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RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

The efficacy of Daclizumab High Yield Process (DAC HYP) was studied in 2 pivotal trials in subjects with relapsing forms of multiple sclerosis (RMS): Study 201, a placebo-controlled study, and Study 301, an active-controlled study versus with IM interferon beta-1a (IFN β -1a) as comparator. Study 201 investigated two doses and results suggested that there was no additional benefit in using the DAC HYP 300 mg dose than the 150 mg dose. Study 301 only investigated the 150 mg dose.

Both Studies 201 and 301 demonstrated a statistically significant effect of DAC HYP 150 mg on the reduction in MS relapse. For the primary efficacy endpoint of annualize relapse rate (ARR), there was a 54% reduction in the drug group vs. placebo in Study 201 and a 45% reduction vs. IFN β -1a in Study 301 (both $p < 0.0001$). The efficacy on ARR was robust, supported by sensitivity analyses and subgroup analyses.

Both studies also showed statistically significant treatment benefits of DAC HYP 150 mg on brain MRI measures. Analysis of the number of new or newly enlarging T2 lesions showed a 70% reduction compared to placebo over 52 weeks and a 54% reduction compared to IFN β -1a over 96 weeks (both $p < 0.0001$). Study 201 also indicated that treatment with DAC HYP 150 mg reduced the number of new Gd-enhancing lesions by 69% ($p < 0.0001$).

2. INTRODUCTION

2.1 Overview

DAC HYP has been developed under Investigational New Drug (IND) application 012120 for the treatment of RMS. The clinical efficacy program consisted of 2 pivotal studies. Study 201 was a randomized, double-blinded, placebo-controlled study conducted in 621 RMS subjects that compared 2 different doses of DAC HYP (150 mg SC every 4 weeks and 300 mg SC every 4 weeks) over a 1-year treatment period. Study 301 was a randomized, double-blinded, active-controlled study comparing DAC HYP 150 mg SC every 4 weeks to weekly IM injections of IFN β -1a in 1841 RMS patients over a 2 to 3 year (96 to 144 weeks) treatment period.

Table 1. Overview of the Pivotal Clinical Studies

Study ID	Initiation Date	Treatment	No. of Sites	No. of patients enrolled
205MS201	15 Feb 2008	150 mg q4W for 48 weeks 300 mg q4W for 48 weeks Placebo	78 sites in 9 countries	621
205MS301	11 May 2010	150 mg q4W up to 96 to 144 weeks IFN β -1a 30 μ g IM weekly for 96 to 144 weeks	245 sites in 28 countries	1841

2.2 Data Sources

The study reports are located at <\\CDSESUB1\evsprod\BLA761029\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-sclerosis\5351-stud-rep-contr>. The datasets are located at <\\CDSESUB1\evsprod\BLA761029\0000\m5\datasets> and <\\CDSESUB1\evsprod\BLA761029\0020\m5\datasets>.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

During the review process, this reviewer was able to trace how the primary endpoint was derived and reproduce the key analysis results.

3.2 Evaluation of Efficacy

3.2.1 Study 301

The date of first treatment was May 11, 2010 and the Last Patient Last Treatment Period Visit date was on March 5, 2014. The date of the last follow-up visit was July 28, 2014. The database lock was on September 16, 2014.

A Special Protocol Assessment (SPA) Agreement letter was issued on June 7, 2010. The final protocol was dated April, 29 2013. The major changes in the final version of the protocol include the ranking of the secondary endpoint and the testing procedure for the efficacy analyses. A No Agreement letter to proposed modifications to the Statistical Analysis Plan (SAP) was issued on April 28, 2014. In response to the non-agreement letter, the Sponsor modified the statistical analysis plan prior to database lock. The SAP was finalized on May 23, 2014 and was considered acceptable by the Agency.

3.2.1.1 Study Design and Statistical Methodology

Study 301 was a double-blind, randomized, parallel-group, monotherapy, active-control study in patients with RMS. Subjects were randomized 1:1 to receive DAC HYP 150 mg SC once every 4 weeks and IFN β -1a intramuscular (IM) injection once weekly for at least 96 weeks but no more than 144 weeks. Randomization was stratified by site and prior use of IFN- β .

An Expanded Disability Status Score (EDSS) assessment was performed at scheduled visits every 12 weeks and at the time of relapse. An MRI scan was done at week 24 and week 96 or end of study. The treating neurologist made the decision as to whether symptoms of a potential relapse reported by a subject should be further evaluated by the examining neurologist or dismissed as not related to a relapse. A blinded independent neurology evaluation committee (INEC) made the final determination as to whether a relapse had occurred based on the data transmitted by the treating and examining neurologist/technician.

