CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	125499 (0000)
Drug Name:	Pegylated Interferon Beta 1A (BIIB017)
Indication(s):	Relapsing Multiple Sclerosis
Applicant:	Biogen IDEC
Date(s):	May 16, 2013
Review Priority:	Standard
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Keywords: Futility Analysis, Blinded Sample Size re-estimation

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1 EXECUTIVE SUMMARY

The Year 1 data from the 1512 randomized patients with relapsing Multiple Sclerosis (MS) in study 301 seems to support the efficacy of BIIB017 125 mcg every 2 weeks and BIIB017 125 mcg every 4 weeks relative to placebo. Note that placebo was re-randomized to BIIB017 in Year 2 but this part of the study was not the primary hypothesis and was not complete prior to the BLA submission. Only one study was required to support the application since the active ingredient in this product is approved in another formulation.

The primary endpoint was the annualized relapse rate over the first year. Relapses were adjudicated by a centralized committee. The multiplicity adjustment was sequential testing of a hierarchy of endpoints testing the more frequent administration first for each endpoint, and only formally testing the next endpoint if both doses won on the current one.

The trial did incorporate an interim futility analysis of MRI Lesion imaging data after the first 200 total patients had completed 24 weeks. The sample size was also blindly monitored and increased by 80 patients per group based on this monitoring. There is no indication that this compromised the integrity of the trial (see section 3.2.1.4.4 for more details).

It is notable that only 3% of the randomized patients were randomized in the US. Efficacy of the every 2 week regimen in the US subgroup favored placebo numerically for the Annualized Relapse Rate and Time to First Relapse but this may have been due to chance, e.g., the high variability associated with the small subgroup sample size. Also, this trend moved towards the right direction when the subgroup was expanded to include Canada. Furthermore, for the MRI T2 Lesion data the BIIB017 every 2 week group was numerically better than placebo so the suggestion of inferior effect in the US subgroup was not consistent across all key endpoints. In summary, it seems difficult to justify celebrating this US subgroup effect apparently going numerically in the wrong direction except for the fact that it speaks to the need to plan at the outset for a higher proportion of US subjects.

In conclusion, the Year 1 annualized relapse rate data from the 1512 randomized patients in study 301 seems to support the efficacy of BIIB017 125 mcg every 2 weeks and BIIB017 125 mcg every 4 weeks.

2 INTRODUCTION

2.1 Overview

Peginterferon beta-1a is a glycosylated recombinant 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 is the company product code for this new active substance, peginterferon beta-1a. PEGylation is a well-established process by which one or more units of chemically activated PEG moieties are attached to a therapeutic molecule. Generally, PEGylation shields a protein from enzymatic degradation or other clearance mechanisms. This product was developed under IND 100110.

Study 301 was a 2-year, global, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study of BIIB017 subcutaneous (SC) administered with 2 dosing frequencies (dosing every 2 or 4 weeks) in comparison to placebo in subjects with Relapsing Remitting Multiple Sclerosis (RRMS). The treatment period was 96 weeks (2 years). In Year 1 (Week 0 to Week 48, referred to as the placebo-controlled phase of the study), subjects were randomized to receive placebo or BIIB017 125 μg SC administered every 2 weeks or every 4 weeks. At the end of treatment Year 1, subjects in the placebo group were re-randomized to receive BIIB017 treatment so that during treatment Year 2 (Week 48 to Week 96), all subjects received BIIB017 125 μg every 2 weeks or every 4 weeks. Treatment group assignment remained blinded during the second year of treatment.

The sponsor's Summary of Clinical Efficacy (SCE) provides complete results up to the time of the pre-planned data cutoff for both Study 301 and Study 302 (24 October 2012), which corresponds to the date that all subjects had completed the placebo-controlled Year 1 of Study 301.

A total of 183 investigational sites in 26 countries worldwide participated in the study and randomized 1516 subjects. The highest enrolling countries were Poland (386 subjects), the Ukraine (189 subjects), India (170 subjects), the Russian Federation (145 subjects), and Serbia (134 subjects). All other countries each enrolled fewer than 100 subjects.

Table 1 Key Efficacy Study Characteristics

Study	# of Subjects per Arm	Follow-up Period	Year 1 Completion N (%)	Primary Efficacy Measure	Study Population
301: Parallel Group Study	Placebo N= 500	1 Year (primary) then placebo re-randomized to active for Year 2	456 (91%)	Annualized Relapse Rate in Year 1	3% in N. America 18 to 65 years old; confirmed diagnosis of relapsing MS; 0≤ EDSS score≤5
	BIIB017 125 μg every 4 weeks N= 500		438 (88%)		
	BIIB017 125 μg every 2 weeks N=512		438 (86%)		

2.2 Data Sources

The global submit file location for this application is \\cbsap58\m\ectd_submissions\stn125499\125499.enx.
At the time of review the locations of the primary endpoint data for the key study were as follows.
\\cbsap58\m\eCTD Submissions\STN125499\0000\m5\datasets\105ms301\analysis\legacy\datasets\ADARr.xpt
The rest of the analysis datasets were in the following directory.
\\cbsap58\m\eCTD Submissions\STN125499\0000\m5\datasets\105ms301\analysis\legacy\datasets\
The sdtm (raw) datasets were in the following directory.
\\cbsap58\m\eCTD_Submissions\STN125499\0000\m5\datasets\105ms301\tabulations\sdtm\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The quality of the data that was submitted seems to be adequate in terms of the supporting documentation provided and usability.

3.2 Evaluation of Efficacy

This reviewer was able to very nearly reproduce the primary analysis results from the tabulation (raw) datasets by confirming the number of INEC confirmed relapses in the first year for each patient.

3.2.1 Study 301

The date of first treatment in this study was 05 June 2009 and the date of data cutoff (the open label year 2 portion of the study was ongoing at the time of BLA submission) was 24 October 2012. The original protocol was dated 13 March 2009 and the final protocol was dated 27 March 2012. The original Statistical Analysis Plan for Study 301, is dated 21 September 2010, and the amended final Statistical Analysis Plan, is dated 01 May 2012.

3.2.1.1 Study Design

The primary objective of this study is to determine the efficacy of BIIB017 in reducing the Annualized Relapse Rate (ARR) at 1 year in subjects with RRMS.

This was a global multicenter, randomized, double-blind, parallel-group, placebo-controlled study. The study was to be conducted in approximately 200 sites.
All subjects were to receive a subcutaneous (SC) injection (self administration) of study treatment (either BIIB017 or placebo) every 2 weeks. The treatment period is 2 years in duration. The randomization ratio will be 1:1:1 between the following 3 treatment groups:

- Group 1: 420 subjects will receive placebo every 2 weeks for 48 weeks followed by 125 mcg BIIB017 SC every 2 or 4 weeks for 48 weeks.
- Group 2: 420 subjects will receive 125 mcg BIIB017 SC every 2 weeks for 96 weeks
- Group 3: 420 subjects will receive 125 mcg BIIB017 SC every 4 weeks for 96 weeks

To ensure blinding across these treatment groups, each subject was to receive one injection of BIIB017 or placebo every 2 weeks.

Subjects were to participate in this study for up to approximately 108 weeks (2 years, 3 months), which was to consist of: up to a 6 week screening period, a 96-week (2 year) treatment period which was to include a 4 week titration period, and up to a 12 week post-treatment period (Week 100 and/or Week 108).

Treatment Period
For the first treatment year, clinic visits were to occur every 2 weeks up to Week 8 (Weeks 2, 4, 6, 8), then every 4 weeks up to Week 24 (Weeks 12, 16, 20, 24), then every 12 weeks up to Week 48 (Weeks 36, 48).
For the second treatment year, clinic visits were to occur every 2 weeks up to Week 56 (Weeks 50, 52, 54, 56), then every 4 weeks up to Week 60, then every 12 weeks up to Week 96 (Weeks 72, 84, 96).

As necessary, an Unscheduled Relapse Assessment Visit (within 72 hours of the onset of any new neurological symptoms that may indicate the onset of a clinical relapse) and/or an Early Withdrawal Evaluation Visit and/or Week 108 Visit for EDSS evaluation were to occur.

To ensure treatment blinding, each subject was to receive one injection of BIIB017 or placebo every 2 weeks and the titration procedure was to be handled in the same manner between treatment groups. To ensure treatment blinding, all subjects were to undergo re-randomization process via Interactive Voice/Web Response System (IXRS) at Week 48 at which time only placebo subjects were to be re-randomized to receive BIIB017 treatment. After re-randomization, subjects would know they were receiving
BIIB017 treatment, but would remain blinded to the treatment frequency (every 2 or 4 weeks). At the completion of the first year of the treatment period (Week 48) placebo subjects were to be re-randomized to BIIB017 treatment. At re-randomization through IXRS the following was to apply:

· If the subject is receiving BIIB017, the subject will stay on BIIB017 at the same dose frequency.

· If the subject is receiving placebo, the subject will be re-randomized to receive BIIB017 every 2 or 4 weeks for the remainder of the study.

Interim Analysis

An interim analysis using MRI data will be performed after the first 210 subjects complete the 6 month MRI timepoint. The objective of the interim analysis is for futility. The endpoint to be used in the interim analysis is the number of new or newly enlarged T2 lesions on a single MRI scan obtained at the 6 month time point when compared with baseline results. Since the primary endpoint will not be evaluated, no efficacy claim will be made based on the results of the futility look, and the interim analysis will be based on the surrogate MRI endpoint at 6 months from a small proportion of subjects (17%), it is not necessary to adjust the type I error rate.
Any personnel, who are unblinded for this interim analysis will not be involved in the management of the study after unblinding, nor would information be shared with anyone who has a role in subject management during the study.

Early termination criteria of the study for futility

The sponsor planned to consider terminating the study for futility if the following conditions were met in both BIIB017 dosing groups in terms of treatment effect, which was calculated as the percentage reduction from placebo group in the mean new and newly enlarged T2 lesions:

☐ Observed treatment effect < 17%

AND

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

These stopping boundaries were selected in order to ensure the probability of falsely stopping the trial due to sampling variability would be less than 5% assuming that the hypothesized effect sizes of BIIB017 45% were true. The final decision to stop the study was to be based on the overall consistency of the data and the assessment of risk benefit and consultation with the independent Data Safety Monitoring Committee (DSMC).

SAMPLE SIZE JUSTIFICATION

The primary endpoint is the 1-year Annualized Relapse Rate (ARR). The sample size calculation was based on the type I error rate of 0.05 and a dropout rate of 10%. It was assumed that the treatment effect for BIIB017 would be 32% reduction from placebo in the 1-year ARR. In Version 1 of protocol, a sample size of 420 per treatment group was planned to provide approximately 90%, 87%, and 85% power when the placebo 1-year ARR was 0.6, 0.55, or 0.5, respectively, and it was specified that the pooled 1-year ARR would be monitored and the placebo 1-year ARR would be estimated by back-calculating from the pooled ARR and the assumed treatment effect. If the placebo 1-year ARR was estimated to be lower than 0.5, the sample size could increase for the study. As permitted by the protocol, the pooled 1-year ARR was monitored and the placebo 1- year ARR was estimated by back-calculating from the pooled ARR and the assumed treatment effect. As a result of this monitoring, the sample size was increased from 420 to 500 subjects per group in Version 4 of the protocol (dated March 14, 2011).

