Study 105HV103 (delivery devices PFS vs. PFP)
replicate design; single / multi dose:	-			
Food-drug interaction studies	-			
Bio-waiver request based on BCS	-			
BCS class	-			
Dissolution study to evaluate alcohol induced dose-dumping	-			
III. Other CPB Studies				
Genotype/phenotype studies	-			
Chronopharmacokinetics	-			
Pediatric development plan	-			
Literature References	X	217		
Total Number of Studies		21		4 Phase 1 + 1 Phase 3 + 15 validation reports + 1 PopPK

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data	X			

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	comparing to-be-marketed product(s) and those used in the pivotal clinical trials?				
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			Generally yes, but as an example the bioanalytical report for Phase 3 study needs to be access via hyperlink in summary reports in Module 2.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

___ Yes ___

Information request:

In Study 105HV103 you concluded the similarity in PK profiles between PFS and autoinjector by comparing the percent difference in geometric means of AUC and Cmax values. However, the Agency recommends using the 90% CI of ratios of log-transformed exposure measures, judged by the 80-125%, for assessing the comparability of two products. Please re-analyze the data accordingly and submit the results to the Agency. If the results fall out of 80-125%, the clinical impact should be addressed.

Ta-Chen Wu

Clinical Pharmacology Reviewer

Date

Angela Men

Team Leader

Date

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Appendix 1. Listing of Clinical Studies

Study Identifier	Study Objective(s)	Study Design	Test Product; Dosage Regimen; Route of Administration	Treatment Period	Number of Subjects Enrolled; Completed		
PK/PD Studies in Healthy Volunteers							
105HV101	To identify the maximum tolerated dose; To characterize PK and PD ; To evaluate safety and tolerability	Phase 1, single-dose, blinded, randomized, IM and SC dose escalation	IFN β -1a / BIIB017; 30 μ g/63, 125, and 188 μ g; IM/IM and SC	Single-dose	37M/23F; 36M/22F		
105HV102	To determine the optimal dose and frequency; To evaluate safety and tolerability; To characterize PK and PD in healthy volunteers	Phase 1, double-blind, randomized, placebo-controlled, multiple-dose, dose-ranging, parallel-group	BIIB017; 63, 125, and 188 μ g; 2 dosing frequencies (Q2W and Q4W); SC	Multiple dose-2 doses for Q4W and 4 doses for Q2W. Total treatment duration of 6 weeks	36M/33F; 35M/30F		
105HV103	To characterize PK of BIIB017 delivered by an autoinjector (PFP) and a PFS in healthy volunteers; To evaluate safety and tolerability	Phase 1, randomized, open-label, 2-sequence, 2-period crossover	BIIB017; 125 μ g; SC	One injection per device with a 3-week washout in between	32M/23F; 14M/10F*		
PK and PD in Renal Impairment Subjects							
105RI101	To characterize PK and PD in healthy volunteers and subjects with various degrees of renal impairment; To evaluate safety and tolerability	Phase 1, single-dose, open-label, multicenter, serial group, non-randomized	BIIB017; 63 and 125 μ g; SC	Single-dose	22M/13F; 22M/13F		
PK and PD Studies in MS Subjects							
105MS301	To determine efficacy and safety; To characterize PK and PD in subjects with relapsing MS	Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled	BIIB017; 125 μ g at 2 dosing frequencies (Q2W and Q4W); SC	2 years	441M/1071F; Year 2 ongoing		
Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
105MS302	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	At time of data cutoff (24 October 2012): 517 enrolled; 508 dosed; 0 completed	Relapsing Remitting Multiple Sclerosis	96 weeks	Ongoing; Interim
105MS302 AI Sub-Study	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	39 subjects enrolled and dosed; 39 completed treatment; 34 completed follow up	Relapsing Remitting Multiple Sclerosis	6 weeks	Complete; Full sub-study report appended to main interim study report

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

/s/

TA-CHEN WU
07/10/2013

YUXIN MEN
07/16/2013