Efficacy Endpoints

The primary Endpoint was annualized relapse rate (ARR).

The secondary endpoints (rank ordered) were

1. number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks;
2. proportion of subjects with confirmed disability progression;
3. proportion of subjects who are relapse-free;
4. proportion of subjects with a ≥ 7.5 -point worsening from baseline in the MSIS-29 Physical Impact score at 96 weeks.

Efficacy analyses

The intent-to-treat (ITT) population was the primary efficacy population and included all randomized subjects who received at least 1 dose of study medication.

Analysis of Relapse

The primary endpoint of ARR was analyzed using a negative binomial regression model adjusting for the baseline relapse rate (number of relapses in the 3 years prior to study entry divided by 3), history of prior IFN β use, baseline EDSS score (≤ 2.5 vs. > 2.5), and age (≤ 35 vs. > 35 years). The logarithmic transformation of the number of years in the study was included in the model as the “offset” parameter. Only INEC-confirmed relapses until either the end of the treatment period, switch to alternative MS medication, or withdrawal from the study were included in the primary analysis.

The following sensitivity analyses were planned:

1. including all data until Last Patient Last Treatment Period Visit instead of the End of Treatment Period Visit;
2. including all relapses that occur after starting alternative medication;
3. including all protocol defined relapses (INEC approved or not);
4. censoring all subjects at the earliest of 1) the start of alternative MS medications, 2) End of Treatment Period Visit date or 3) 96 weeks after the First Dosing Date;
5. a Poisson regression model.

Analysis of the number of new or newly-enlarging T2 hyperintense lesions

The primary analysis of the number of new or newly enlarging T2 lesions at Week 96 included observed data and was analyzed using a negative binomial regression model adjusting for the baseline number of T2 lesions, history of prior IFN β use, and baseline age (≤ 35 vs. > 35 years). The logarithmic transformation of the number of scans was included in the model as the “offset” parameter.

Analysis of Disability Progression

Confirmed disability progression was defined as at least a 1.0-point increase on the EDSS from a baseline EDSS ≥ 1.0 or at least a 1.5-point increase from a baseline EDSS = 0 that was sustained for 12 weeks. Progression must have started prior to or at the End of Treatment Period Visit and prior to the start of alternative MS medication. Death due to MS was counted as progression. EDSS progression was confirmed if an EDSS change of at least the minimum magnitude was

present on the next study visit occurring at least 74 days from the initial observation. The EDSS assessment obtained in the follow-up period or the extension study could be used to confirm the tentative progression. Progression could not be confirmed at a visit where a relapse was occurring (29 days after the start date of an INEC-confirmed objective relapse). If the subject met the defined criteria of confirmed progression and was also having a relapse, then the subject was required to meet the defined minimum criteria at the subsequent visit.

The difference between treatment groups in confirmed disability progression was assessed using a Cox proportional hazards model, adjusted for baseline EDSS (as a continuous variable), history of prior IFN β use, and baseline age (age ≤ 35 versus age > 35 years). Subjects who did not have a confirmed progression were censored on the date of the last follow-up EDSS assessment on or prior to the End of Treatment Period Visit or the last EDSS assessment prior to the alternative MS medication. For subjects with a tentative progression that could not be confirmed, the censor date was the date of the tentative progression. It was planned that if the proportional hazards assumption for the Cox assumption did not hold, the log rank test would be used instead.

The following sensitivity analyses were planned:

1. using multiple imputation (MI) method for subjects who had a tentative progression but then dropped out of the study. The probability of confirmation was estimated via a logistic regression model and confirmed progression flags were imputed. The MI was conducted 50 times with random seed pre-specified to generate 50 analysis datasets. The Cox proportional hazards model was conducted on each of the 50 data sets, and the analysis results were combined using Rubin's method;
2. progression was not counted if it is started during a relapse;
3. all tentative progressions with no confirmatory EDSS assessments > 74 days after the tentative progression were assumed confirmed.

Analysis of Proportion of Subjects who are relapse-free

The proportion of subjects who are relapse-free was estimated using the Kaplan-Meier estimator. The treatment groups was compared using a Cox proportional hazards model for time to first relapse, adjusted for baseline relapse rate, history of prior IFN β use, baseline EDSS score (≤ 2.5 vs. > 2.5), and age (≤ 35 vs. > 35 years). Subjects who prematurely withdrew from the study without experiencing an INEC-confirmed relapse prior to withdrawal were censored on the End of Treatment Period Visit. Additionally, subjects who started an alternative MS medication prior to relapsing were censored on the day they started the medication if that was earlier.