Multiplicity Adjustment

Statistical testing for efficacy endpoints was to be made between the BIIB017 every 2 week group and the placebo group, and between the BIIB017 every 4 week group and the placebo group separately. A sequential (closed) testing procedure was to be used to control the overall Type I error rate due to multiple comparisons for the primary endpoint. If the first comparison (the every 2 week group versus placebo) was statistically significant ($p \leq 0.05$) then the second comparison (the every 4 week group versus placebo) would also be made at the 0.05 alpha level. However, if the first comparison was not statistically significant, then the second comparison could not be considered statistically significant. Secondary endpoints were rank prioritized. In order to control for a Type I error for the secondary endpoints, the sequential closed testing procedure was to include both the order of the secondary endpoints and dose groups. Specifically, for each of the secondary endpoints, a sequential (closed) testing procedure was to be used to control the overall Type I error rate due to multiple comparisons with the first comparison (the BIIB017 every 2 week group versus placebo) and the second comparison (the every 4 week group versus placebo). If statistical significance was not achieved for one or both comparisons, all endpoint(s) of a lower rank could not be considered statistically significant for one or both comparisons, respectively. There were to be no multiple comparison adjustments for tertiary endpoints.

Analysis Population

The intent-to-treat (ITT) population defined below was to be used for the efficacy analyses.

Intent-to-Treat Population

The ITT population was defined as all subjects who were randomized and received at least 1 dose of study treatment (BIIB017 or placebo).

Per-protocol Population

The per-protocol population was defined as subjects from the ITT population without any major protocol deviations (e.g. major inclusion/exclusion criteria violation, study drug non-compliance, taking prohibited medications). All efficacy endpoints were to be evaluated on the ITT population. The primary and secondary efficacy endpoints were also to be analyzed based on the per-protocol population, in addition to the ITT population. The analyses performed on the ITT population were to be considered the primary analyses, and the analysis based on per-protocol population was to be considered a supportive analysis.

Primary Endpoint – Annualized Relapse Rate (ARR) at 1 year

Definition of Relapses

Only relapses that were determined to meet the following protocol-defined criteria were to be included in the analysis: new or recurrent neurologic symptoms, not associated with fever or infection, lasting for at least 24 hours, and accompanied by new objective neurological findings upon examination by the *examining neurologist*. In addition, these events need to be to be confirmed by the Independent Neurology Evaluation Committee (*INEC)*.

New or recurrent neurologic symptoms that occur less than 30 days following the onset of a protocol-defined relapse were to be considered part of the same relapse, i.e., if 2 relapses have onset days that are within 29 days of one another, they were to be counted only as 1 relapse, and the onset date used in the analysis was to be the onset date of the first relapse.

Relapses that occur after subjects receive any alternative drug treatments directed toward the treatment of MS such as chronic immunosuppressant therapy or other immunomodulatory treatments (including, but not limited to: interferon beta, interferon alpha, glatiramer acetate, natalizumab, cyclophosphamide, methotrexate, azathioprine, mycophenylate, 4-aminopyridine or related products.) were to be excluded from the analyses of relapse rate, and the subject's time on study was to be censored at the time the alternative MS medication was started.

Days on Study, and Relapse Rate

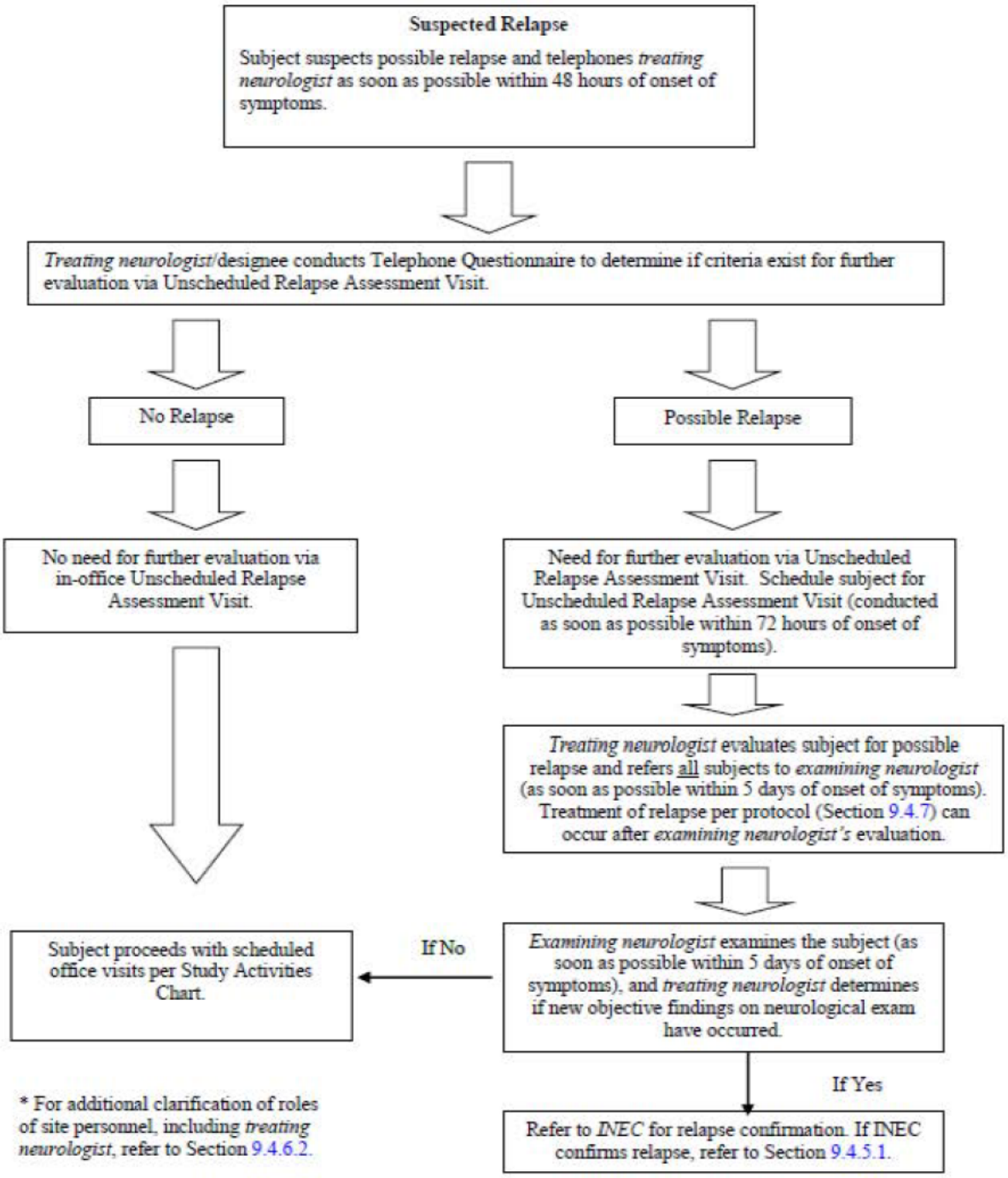
For ARR at 1 year, the total number of days on study is defined as the number of days from the date of the first dose to the date of Week 48 visit if subjects stay on the study for longer than a year. If subjects withdraw from the study or switch to an alternative MS therapy prior to 1 year, the total number of days on study is defined as the number of days from the date of the first dose to the last date on study or last date prior to the switch. The relapse rate for each treatment group was to be calculated as the total number of relapses experienced in the group divided by the total number of days in the study for the group, and the ratio multiplied by 365. This is the unadjusted relapse rate. In addition, the relapse rate for an individual subject was to be calculated as the number of relapses for that subject divided by the number of days the subject participated in the study, and the ratio multiplied by 365. Based on these individual relapse rates, the mean and median for each treatment group were to be presented.

Analysis Method

The primary analysis method for annualized relapse rate was to be negative binomial regression (log-likelihood ratio test assuming the number of relapses follows a negative binomial distribution). If the data is under-dispersed or if the negative binomial regression model does not converge a Poisson model was to be used instead of the negative binomial regression model. Dispersion was to be evaluated from the Pearson Chi-Square statistic. If the ratio of the Pearson Chi-Square statistic to the degrees of freedom is < 1 then a Poisson regression model was to be used. In any case, as a sensitivity analysis, the Poisson regression method was also be used to analyze the primary endpoint. The number of relapses was to be the response variable analyzed. Logarithmic transformation of the time on study was to be included as an independent variable in the model as the "offset" parameter. The model was to include a term for treatment, the baseline relapse rate, age (<40 vs. ≥ 40), and EDSS (<4 or ≥ 4). Baseline relapse rate is defined as the number of relapses over the 3 years prior to the day of screening, divided by 3. The adjusted relapse rate from the regression analyses was to be presented for each group. The rate ratio for each BIIB017 group vs. placebo was also to be presented.

In a sensitivity analysis for the primary endpoint, all relapses (regardless of whether or not they are confirmed by INEC) were to be included. Other rules were to be similar to the analysis of the primary analysis method.

Figure 1 Relapse Confirmation Procedures



Proportion of Subjects Relapsed at 1 Year

Definition of Relapses

Only protocol-defined relapses confirmed by INEC were to be included in the analysis for this endpoint. The definition of relapse was the same as the definition used in the primary endpoint analysis.

Censoring Rules and Start Date

If a subject prematurely withdraws from the study prior to 1 year, and the subject did not experience a protocol-defined relapse prior to withdrawal, the subject was to be censored on the last date of the 1-year treatment phase. If a subject started alternative MS medication without experiencing a protocol-defined INEC-confirmed relapse, data for the subject was to be censored at the time of starting MS medication. If a subject stays in the study for longer than a year without experiencing a protocol-defined INEC-confirmed relapse, data for the subject was to be censored at the Week 48 visit date. The start date for calculation of day to censor or relapse was to be date of first dose, and if date of first dose was incomplete, date of randomization was to be used.

Analysis Method

The analysis method for the proportion of subjects relapsed at 1 year was to be a Cox proportional hazards model for time to first relapse, adjusted for baseline EDSS score (<4 or ≥ 4), baseline age (<40 vs. > 40 years old), baseline relapse rate, and Gd enhancing lesions at baseline (Presence vs. absence). Baseline relapse rate was to be defined as the number of relapses over 3 years prior to study entry. Estimated proportions of subjects relapsed from the Kaplan-Meier curve were to be presented. The proportions of subjects relapsed over 2 years were to be presented with descriptive statistics. One sensitivity analysis was to be performed. In the analysis, all relapses (regardless of whether or not they were confirmed by the INEC) were to be included, using the same model as stated above.

Progression of Disability as Measured by EDSS Score at 1 and 2 Years

Definition of disability progression

Tentative EDSS (Expanded Disability Status Scale) progression is defined as a minimum change (i.e., at least a 1.0 point increase on the EDSS from baseline EDSS ≥ 1.0 or at least a 1.5 point increase on the EDSS from baseline EDSS = 0) that is present on a scheduled or unscheduled study visit. The EDSS progression is defined as confirmed when this minimum EDSS change is present on the next study visit occurring after 74 days from the initial observation. EDSS evaluations after re-randomization at week 48 were to be used to determine the occurrence of sustained progression for subjects who were randomized to placebo and who had a tentative progression at week 48. EDSS evaluation during post-treatment after week 96 would be used to determine the occurrence of sustained progression for subjects who had a tentative progression at week 96. For subjects who switched to alternative MS medications, the EDSS evaluation after subjects started MS alternative MS medication was to be used to determine the occurrence of sustained progression if the subjects had a tentative progression before switching. Progression was not to be confirmed at a visit where a relapse was also occurring. A subject was considered to be having a relapse for at least 29 days after the start date of a protocol defined relapse. If a subject met the defined criteria of sustained progression and was also having a relapse, the subject was to be required to meet the defined minimum criteria at the subsequent visit. Disability progression could be confirmed at the early (premature) study withdrawal visit, according to the rules above, as long as the early withdrawal visit was not also a relapse assessment visit.

Time to disability progression over 1 year (comparing each BIIB017 group with placebo) and over 2 years (comparing each BIIB017 group with the 1 yr placebo+1 yr BIIB017 group) were to be analyzed by a Cox proportional hazards model. The model was to include a term for treatment group and adjust for baseline EDSS values, and age (<40 vs. ≥40).

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

Magnetic Resonance Imaging (MRI) scans were performed in the global study on all subjects with and without Gadolinium (Gd) during the Screening period (30 days prior to the first dose, and not less than 5 days prior to the first dose), and at the Week 24, Week 48, and Week 96 visits during the treatment period. Brain scans were sent to a central MRI reading center where 2 qualified MRI readers independently performed a thorough review of all brain slices and identified the Gd-enhancing lesions. For exploratory purposes, additional MRI scans were conducted in a subset of subjects participating in a country-specific frequent MRI substudy every 4 weeks between Screening and Week 24. Participation in this substudy of frequent MRI analysis was optional for subjects who signed a separate Informed Consent Form if they wanted to participate.

Criteria for the Endpoint

For all MRI endpoints, 2 year referred to the Week 96 assessment and 1 year referred to the Week 48 assessments. Baseline MRI assessments referred to the assessment taken at the Screening Visit. MRI measurements taken from early withdrawal visits were assigned to the scheduled visits using a windowing scheme. The window for the early withdrawal visits was ± 30 days around the scheduled visit date (24 weeks, Year 1 and Year 2). MRI data measured after subjects started any approved alternative MS medications was set to missing. Alternative MS medications included, but were not limited to, interferon beta, interferon-alpha, glatiramer acetate, natalizumab, cyclophosphamide, methotrexate, azathioprine, mycophenylate, 4-aminopyridine or related products. These missing MRI data were imputed up to Week 48, regardless of reasons, using the principle of constant rate of lesion development and the method of last observation carried forward (LOCF), described as follows: The number of new or newly enlarging T2 hyperintense lesions were measured at Week 24 (comparing Week 24 scans with the baseline scans) and Week 48 (comparing Week 48 scans with Week 24 scans). If the Week 48 data were missing, the number of new or newly enlarging T2 hyperintense lesions from the period between Week 24 to Week 48 was imputed using the number of new or newly enlarging T2 hyperintense lesions from the period between baseline to Week 24, assuming the rate of lesion development was constant (which was the same as the method of LOCF). Then the number of new or newly enlarging T2 hyperintense lesions from baseline to Week 48 was calculated by adding the Week 24 (relative to baseline) and Week 48 (relative to baseline) number after imputation. If there were no nonmissing MRI values to be carried forward (e.g., Week 24) for those subjects with at least 1 post-baseline value, then the mean from subjects from the same treatment group in the same visit was used to impute the missing value.

For all other MRI endpoints, the same criteria for the endpoints for data inclusion/missing data imputation were to be used.

Analysis method

The negative binomial regression model was to be used for the analysis of MRI number of new or newly-enlarging T2 hyperintense lesions at week 24 and 1 year. The model was to include the treatment group and adjust for the baseline number of T2 hyperintense lesions.

A sensitivity analysis was to be performed. In the sensitivity analysis, only observed data was to be used for the analysis, using the same analysis model as described above. Number of new and newly enlarging T2 hyperintense lesions in year 2 and over 2 years periods were to be summarized by descriptive statistics.

3.2.1.2 Patient Disposition

A total of 183 investigational sites in 26 countries worldwide participated in the study and randomized 1516 subjects. The highest enrolling countries were Poland (386 subjects), the Ukraine (189 subjects), India (170 subjects), the Russian Federation (145 subjects), and Serbia (134 subjects); all other countries each enrolled fewer than 100 subjects. Of the 1516 subjects randomized for the study, 4 subjects were never dosed (3 had been randomized in error, and 1 reported a pre-treatment adverse event and became ineligible to participate in the study). The 1512 subjects who received at least 1 dose of study treatment comprised the ITT and safety populations. The per-protocol population, defined as all subjects in the ITT population who did not have any major protocol deviations, included 1465 subjects (97%) overall with 482, 486, and 497 subjects in the placebo, BIIB017 every 4 weeks, and BIIB017 every 2 weeks groups, respectively. The first subject was dosed on 05 June 2009. The placebo-controlled phase of the study (Year 1) was completed on 24 October 2012. Of the 1512 subjects who received treatment, 1332 (88%) completed Year 1 treatment. Of the 1332 subjects who received treatment in Year 2, 608 subjects (46%) had completed the 2-year treatment period (completed the study), and 625 subjects (47%) were continuing Year 2 treatment and assessments at the data cutoff date (24 October 2012).

Table 2 Study 301 Subject Disposition

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

Note: This table was copied from pages 119 and 120 of the sponsor's study report

Year 1

Among the 1512 subjects who received study treatment, 500 received at least 1 dose of placebo, 500 received at least 1 dose of BIIB017 125 µg SC every 4 weeks, and 512 received at least 1 dose of BIIB017 125 µg SC every 2 weeks (Table 9). A total of 1332 subjects (88%) completed the Year 1 study treatment period (placebo-controlled phase of the study). The number of subjects who completed Year 1 by country and site was generally balanced across treatment groups.

For all 3 treatment groups, withdrawal of consent was the most common reason for discontinuing study treatment and was similar across groups: 6% for placebo, 6% for BIIB017 every 4 weeks, and 7% for BIIB017 every 2 weeks (Table 9). Numbers of withdrawals from the study during Year 1 were the same as treatment discontinuations, with the exception of 1 subject (BIIB017 every 2 weeks) who discontinued study treatment but remained in the study for follow-up. The percentage of subjects who discontinued study treatment or withdrew in Year 1 was slightly lower in the placebo group compared with the BIIB017 treatment groups: 9% for placebo, 12% for BIIB017 every 4 weeks, and 14% for BIIB017 every 2 weeks. The difference in discontinuation rates between treatment groups was largely due to the difference in AEs leading to discontinuation or withdrawal (5% in each BIIB017 treatment group, 1% in the placebo group). For the BIIB017 treatment groups, withdrawals occurred more frequently during the first 12 weeks of treatment than in any other 12-week period during Year 1 (Section 14, Table 76).

Year 2

Of the 1332 subjects who completed Year 1, all subjects received at least 1 dose of study treatment during Year 2. The 456 subjects in the placebo group who completed Year 1 were re-randomized to the BIIB017 treatment groups, with 228 subjects randomized into the BIIB017 every 4 weeks group, and 228 subjects randomized into the BIIB017 every 2 weeks group. Subjects who were in the BIIB017 treatment groups in Year 1 continued in the same BIIB017 treatment group in Year 2.

As of the data cutoff date for this report, 608 (46%) of the 1332 subjects who entered Year 2 completed the Year 2 treatment period (completed the study), and 625 subjects (47%) were continuing in the Year 2 treatment period (Table 10). The percentage of subjects who completed Year 2 was similar across treatment groups. The number of subjects who completed Year 2 by country and site was generally balanced across treatment groups (Table 77). The percentage of subjects who discontinued study treatment during Year 2 was slightly higher in subjects who were re-randomized from placebo to BIIB017 treatment (9% in the placebo to BIIB017 every 4 weeks group and 11% in the placebo to BIIB017 every 2 weeks group), compared with subjects who received BIIB017 in Year 1 and continued in the same BIIB017 treatment group in Year 2 (8% in the BIIB017 every 4 weeks group and 5% in the BIIB017 every 2 weeks group. Similar to Year 1, the most common reason for discontinuation of study treatment or withdrawal from the study was withdrawal of consent, followed by discontinuation due to an AE (Table 10).

Discontinuations and Withdrawals Due to Relapse or Lack of Effect

After the data cutoff, the Study 301 database was reviewed to identify subjects whose reason for treatment discontinuation or study withdrawal, as recorded on the CRF, the sponsor thought could possibly be attributed to MS relapse or a lack of treatment effect. This review done by the

sponsor identified 30 out of 1512 subjects (2%) in the ITT population who withdrew from the study or discontinued study treatment due to MS relapse or lack of beneficial effect during the 2 years of the study in the sponsor's opinion.
Of these 30 subjects, 5 subjects discontinued as a direct result of MS relapse AEs, 19 subjects withdrew consent, 4 discontinued due to Investigator decision, 1 was lost to follow-up, and 1 discontinued due to "other" ("Patient feels there is a lack of efficacy and wishes to seek other treatment options"). Of the subjects who discontinued as a direct result of MS relapse, 1 was receiving placebo, 3 were receiving BIIB017 every 4 weeks, and 1 was receiving BIIB017 every 2 weeks at the time of discontinuation. Of the 25 subjects who discontinued due to reasons associated with lack of treatment effect (based on medical review of reasons for discontinuation), 5 were receiving placebo, 11 were receiving BIIB017 every 4 weeks, and 9 were receiving BIIB017 every 2 weeks at the time of discontinuation

Demographic Characteristics
In the ITT population, the 3 treatment groups were generally well balanced with respect to baseline demographic characteristics (Table 3). The majority of subjects (71%) were women. Subjects ranged in age from 18 to 61 years (mean: 36.5 years); 62% of subjects were younger than 40 years of age. The majority of subjects (82%) were white, with 11% Asian, 6% "other," and <1% black or African American. The ethnicity of <1% of subjects was unknown. Mean weight was 69.03 kg and ranged from 36.0 to 176.9 kg. Mean BMI was 24.48 kg/m^2 and ranged from 14.8 to 57.6 kg/m^2.
Geographically, 70% of subjects in the ITT population were from Eastern Europe (Bulgaria, Croatia, the Czech Republic, Estonia, Greece, Latvia, Poland, Romania, the Russian Federation, Serbia, and the Ukraine), 11% were from India, 8% were from Western Europe (Belgium, France, Germany, the Netherlands, Spain, and the UK), 7% were from the Rest of World (Chile, Colombia, Georgia, Mexico, New Zealand, and Peru), and 3% were from North America (Canada and the US).

Table 3 Study 08-05: Baseline Demographic and Disease Characteristics

Variable	Subgroup or Summary Statistic	Placebo	BIIB017 Every 4 WKs	BIIB017 Every 2 WKs	Overall
AGE	Mean (SD)	36.3 (9.7)	36.4 (9.9)	36.9 (9.8)	36.5 (9.8)
Age > 40	No	310 (62.0)	304 (60.8)	320 (62.5)	934 (61.8)
	Yes	190 (38.0)	196 (39.2)	192 (37.5)	578 (38.2)
Sex	F	358 (71.6)	352 (70.3)	363 (70.5)	1073 (70.8)
	M	142 (28.4)	149 (29.7)	152 (29.5)	443 (29.2)
Race	ASIAN	56 (11.2)	56 (11.2)	59 (11.5)	171 (11.3)
	BLACK	3 (0.6)	1 (0.2)	3 (0.6)	7 (0.5)
	OTHER	29 (5.8)	32 (6.4)	33 (6.4)	94 (6.2)
	WHITE	412 (82.4)	410 (82.2)	419 (81.5)	1241 (82.0)
Region	EUROPE	392 (78.4)	395 (78.8)	398 (77.3)	1185 (78.2)
	NORTH AMERICA	17 (3.4)	16 (3.2)	20 (3.9)	53 (3.5)
	REST OF WORLD	91 (18.2)	90 (18.0)	97 (18.8)	278 (18.3)
EDSS	Mean (SD)	2.4 (1.2)	2.5 (1.2)	2.5 (1.3)	2.5 (1.2)
EDSS $\geq$ 4	No	432 (86.4)	413 (82.6)	424 (82.7)	1269 (83.9)
	Yes	68 (13.6)	87 (17.4)	89 (17.3)	244 (16.1)
GD Lesions	0	296 (59.6)	298 (59.7)	336 (65.5)	930 (61.6)
	$\geq$1	201 (40.4)	201 (40.3)	177 (34.5)	579 (38.4)
McDonald criterion	1	445 (89.0)	428 (85.6)	451 (87.9)	1324 (87.5)
	$\geq$2	55 (11.0)	72 (14.4)	62 (12.1)	189 (12.5)
Years since symptoms onset	Mean (SD)	6.3 (6.3)	6.5 (6.1)	6.9 (6.6)	6.6 (6.3)
Relapses in 3yrs prior	Mean (SD)	2.6 (1.0)	2.5 (0.8)	2.6 (1.0)	2.5 (0.9)
Years since Diagnosis	Mean (SD)	3.5 (4.6)	3.4 (4.4)	4.0 (5.1)	3.6 (4.7)
Months since recent pre-study relapse	Mean (SD)	4.8 (2.7)	5.1 (2.9)	5.1 (2.9)	5.0 (2.8)
Anti PEG antibody Ever Positive	No	437 (87.4)	431 (86.0)	459 (89.1)	1327 (87.5)
	Yes	63 (12.6)	70 (14.0)	56 (10.9)	189 (12.5)
IFN Binding Antibody: Ever Positive	No	475 (95.0)	473 (94.4)	461 (89.5)	1409 (92.9)
	Yes	25 (5.0)	28 (5.6)	54 (10.5)	107 (7.1)
IFN Neutralizing Antibody: Ever Positive	No	493 (98.6)	497 (99.2)	503 (97.7)	1493 (98.5)
	Yes	7 (1.4)	4 (0.8)	12 (2.3)	23 (1.5)

3.2.1.3 Sponsor's Results

Primary Efficacy Endpoint: Annualized Relapse Rate at 1 Year

The annualized relapse rate at 1 year was significantly reduced by 27.5% (p = 0.0114) and 35.6% (p = 0.0007) following treatment with BIIB017 every 4 weeks and BIIB017 every 2 weeks, respectively, compared with placebo.