Analysis of Proportion of Subjects With a ≥ 7.5 -Point Worsening From Baseline in the Multiple Sclerosis Impact Scale-29 Physical Impact Score at Week 96

This endpoint was analyzed using a logistic regression model and adjusting for the baseline Physical Impact score, baseline BDI, history of prior IFN β use, and baseline age (age ≤ 35 versus age > 35 years). If a subject is missing data for less than 10 of the 20 items that make up the physical score, then the mean of the non-missing items was used for the missing items. If the patient is missing 10 or more of the 20 items, or if the data is missing for any other reason, a random effects model was to be used to estimate the missing MSIS-29 physical score. MSIS-29

physical score data obtained after subjects take alternative medication for MS during the study was set to missing and an imputed value was used instead.

3.2.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 1841 subjects were randomized at 246 investigational sites in 28 countries worldwide. All 1841 subjects received at least 1 dose of study treatment. The highest enrolling countries were Poland (451 subjects), United States (217 subjects), and Russian Federation (198 subjects).

A similar percentage of subjects in the IFN β -1a and DAC HYP groups completed study treatment (70% and 71%, respectively) and completed the study (75% and 79%, respectively). The most common reason for treatment discontinuation of was an adverse event (AE), with the incidence higher in the DAC HYP group (14%) than in the IFN β -1a group (9%). The discontinuations for lack of efficacy were more common in the IFN β -1a group (7%) than in the DAC HYP group (3%) (Table 2).

Table 2. Study 301: Subject Disposition

	IFN beta-1a 30 mcg	DAC HYP 150 mg	Total
Number of subjects randomized	922	919	1841
Number of subjects dosed	922 (100)	919 (100)	1841 (100)
Study treatment			
Completed	644 (70)	653 (71)	1297 (70)
Discontinued study treatment (a)	278 (30)	266 (29)	544 (30)
Adverse event	83 (9)	130 (14)	213 (12)
Lack of efficacy	68 (7)	31 (3)	99 (5)
Lost to follow-up	10 (1)	5 (<1)	15 (<1)
Consent withdrawn	91 (10)	68 (7)	159 (9)
Investigator decision	5 (<1)	5 (<1)	10 (<1)
Death	3 (<1)	0	3 (<1)
Pregnancy	7 (<1)	12 (1)	19 (1)
Non-compliance	8 (<1)	10 (1)	18 (<1)
Site closure	3 (<1)	5 (<1)	8 (<1)
Study completion			
Completed	694 (75)	724 (79)	1418 (77)
Withdrawn (a)	228 (25)	195 (21)	423 (23)
Adverse event	47 (5)	56 (6)	103 (6)
Lack of efficacy	46 (5)	23 (3)	69 (4)
Lost to follow-up	12 (1)	9 (<1)	21 (1)
Consent withdrawn	98 (11)	80 (9)	178 (10)
Investigator decision	4 (<1)	6 (<1)	10 (<1)
Death	4 (<1)	0	4 (<1)
Pregnancy	4 (<1)	7 (<1)	11 (<1)
Non-compliance	7 (<1)	8 (<1)	15 (<1)
Site closure	4 (<1)	5 (<1)	9 (<1)
Other	2 (<1)	1 (<1)	3 (<1)

Note: AEs with term Multiple Sclerosis Relapse are mapped programmatically to Lack of Efficacy category.
Source: Study 301 CSR Table 17.

The demographic and baseline characteristics were similar between the 2 treatment groups (Table 3). Overall, the mean age was 36 years, and most were White (90%), female (68%).

Table 3. Study 301: Demographic Characteristics

	IFN beta-1a 30 mcg	DAC HYP 150 mg	Total
Number of subjects in the ITT population	922 (100)	919 (100)	1841 (100)
Age (yrs)			
Mean	36.2	36.4	36.3
SD	9.32	9.36	9.34
<=35	449 (49)	451 (49)	900 (49)
>35	473 (51)	468 (51)	941 (51)
Sex			
Female	627 (68)	625 (68)	1252 (68)
Male	295 (32)	294 (32)	589 (32)
Race			
White	828 (90)	823 (90)	1651 (90)
Asian	28 (3)	27 (3)	55 (3)
Other	28 (3)	27 (3)	55 (3)
Black or African American	12 (1)	13 (1)	25 (1)
American Indian or Alaska native	1 (<1)	0	1 (<1)
Native Hawaiian or other Pacific Islander	0	0	0
Not Reported(a)	25 (3)	29 (3)	54 (3)

Source: Study 301 CSR Table 18.