The analysis of the primary efficacy endpoint (annualized relapse rate for the ITT population at 1 year) was based on INEC-confirmed relapses. Data after subjects switched to an approved alternative MS therapy were excluded. No data imputation was performed. The endpoint was analyzed using negative binomial regression, adjusted for baseline EDSS score (<4 versus ≥4), baseline age (<40 versus ≥40 years), and baseline relapse rate (number of relapses in 3 years prior to study entry divided by 3).

During Year 1, a total of 487 possible relapses were reported (all relapses). Of those, 464 were assessed as protocol-defined relapses and 422 were confirmed by INEC. Table 4 presents the distribution of relapse events by definition and treatment group.

Table 4 Summary of Relapses in First Year by Randomized Group

	Placebo Group	BIIB017 Q4W Group	BIIB017 Q2W Group	Total
All relapses	213	142	132	487
Protocol-defined relapses	204	134	126	464
INEC-confirmed relapses	181	125	116	422

Source: Table 28 and Section 14, Table 96 and Table 97. Q4W = every 4 weeks, Q2W = every 2 weeks.

Note: This table was copied from page 172 of the sponsor's study report

The adjusted annualized relapse rate at Year 1 was 0.397 (95% CI, 0.328, 0.481) in the placebo group, compared with 0.288 (95% CI, 0.234, 0.355) in the BIIB017 every 4 weeks group and 0.256 (95% CI, 0.206, 0.318) in the BIIB017 every 2 weeks group (see Table 5 and Figure 2). The rate ratios obtained from the model were 0.725 (p = 0.0114) for BIIB017 every 4 weeks versus placebo and 0.644 (p = 0.0007) for BIIB017 every 2 weeks versus placebo. This indicated that the annualized relapse rate at Year 1 was significantly reduced by 27.5% and 35.6% following treatment with BIIB017 every 4 weeks and BIIB017 every 2 weeks, respectively, compared with placebo. Analyses of the per subject relapse rates were consistent with the analysis of annualized relapse rate at Year 1.

Table 5 Sponsor's Analysis of Annualized Relapse Rate (INEC confirmed) in ITT Population at 1 Year

	Placebo	BIIB017 125 (mcg) SC	
		Every 4 weeks	Every 2 weeks
Number of subjects in ITT population	500 (100)	500 (100)	512 (100)
Number of subjects with relapses of			
0	358 (72)	395 (79)	422 (82)
1	110 (22)	90 (18)	71 (14)
2	26 (5)	12 (2)	13 (3)
3	5 (1)	1 (<1)	5 (<1)
>=4	1 (<1)	2 (<1)	1 (<1)
Total number of relapses	181	125	116
Total number of subject-years followed	445.25	434.10	435.74
Unadjusted annualized relapse rate (a)	0.407	0.288	0.266
Adjusted annualized relapse rate	0.397	0.288	0.256
95% CI (b)	(0.328,0.481)	(0.234,0.355)	(0.206,0.318)
Rate ratio (active/placebo)		0.725	0.644
95% CI (b)		(0.565,0.930)	(0.500,0.831)
p-value (compared to placebo)		0.0114	0.0007

NOTE 1: Only relapses confirmed by INEC are included in the analysis.
2: Data after subjects switched to alternative MS medications are excluded.
3: Numbers in parentheses are percentages.

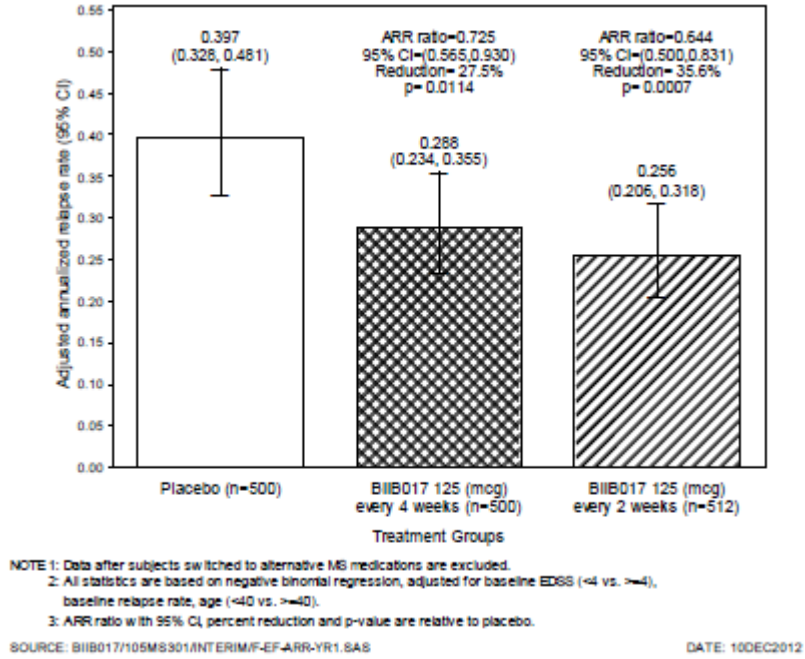
(a) The annualized relapse rate is calculated as the total number of relapses occurred during year 1 for all subjects, divided by the total number of subject-years followed in year 1.

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

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

Note: This table was copied from page 175 of the sponsor's study report

Figure 2 Adjusted Annualized Relapse Rate by Group



Note: This figure was copied from page 174 of the sponsor's study report

Five sensitivity analyses (3 prespecified and 2 post hoc) of the annualized relapse rate at Year 1 were performed by the sponsor and are described below. Results of all 5 analyses were consistent with the primary results presented above, showing that both BIIB017 dose frequencies resulted in statistically significant reductions over placebo in the annualized relapse rate, ranging from 26.5% to 31% for the BIIB017 every 4 weeks group versus the placebo group, and 33.8% to 38% for BIIB017 every 2 weeks group versus the placebo group. These 5 sensitivity analyses (1 through 3 were prespecified in the SAP; 4 and 5 are post-hoc analyses) differed from the primary analysis by using:

1. The per protocol population
2. Poisson regression model
3. All relapses recorded on the unscheduled relapse assessment CRF
4. Protocol-defined objective relapses recorded on the unscheduled relapse assessment CRF
5. Baseline Gd-enhancing lesion (presence versus absence) as a covariate in the model

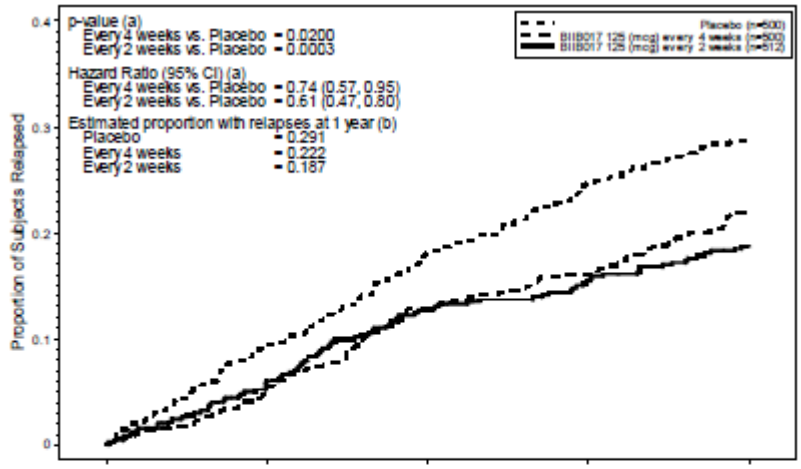
Proportion of Subjects Relapsed at Year 1

As compared with placebo, the risk of relapse over 1 year was significantly reduced by 26% (p = 0.0200) following treatment with BIIB017 every 4 weeks and 39% (p = 0.0003) following treatment with BIIB017 every 2 weeks. The primary analysis for this endpoint was based on INEC-confirmed relapses in the ITT population at Year 1 and included the data from all subjects in the ITT population until they completed Year 1 of study, or switched to approved alternative MS medication, or withdrew from the study. No data imputation was performed. The endpoint was analyzed using Cox proportional hazards model, adjusted for baseline EDSS (<4 versus ≥4),

age (<40 versus ≥40), baseline relapse rate, and baseline Gd-enhancing lesions (presence versus absence). Estimated proportion of subject relapse was calculated using a Kaplan Meier curve. A statistically significant reduction in the proportion of subjects who experienced a relapse at Year 1 was achieved in both BIIB017 treatment groups relative to placebo in the ITT population (Figure 3). The proportion of subjects relapsed at Year 1 was 0.291 in the placebo group as compared with 0.222 in the BIIB017 every 4 weeks group and 0.187 in the BIIB017 every 2 weeks group. The hazard ratios obtained from the model were 0.74 (95% CI, 0.57, 0.95) for the BIIB017 every 4 weeks group versus placebo and 0.61 (95% CI, 0.47, 0.80) for the BIIB017 every 2 weeks group versus placebo, representing risk of relapse reductions of 26% (p = 0.0200) following treatment with BIIB017 every 4 weeks and 39% (p = 0.0003) following treatment with BIIB017 every 2 weeks relative to placebo.

Visual inspection of the Kaplan-Meier plot of the time to first relapse revealed a separation between the curve for the placebo group and the nearly overlapping curves for the 2 BIIB017 groups from Week 4 through Week 36. After Week 36 through the end of Year 1, the separation between the placebo and BIIB017 every 4 weeks curves remained relatively constant, whereas the curves for the placebo and BIIB017 every 2 weeks groups continued to diverge (Figure 3). Similar results were obtained for the per protocol population analysis, with risk of relapse reductions of 25% (p = 0.0282) following treatment with BIIB017 every 4 weeks and 40% (p = 0.0003) following treatment with BIIB017 every 2 weeks, as compared with placebo. The results of a sensitivity analysis using all relapses (not necessarily INEC confirmed) were consistent with the primary analysis.

Figure 3 Cumulative Hazard of Relapse over Time in Year 1



Note: This figure was copied from page 183 of the sponsor's study report

Disability Progression by EDSS at Year 1

As compared to placebo, the risk of progression of disability (12-week confirmation) over 1 year was significantly reduced by 38% (p = 0.0380) following treatment with BIIB017 every 4 weeks and 38% (p = 0.0383) following treatment with BIIB017 every 2 weeks.

For the primary analysis, a progression could start but could not be confirmed when a subject was experiencing an INEC-confirmed relapse. Data after subjects switched to approved alternative MS medications could be used to confirm a progression that began before alternative MS medication was initiated. No data imputation was performed. Time to onset of sustained disability progression was assessed using a Cox proportional hazards model, adjusting for the baseline EDSS score as a continuous variable, and age (<40 versus ≥40 years). In the ITT population at Year 1, the proportion of subjects with sustained disability progression at Year 1 was 0.105 in the placebo group as compared with 0.068 in both BIIB017 every 4 weeks group and BIIB017 every 2 weeks group. The hazard ratios obtained from the model were 0.62 (95% CI, 0.40, 0.97) for both of the BIIB017 groups versus placebo, indicating that the risk of progression of disability over 1 year was significantly reduced by 38% (p = 0.0380) following treatment with BIIB017 every 4 weeks and 38% (p = 0.0383) following treatment with BIIB017 every 2 weeks relative to placebo (Table 6 and Figure 4)

Consistent results were obtained from 3 sensitivity analyses, 2 pre-specified and 1 post hoc (Gd-enhancing lesions). One sensitivity analysis was conducted by using the per protocol population, showing the risk of progression of disability reduction over 1 year was 38% (p = 0.0392) following treatment with BIIB017 every 4 weeks and 40% (p = 0.0287) following treatment with BIIB017 every 2 weeks relative to placebo. Another sensitivity analysis was conducted by taking the tentative disability progression prior to withdrawal from study as sustained disability progression, which indicates that the risk of progression of disability reduction over 1 year was 39% (p = 0.0197) following treatment with BIIB017 every 4 weeks and 29% (p = 0.0928) following treatment with BIIB017 every 2 weeks, relative to placebo. The third sensitivity analysis was conducted by adding baseline Gd-enhancing lesion (presence versus absence) as a covariate in the model, which resulted in risk reduction of progression of disability over 1 year of 38% (p = 0.0417) following treatment with BIIB017 every 4 weeks and 35% (p = 0.0623) following treatment with BIIB017 every 2 weeks relative to placebo.

Table 6 Summary of Time to Sustained Disability Progression at 1 year as measured by EDSS--ITT population

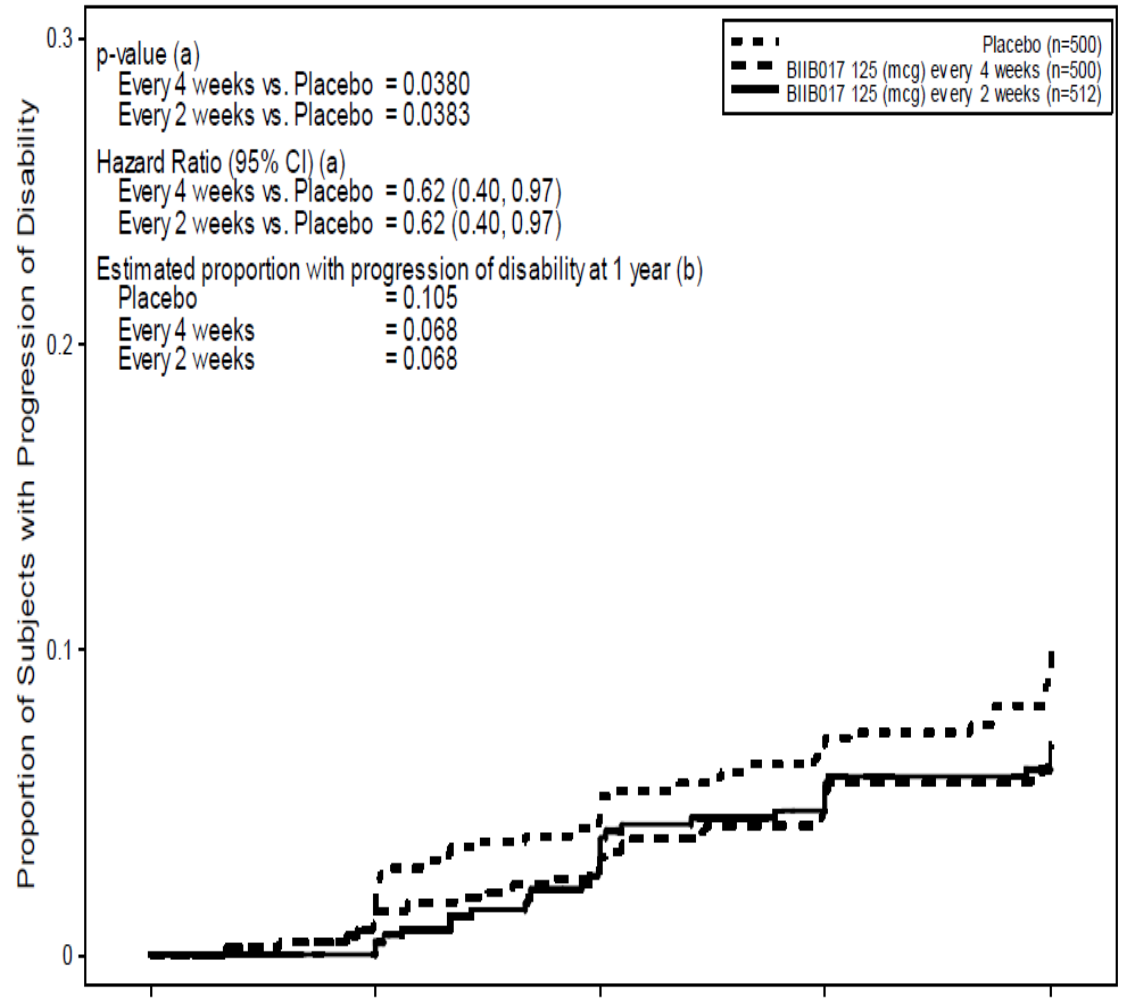
	Placebo	BIIB017 125 (mcg) SC	
		Every 4 weeks	Every 2 weeks
Number of subjects in ITT population	500 (100)	500 (100)	512 (100)
Number of subjects progressed	50 (10)	31 (6)	31 (6)
Time (weeks) to progression (a)			
10th percentile	48.1	NA	NA
25th percentile	NA	NA	NA
50th percentile	NA	NA	NA
Estimated proportion of subjects progressed at (a)			
12 weeks	0.023	0.015	0.004
24 weeks	0.052	0.032	0.038
36 weeks	0.071	0.054	0.056
48 weeks	0.105	0.068	0.068
Hazard ratio (active/placebo) and 95% CI (b)		0.62 (0.40, 0.97)	0.62 (0.40, 0.97)
p-value (compared to placebo) (b)		0.0380	0.0383

NOTE 1: Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.
2: Subjects are censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression.
3: Numbers in parentheses are percentages.
(a) Estimated time to progression and proportion of patients with progression based on the Kaplan-Meier product limit method.
(b) Based on Cox Proportional Hazards model, adjusted for baseline EDSS and age (<40 vs. >=40).
Abbreviations: NA = not available since the proportion of subjects with progression within the 48 weeks follow-up is less than the specified percentage.

Note: This table was copied from page 187 of the sponsor's study report

Figure 4 shows the cumulative hazard of EDSS progression.

Figure 4 Time to Sustained Progression of Disability as Measured by increase in EDSS score-Year 1



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

Note: This table was copied from page 186 of the sponsor's study report

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

Treatment with BIIB017 every 4 weeks and BIIB017 every 2 weeks significantly reduced the number of new or newly enlarging T2 hyperintense lesions that developed over 1 year by 28% (p=0.0008) and 67% (p<0.0001), respectively, compared with placebo. The number of new or

newly enlarging T2 hyperintense lesions was analyzed using a negative binomial regression model, adjusted for baseline number of T2 hyperintense lesions. Observed data after subjects had switched to approved alternative MS medications were excluded. Missing data at Week 48 were imputed based on Week 24 data assuming the constant rate of lesion development. The number of subjects with imputed data at Week 48 was 18, 23, and 18 for the placebo, BIIB017 every 4 weeks, and BIIB017 every 2 weeks groups, respectively.

In the ITT population, a statistically significant reduction in the number of new or newly enlarging T2 hyperintense lesions was achieved in both BIIB017 treatment groups compared to placebo at Year 1. A mean of 13.3 new or newly enlarging T2 hyperintense lesions developed in subjects who received placebo, as compared with means of 9.2 in subjects who received BIIB017 every 4 weeks and 4.1 in subjects who received BIIB017 every 2 weeks (Table 7). The adjusted lesion mean ratios obtained from the model were 0.72 (95% CI, 0.60, 0.87; p=0.0008) for BIIB017 every 4 weeks versus placebo and 0.33 (95% CI, 0.27, 0.40; p<0.0001) for BIIB017 every 2 weeks versus placebo, representing reductions of 28% (p=0.0008) and 67% (p<0.0001), respectively, in the number of new or newly enlarging T2 hyperintense lesions that developed over 1 year, compared with placebo.

Table 7 Number of New or Newly Enlarging T2 Hyperintense Lesions on MRI at Year 1

	Placebo	BIIB017 125 (mcg) SC	
		Every 4 weeks	Every 2 weeks
Week 48 (new lesions from baseline to week 48)			
0	91 (19)	115 (25)	187 (41)
1	47 (10)	56 (12)	69 (15)
2	32 (7)	37 (8)	47 (10)
3	26 (5)	36 (8)	27 (6)
>=4	280 (59)	218 (47)	127 (28)
n	476	462	457
Mean	13.3	9.2	4.1
SD	19.51	15.84	8.55
Median	6.0	3.0	1.0
25th, 75th percentile	1.0, 17.0	1.0, 11.0	0.0, 4.0
Min, Max	0, 148	0, 113	0, 69
Adjusted mean (a)	10.9	7.9	3.6
Lesion mean ratio (95% CI) (a)		0.72 (0.60, 0.87)	0.33 (0.27, 0.40)
p-value (a)		0.0008	<0.0001

NOTE 1: Numbers in parentheses are percentages.
2: Observed data after subjects switched to alternative MS medications are excluded. Missing data prior to alternative MS medications and visits after subjects switched to alternative MS medications are imputed based on previous visit data assuming the constant rate of lesion development or group mean at same visit. Number of subjects with imputed data for each group are 2, 1, 1 for week 24, and 18, 23, 18 for week 48.
(a) Adjusted mean, lesion mean ratio (95% CI) and p-value for comparison between the active and placebo groups, based on negative binomial regression, adjusted for baseline number of T2 lesions.