Both treatment groups were balanced with respect to baseline EDSS scores, relapse history, and prior multiple sclerosis therapy. Subjects had a mean EDSS of 2.5 at baseline and a mean of 2.7 relapses in the 3 years prior to study entry and mean of 1.6 relapses in the prior 12 months). The mean time since diagnosis was 4.2 years (Table 4).

Table 4. Study 301: Baseline Disease Characteristics

	IFN beta-1a 30 mcg	DAC HYP 150 mg	Total
Number of subjects in the ITT population	922 (100)	919 (100)	1841 (100)
EDSS Score			
n	922	919	1841
Mean	2.54	2.48	2.51
SD	1.257	1.206	1.232
Median	2.25	2.00	2.00
Min, Max	0.0, 6.0	0.0, 5.5	0.0, 6.0
<=2.5	540 (59)	562 (61)	1102 (60)
>2.5	382 (41)	357 (39)	739 (40)
Time since diagnosis of MS (years)			
n	922	919	1841
Mean	4.1	4.2	4.2
SD	4.70	4.97	4.83
Median	2.0	2.0	2.0
Min, Max	0, 26	0, 27	0, 27
Number of relapses within the past 3 years			
n	922	918	1840
Mean	2.7	2.7	2.7
SD	1.29	1.21	1.25
Median	2.0	2.0	2.0
Min, Max	1, 14	1, 15	1, 15
Number of relapses within the past 12 months			
n	922	919	1841
Mean	1.6	1.5	1.6
SD	0.75	0.72	0.73
Median	1.0	1.0	1.0
Min, Max	0, 6	0, 5	0, 6
Number of T2 hyperintense lesions			
n	908	900	1808
Mean	51.8	49.2	50.5
SD	37.39	35.52	36.49
Number of Gd-enhancing lesions			
n	909	900	1809
Mean	2.3	2.0	2.1
SD	5.85	5.86	5.85

Source: Study 301 CSR Table 20-Table 23.

3.2.1.3 Results and Conclusions

Annualized relapse rate

In the primary analysis, the adjusted ARR were 0.393 in the IFN β -1a group and 0.216 in the DAC HYP group. The ARR ratio (DAC HYP/ IFN β -1a) was 0.55, indicating that DAC HYP reduced the ARR by 45% compared with IFN β -1a ($p < 0.0001$).

Table 5. Study 301: Analysis Result of annualized relapse rate

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects with a relapse	392 (43)	260 (28)
Adjusted annualized relapse rate (95% CI) (b)	0.393 (0.353, 0.438)	0.216 (0.191, 0.244)
Rate ratio (DAC HYP/IFN beta-1a) (95% CI) (b)		0.550 (0.469, 0.645)
p-value vs IFN beta-1a (b)		<0.0001

Source: Study 301 CSR Table 29, confirmed by the reviewer.

Pre-specified sensitivity analysis of all protocol defined relapses (INEC approved or not) and post hoc sensitivity analysis of subject-reported relapses yielded similar results to that of the primary analysis, indicating that the process of relapse evaluation does not have a significant impact on the assessment of treatment effect.

Site 235 (11 subjects) in Brazil and Site 453 (40 subjects) in Italy were noted to be noncompliant with GCP. The results of the analysis that excluded Sites 453 and 235 were similar to those of the ITT population.

Results of all the other planned sensitivity analyses and post hoc analyses of ARR all support the robustness of the primary analysis.

Number of new or Newly Enlarging T2 Hyperintense Lesions at Week 96

The adjusted mean number of new or newly enlarging T2 hyperintense lesions at Week 96 was 9.44 in the IFN β -1a group and 4.31 in the DAC HYP group. DAC HYP reduced the number of new or newly enlarging T2 lesions by 54.4% compared with IFN β -1a ($p < 0.0001$). The results of the pre-specified sensitivity analyses were consistent with the primary analysis.

Table 6. Study 301: Number of New or newly-enlarging T2 hyperintense lesions at week 96

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922	919
Number of subjects included in analysis (a)	841	864
Adjusted mean number of lesions at Week 96 (95% CI) (b)	9.44 (8.46, 10.54)	4.31 (3.85, 4.81)
Lesion mean ratio (compared to IFN beta-1a) (95% CI) (b)		0.46 (0.39, 0.53)
Percent reduction (compared to IFN beta-1a) (95% CI) (b)		54.4 (46.9, 60.8)
p-value vs IFN beta-1a (b)		<0.0001

Source: Study 301 CSR Table 30, confirmed by FDA reviewer.