Note: This table was copied from the sponsor's study report

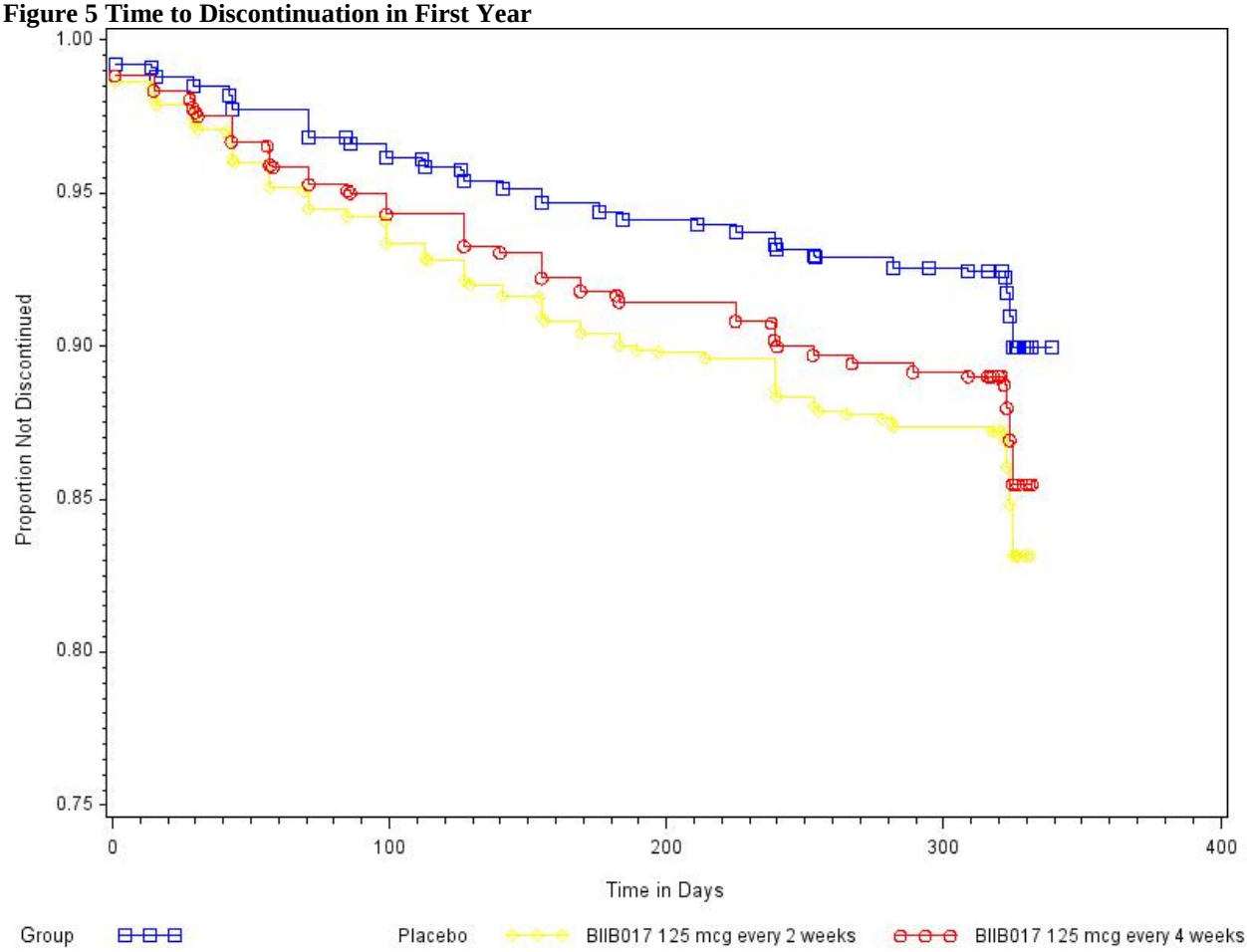
An additional sensitivity analysis based on multiple imputation was performed by the sponsor. The multiple imputation model was chosen to be identical to the model that was used for analysis [Little and Rubin 2002]: negative binomial regression with treatment group and baseline number of T2 hyperintense lesions. Thirty imputations were performed and determined to be sufficient, based on the rate of missing values, i.e., approximately of 12% of subjects discontinued study treatment in Year 1. This sensitivity analysis result was essentially consistent with the primary analysis of T2 lesions.

3.2.1.4 Reviewer's Results

This reviewer was able to very nearly reproduce the primary analysis results from the tabulation (raw) datasets by confirming the number of INEC confirmed relapses in the first year for each patient.

There was a slight imbalance in time to discontinuation in the first year with dropout rates slightly higher in the BIIB017 groups. The Log Rank test p-values for assessing differences in time to discontinuation compared to placebo were p=0.0007 for BIIB017 every 2 weeks and p=0.0183 for BIIB017 every 4 weeks (see Figure 5).

Figure 5 Time to Discontinuation in First Year



3.2.1.4.1 Sensitivity Analyses for Annualized Relapse Rate at Year 1

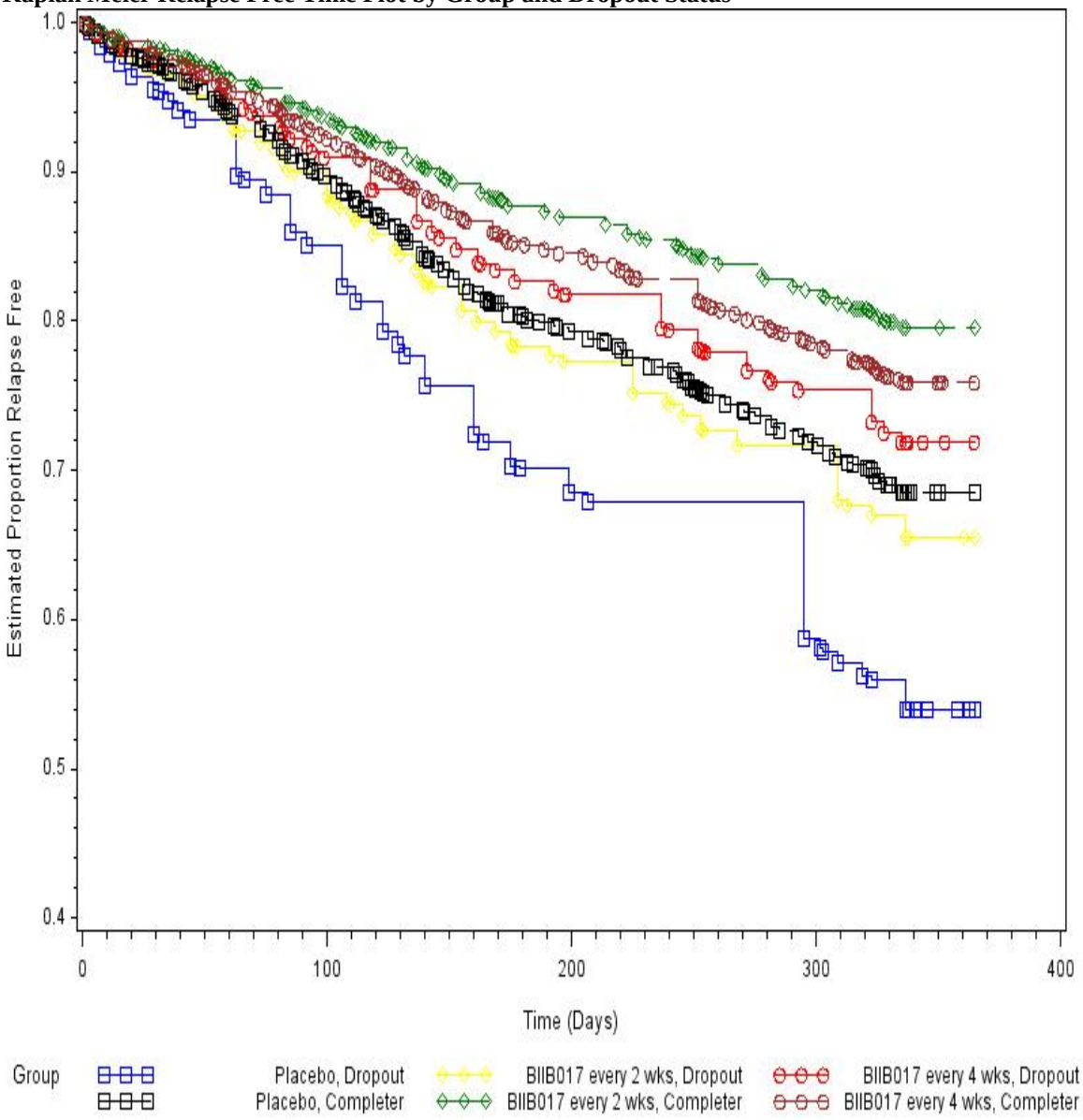
Seven (7), 13, and 11% of placebo, BIIB017 every 2 weeks, and BIIB017 every 4 weeks, respectively, were assessed for relapses for less than 9/10's of their first years.
We may consider imputing for the missing part of the first year for these patients in order to check for sensitivity to this incomplete assessment.
Multiple Imputation of Incomplete data for Annualized Relapse Rate assuming the highest observed rate (5.3) pertains to the missing periods irrespective of the patient with incomplete data's actual group gave the following results for the log of the ratio of the relapse event rates:-.60 p=0.056 for BIIB017 every 4 weeks and -.89 p=0.009 for BIIB017 every 2 weeks.
This reviewer's multiple imputation sensitivity analysis using imputations based on assuming the placebo rate of episodes-for the missing period of time irrespective of the patient's actual group gave the following log event rate ratios: -0.56, p= 0.0764 for BIIB017 every 4 weeks and -0.83, p= 0.0056 for BIIB017 every 2 weeks.

Analysis of the Annualized Relapse Rate for Completers only gave the following log event rate ratios: -0.2887 p=0.0282, and -0.5078, p= 0.0002 for BIIB017 every 4 weeks and every 2 weeks, respectively, compared to placebo. After exponentiating, the corresponding event rate ratios to placebo were 0.60 for BIIB017 every 4 weeks and 0.75 for BIIB017 every 2 weeks (compared to the placebo estimated ARR of 0.38).
Therefore, in summary, the existence of incomplete periods of assessment during the first year for around 10 percent of patients does not seem to have had a significant impact on the ARR results.

3.2.1.4.2 Sensitivity Analyses for Relapse Event by Year 1

Figure 6 shows that dropouts had a higher risk of a first relapse than completers regardless of treatment assignment. This reviewer did some additional post hoc sensitivity analyses to investigate this. Analyses of time to first relapse event randomly assigning failures for discontinuation due to AE or Withdrawn consent: This reviewer's post hoc sensitivity analysis of time to first relapse which assumed dropouts due to AE were relapses at the time of dropout gave first relapse hazard ratio results of 0.838, p=0.1543 for BIIB017 every 4 weeks and 0.758, p=0.0290 for BIIB017 every 2 weeks. If randomly selecting 75% instead of assuming all of these dropouts were events the results were 0.860, p=0.2021 for BIIB017 every 4 weeks and 0.805, p=0.0705 for BIIB017 every 2 weeks. If randomly selecting 67% instead of assuming all of these dropouts were events the results were 0.858, p=0.1993 for BIIB017 every 4 weeks and 0.789, p=0.0513 for BIIB017 every 2 weeks. These analyses may be overly conservative, with their strong assumption about discontinuation due to AE or withdrawal of consent actually being due to a relapse, and the BIIB017 every 2 week result seems reasonably robust to this.

Figure 6 Kaplan Meier Relapse Free Time Plot by Group and Dropout Status



N=42 Placebo Dropouts ,75 BIIB017 every 2 wk Dropouts, 62 BIIB017 every 4wk Dropouts, 458 Placebo Completers, 440 BIIB017 every 2wk Completers,439 BIIB017 every 4wk Completers

3.2.1.4.3 New or Newly Enlarging T2 Lesions on MRI

Percentages missing a Week 48 (Year 1) MRI assessment were 14.56 (N=72), 12.38 (N=61), and 8.40 (N=42) for BIIB017 125 mcg every 2 weeks, every 4 weeks, and Placebo, respectively. Although the differences from placebo in terms of these missing

assessments may not seem too large they were in fact nominally statistically significant: BIIB017 every 2 weeks p=0.0021 and every 4 weeks p=0.0393, respectively.
The sponsor's prespecified analysis of the Week 48 MRI was to impute using either the last post-baseline MRI assessment carried forward, if applicable, or to impute with the corresponding group mean if there was no post baseline assessment available to be carried forward. The sensitivity analysis based on only observed MRI data at Week 48 (N=456, 440, 438) yielded estimated hazard ratios for BIIB017 every 2 weeks to placebo of 0.3302, p<0.0001 and for BIIB017 every 4 weeks to placebo of 0.7473, p=0.0029. Therefore, the imputation rule doesn't seem to have made much difference.

3.2.1.4.4 Interim Futility Analysis of MRI T2 Lesion Data and Blinded Sample Size Re-estimation

The sponsor's study report suggests on page 108 that the interim futility analysis evaluated only the MRI endpoints, i.e., not the primary endpoint, annualized relapse rate.
About 870 subjects had already been randomized at the time of the protocol amendment dated 14 March 2011 which called for a sample size increase of 80 additional patients per group. The 210th patient completed his or her week 24 assessment (the prespecified timing of the unblinded interim analysis of MRI data) in September 2010.

In their response (dated March 11, 2013) to FDA pre-BLA meeting comments the sponsor provided the following details regarding the futility analysis and sample size increase.
Futility Analysis(Excerpt from Sponsor's Responses to FDA pre-BLA meeting comments)
The interim futility analysis for protocol 105MS301 occurred on December 1, 2010. This futility analysis was pre-specified in the protocol version 3.1 (submitted April 16, 2010), Statistical Analysis Plan (SAP), and unblinding plan (submitted October 5, 2010) to be performed after the first 210 subjects completed the 24 week MRI time point. As detailed in the protocol and SAP, unblinding was restricted to the following three efficacy variables necessary for this analysis:
1) Number of new or newly enlarging T2 lesions on MRI at Week 24
2) Number of new active lesions on MRI at Week 24
3) Number of gadolinium-enhancing lesions on MRI at Week 24.
As described in the SAP, the futility analysis was performed by the independent DSMB statistician. Biogen Idec provided blinded data to the independent DSMB statistician who received treatment assignment codes directly from the external vendor which assigns randomization numbers using a centralized Interactive Voice/Web Response System (IXRS). The independent DSMB statistician presented the outcome of the analysis, as pre-specified in the SAP, to the DSMB. No Biogen Idec personnel had access to the unblinded data or analysis.

Sample size increase (Excerpt from Sponsor's Responses to FDA pre-BLA meeting comments)
As permitted by the 105MS301 protocol, Biogen Idec calculated the pooled 1-year ARR in January 2011 based on blinded data. The timing of this calculation was determined based on the amount of person years follow up during which relapse data could be collected. By January 2011, there were approximately 300 person years (i.e. 100 per years per group) of data, which were felt to be able to provide a reasonable stable estimate of pooled ARR. The calculated pooled 1-year ARR was approximately 0.335. Then the following formulas were used in back-

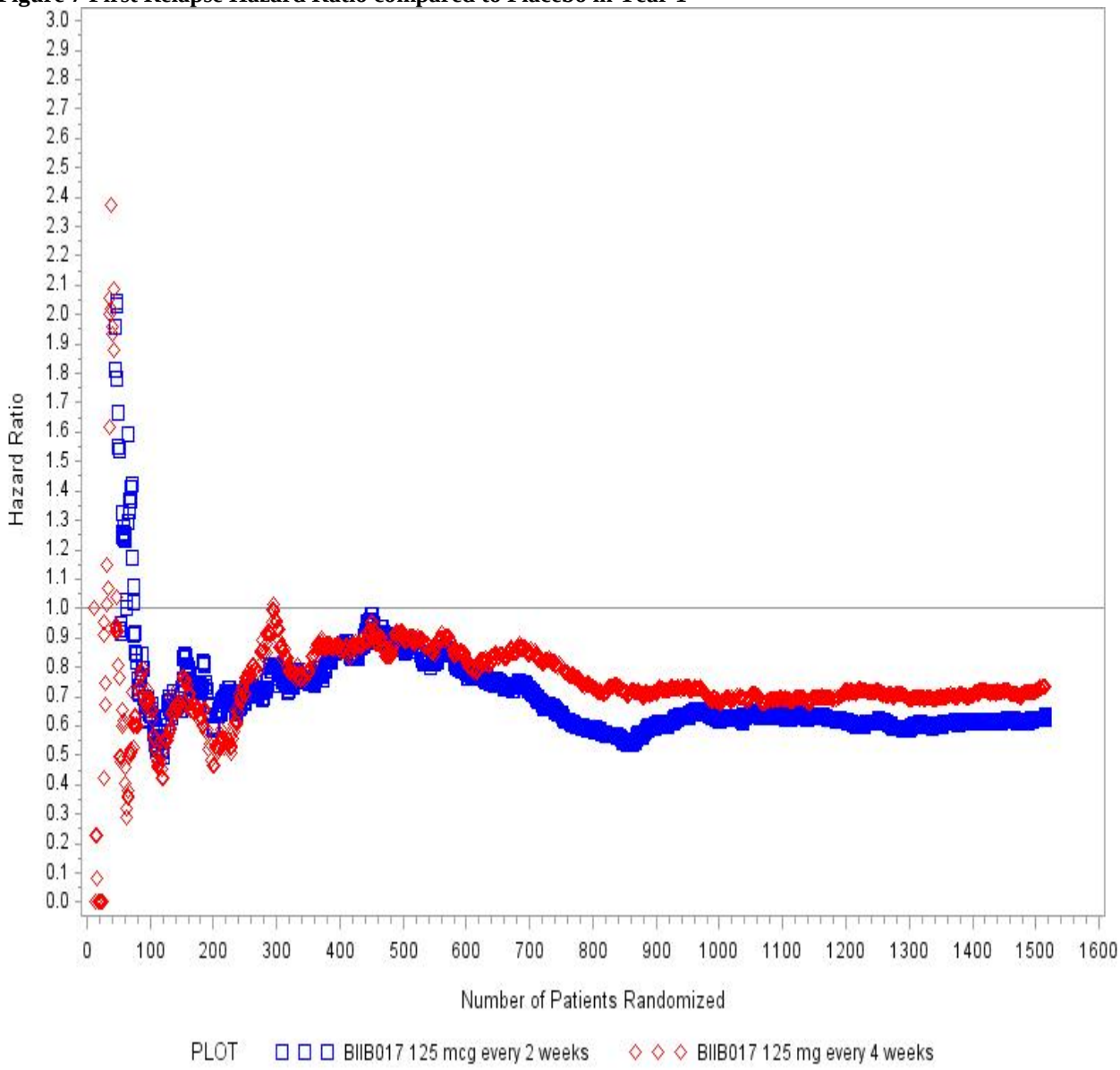
calculating the placebo 1-year ARR, assuming a 32% reduction in ARR in each of the two BIIB017 groups compared with the placebo group. This 32% reduction was assumed in the original sample size calculation in the protocol.

(b) (4)

Since the calculated placebo ARR was less than 0.5, a new sample size was calculated based on the revised assumption on the placebo ARR while keeping all other assumptions the same as the original sample size calculation, including the treatment effect of 32% reduction. A sample size of 450 per treatment group was thus calculated to provide approximately 85% power when the placebo 1-year ARR was assumed to be 0.43 and the treatment effect for BIIB017 is 32 % reduction from placebo in the 1-year ARR, with a two sided type I error rate of 0.05. Consistent with the approach taken during the original sample size calculation, the sample size of 450 was also adjusted to 500 per treatment group to account for the drop-out rate of 10% over 1 year. This resulted in a new sample size of 500 per treatment group.

Figure 7 shows how the hazard ratio associated with the analysis of time to first relapse evolved over time as more and more patients were randomized into the trial.

Figure 7 First Relapse Hazard Ratio compared to Placebo in Year 1



Sensitivity Analyses including only the first 420 patients/group (the originally planned maximum sample size) did not differ substantially from those for the larger ultimate sample based on the blindly re-estimated sample size. The results of these subset analyses were as follows.
Estimated ratios over placebo of the group Year 1 based Annualized Relapse Rate were 0.648, p=0.0025 for BIIB017 every 2 weeks, and 0.691 p=0.0091 for BIIB017 every 4 weeks.
Estimated time to first relapse hazard ratios over placebo of the BIIB017 groups during Year 1 were 0.612, p=0.0010 for BIIB017 every 2 weeks, and 0.716 p=0.0192 for BIIB017 every 4 weeks.

3.3 Evaluation of Safety

Please see the medical officer's review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Gender, Race, Age

Overall, 71% of randomized patients were female. With respect to races of the randomized population 82% were White, 11% Asian and 7% were designated as 'Other'. The characterization of the age of the randomized population was 62% were under age 40 and 100% under age 62.

Subgroup analyses of annualized relapse rate at Year 1 are summarized in Table 8.

Table 8 Annualized Relapse Rate by Subgroups of Interest

Subgroup	Placebo Rate	BIIB017 Every 2wks to Placebo Ratio with 95% C.I.	BIIB017 Every 4 wks to Placebo Ratio with 95% C.I.	Pvalue for Subgroup Interaction with Treatment
FEMALE	0.39	0.67(0.49;0.90)	0.80(0.60;1.07)	0.4292
MALE	0.42	0.59(0.37;0.95)	0.55(0.34;0.90)	
ASIAN	0.35	0.60(0.27;1.31)	0.72(0.35;1.48)	0.7495
OTHER	0.67	0.37(0.14;0.96)	0.72(0.32;1.64)	
WHITE	0.39	0.68(0.52;0.90)	0.72(0.54;0.96)	
AGE≤40	0.47	0.71(0.52;0.96)	0.82(0.61;1.10)	0.3055
AGE>40	0.36	0.52(0.32;0.82)	0.55(0.35;0.87)	

Subgroup analyses of time to first relapse rate within Year 1 are summarized in Table 9.

Table 9 Time to First Relapse Hazard Ratio by Subgroups of Interest

Subgroup	Hazard Ratio of BIIB017 Every 4wks/Placebo with 95% C.I.	Hazard Ratio of BIIB017 Every 2 wks/ Placebo with 95% C.I.	Pvalue for Subgroup Interaction with Treatment
FEMALE	0.87(0.65;1.17)	0.64 (0.47;0.88)	0.1218
MALE	0.47(0.28;0.79)	0.55 (0.34;0.90)	
ASIAN	0.61(0.27;1.34)	0.71 (0.32;1.56)	0.8729
OTHER	0.80(0.34;1.85)	0.44 (0.17;1.18)	
WHITE	0.75(0.56;1.00)	0.62 (0.46;0.83)	
AGE≤40	0.81(0.60;1.10)	0.67 (0.49;0.92)	0.4313
AGE>40	0.60(0.37;0.95)	0.49 (0.30;0.80)	

Subgroup analyses of number of new or newly active T2 Lesions on MRI within Year 1 are summarized in Table 10.

Table 10 Subgroup Analyses of the number of new or newly active T2 Lesions on MRI within Year 1

Subgroup	New Lesion Ratio of BIIB017 Every 4wks/Placebo' with 95% C.I.	New Lesion Ratio of BIIB017 Every 2 wks/ Placebo with 95% C.I.	P-value for Subgroup Interaction with Treatment
FEMALE	0.66 (-0.64;-0.19)	0.31 (-1.41;-0.96)	0.3186
MALE	0.89 (-0.46; 0.23)	0.40 (-1.28;-0.57)	
Age≤40	0.79 (-0.47;-0.01)	0.35 (-1.29;-0.82)	0.196
Age>40	0.56 (-0.88;-0.28)	0.28 (-1.59;-0.96)	
ASIAN	0.79 (-0.79; 0.33)	0.34 (-1.65;-0.51)	0.9001
OTHER	1.00 (-0.75; 0.75)	0.44 (-1.57;-0.06)	
WHITE	0.70 (-0.57;-0.15)	0.32 (-1.35;-0.92)	

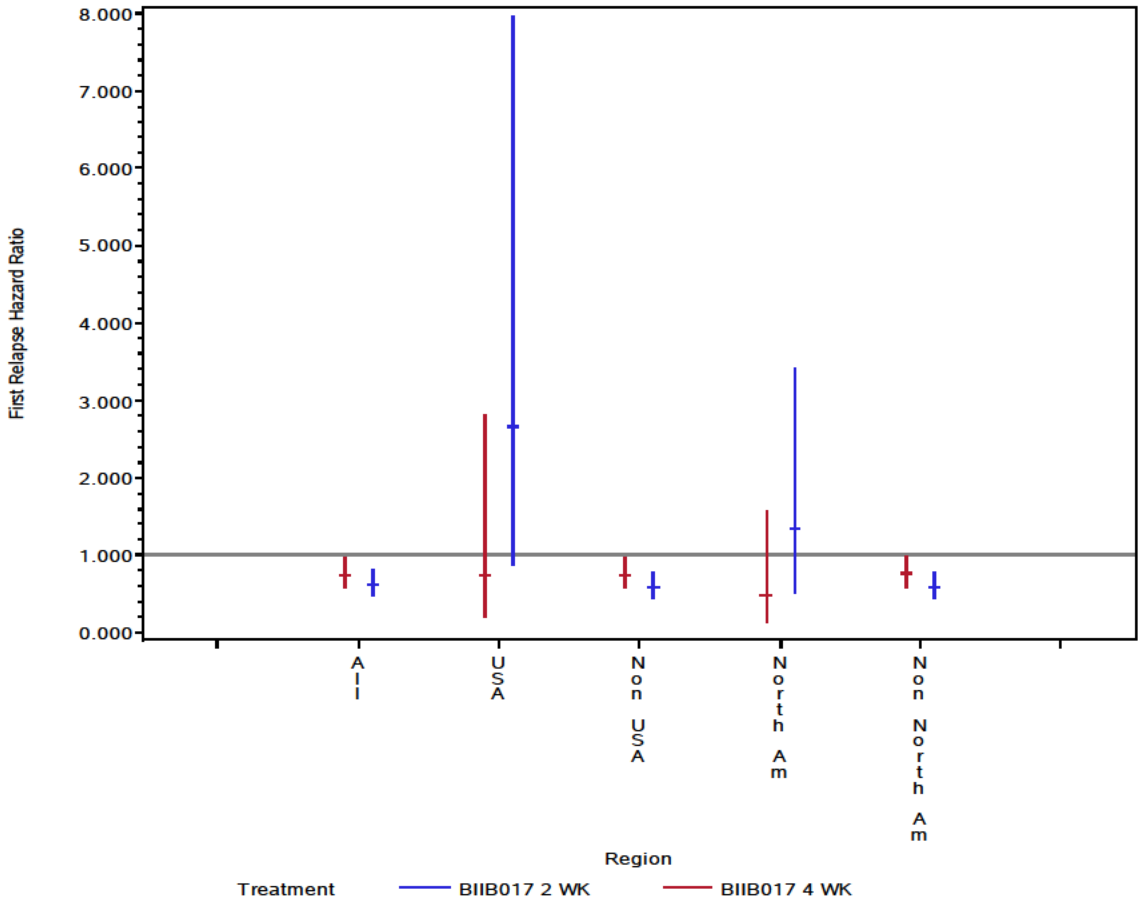
4.1.2 Geographic Region

Only 3% of the trial population were randomized in the US (70% was classified as E. Europe, 11% India, 8% W. Europe, and 8% Rest of World). As prespecified, the primary analysis was not to incorporate an adjustment for region or country. Regions were created in the analysis plan as described below.

An analysis of the Annualized Relapse Rate investigating regional differences in treatment effects found a p-value of 0.2408 based on the regions (North America, Europe and Rest of World). The corresponding p value of 0.4124 was found when the regions were E. Europe, India, North America, W. Europe, and the Rest of World. This suggests that there was not significant variation in the region specific treatment effects. Despite the small sample size this reviewer examined the USA subgroup (N=15, 13 and 13 for BIIB017 every 2 weeks, every 4 weeks, and placebo, respectively). Expanding this to North America increased these sample size numbers just slightly to 19, 16, and 17, respectively.

The hazard ratio of time to first relapse for BIIB017 vs. placebo was numerically in the wrong direction in the US subgroup and likewise but to a less extent for the North America subgroup (see Figure 8).

Figure 8 Hazard Ratio for First Relapse by Regional Subgroups of Interest (Reviewer's Analysis)



The estimated hazard ratio compared to placebo of time to first relapse in the US subgroup for BIIB017 every 2 weeks over Year 1 was 2.664 as compared to 0.574 outside the USA (t test for interaction p=0.0077). This numerical trend in the wrong direction for BIIB017 every 2 weeks compared to placebo was not as bad when Canada was pooled with the US. In particular, for North America vs. non- North America the interaction p-value looking for any treatment by

region differences over all experimental treatment groups was p=0.0620, while focused on BIIB017 every 2 weeks it was p=0.0907. The estimated first relapse hazard ratio of BIIB017 every 2 weeks over placebo in North America in Year 1 was 1.343 as compared to 0.581 for Non North America.

A test for an interaction differential treatment effect on Annualized Relapse Rate by region, US or non-US, gave a p-value of 0.0829. For BIIB017 every 2 weeks the estimated ratio of the group ARR over placebo was 0.60 for Non-US and 1.84 for US. For BIIB017 every 4 weeks the estimated ratio of the group ARR over placebo was 0.72 for Non-US and 0.69 for US.

A test for a differential treatment effect by region in terms of New or Newly Active T2 Lesions on MRI at Week 48 gave a p-value of 0.6501, suggesting no such difference and for this endpoint the BIIB017 every 2 week group was numerically in the right direction compared to placebo (Lesion ratio compared to placebo 0.33 Non-US; 0.48 US). The estimated T2 Lesion ratio compared to placebo for BIIB017 every 4 weeks was 0.72 for Non-US and 1.25 US.

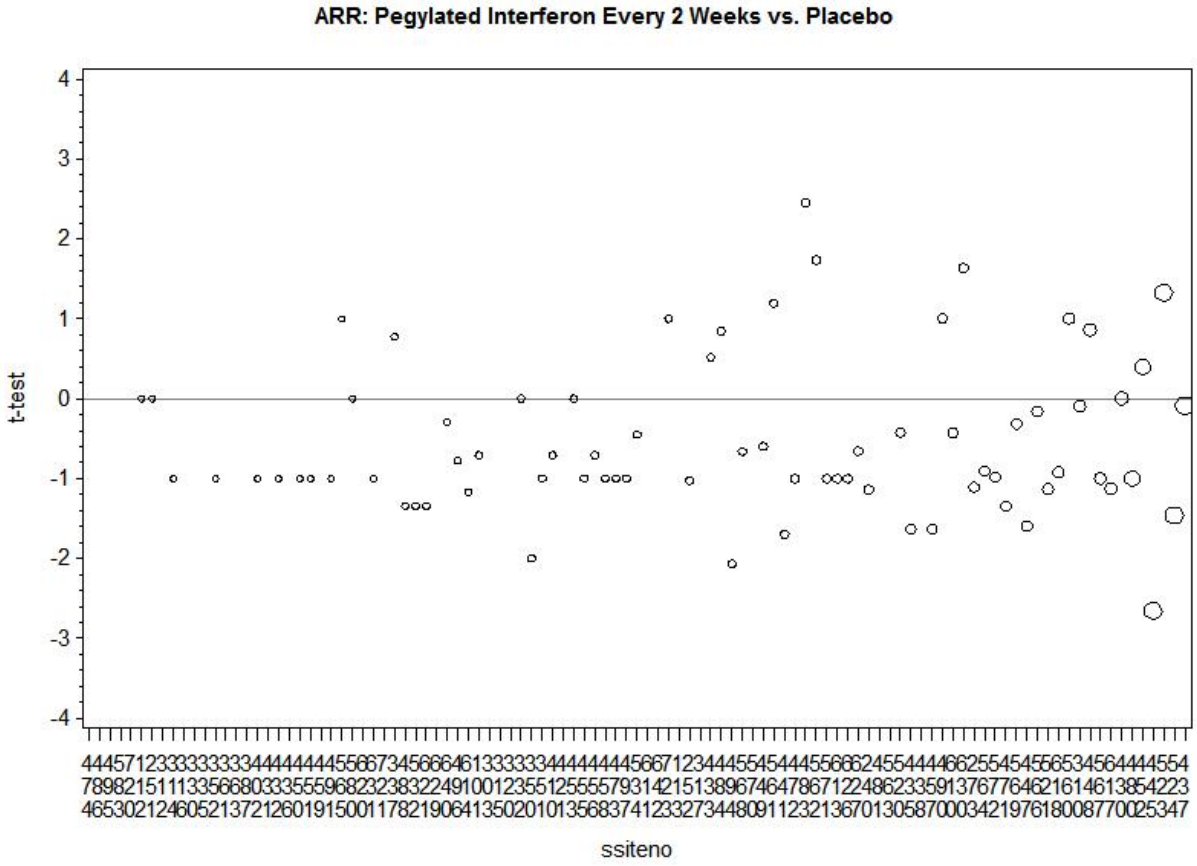
Therefore, overall, while it would have been desirable to have more patients randomized in the US, since the US vs. non-US by treatment interaction are not consistent over all the endpoints the US result being in the wrong direction in several cases may well be due to chance.

Individual Centers

The study was conducted at 176 centers worldwide. Between the BIIB017 125 mcg every 2 week and placebo groups at these centers sample sizes ranged from 1 to 55. It should be noted that deleting any one center's data did not result in a Year 1 ARR p-value of greater than 0.05 (for either regimen).

Figure 9 shows treatment differences between BIIB017 125 mcg every 2 weeks and placebo by center for annualized relapse rate over Year 1and time to first relapse (here analyzed only for occurrence of a relapse, i.e., not using the time). Note that the further to the right on the graph the bigger the sample size of the center (as indicated by the larger plotting symbol) and negative differences favor BIIB017.

Figure 9 Ratio of ARR over Year 1 for BIIB017 every 2 weeks to Placebo by Center



The time to EDSS progression analysis was sensitive to exclusion of data from certain individual centers. For example, excluding the EDSS data from any one of 8 different centers resulted in a p-value of greater than 0.05 for the BIIB017 every 2 weeks group vs. placebo comparison (a similar claim can be made for the every 4 weeks regimen). Although there was no reason to justify excluding data from these centers it illustrates that the EDSS progression analysis results were not very robust.

4.2 Other Special/Subgroup Populations

No other special/subgroup populations were examined by this reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The trial did incorporate an interim futility analysis of MRI Lesion imaging data (not the primary endpoint) after the first 200 total patients had completed 24 weeks. The sample size was also blindly monitored and increased by 80 patients per group (from 420 to 500) based on this monitoring. There is no indication that these procedures compromised the integrity of the trial.

It is notable that only 3% of the randomized patients were randomized in the US. Efficacy of the every 2 week regimen in the US subgroup favored placebo numerically for the Annualized Relapse Rate and Time to First Relapse but this may have been due to chance, e.g., the high variability associated with the small subgroup sample size. Also, this trend moved towards the right direction when the subgroup was expanded to include Canada. Furthermore, for the MRI T2 Lesion data the BIIB017 every 2 week group was at least numerically better than placebo so the suggestion of inferior effect in the US subgroup was not consistent across all key endpoints. In summary, it seems difficult to justify celebrating this US subgroup effect apparently going numerically in the wrong direction except for the fact that it speaks to the need to plan at the outset for a higher proportion of US subjects.

5.2 Conclusions and Recommendations

The Year 1 data from the 1512 randomized patients with relapsing Multiple Sclerosis (MS) in study 301 seems to support the efficacy of BIIB017 125 mcg every 2 weeks and BIIB017 125 mcg every 4 weeks relative to placebo. Note that placebo was re-randomized to BIIB017 in Year 2 but this part of the study was not the primary hypothesis and was not complete prior to the BLA submission. Only one study was required to support the application since the active ingredient in this product is approved in another formulation.

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

/s/

TRISTAN S MASSIE
01/17/2014

KUN JIN
01/17/2014
I concur with the review.

KOOROS MAHJOOB
01/22/2014
I concur with the review.