Confirmed Disability Progression on EDSS

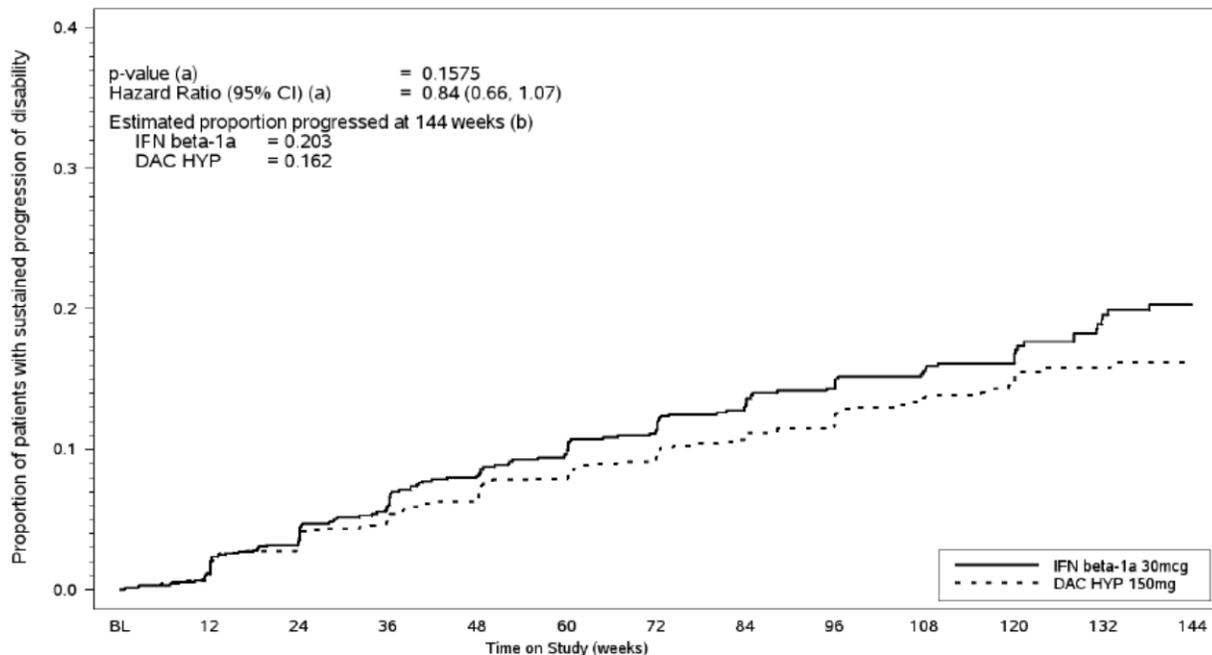
In the primary analysis of disability progression (PD), the hazard ratio for DAC HYP/IFN β -1a was 0.84, indicating DAC HYP reduced the risk of disability progression by 16% (p=0.1575) compared with IFN β -1a. Kaplan-Meier analysis estimated that 20.3% of subjects in the IFN β -1a group and 16.2% in the DAC HYP group had 12-week confirmed disability progression over 144 weeks.

Table 7. Study 301: Summary of time to 3-month sustained disability progression

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects progressed	140 (15)	121 (13)
Estimated proportion progressed (a) 144 weeks	0.203	0.162
Hazard ratio (DAC HYP/ IFN beta-1a) and 95% CI (b)		0.84 (0.66, 1.07)
p-value vs IFN beta-1a (b)		0.1575

Source: Study 301 CSR Table 31, confirmed by FDA reviewer.

Figure 1. Study 301: Time to 3-Month Sustained Progression of Disability



Source: Study 301 CSR Figure 5.

There are a total of 261 subjects with confirmed disability progression and 67 subjects censored after a tentative disability progression (43 in IFN β -1a group vs. 24 in the DAC HYP group). Note that in this study, the risk of confirmed disability progression after a tentative disability progression among subjects with 3-month confirmatory visits was 34% in the IFN β -1a group and 37% in the DAC HYP group. Sensitivity analyses were conducted to impute the confirmation status for those tentative progressions.

A pre-specified sensitivity analysis in which all tentative progressions with no confirmation assessment were assumed to be confirmed yielded a hazard ratio of 0.76 (nominal p-value = 0.0157). As there are more subjects with a tentative progression in the IFN β -1a group compared to the DAC HYP group, this analysis biased in favor of the IFN β -1a group.

Another pre-specified sensitivity analysis used multiple imputation based on the probability of confirmation estimated via a logistic regression model. The logistic regression was adjusted for treatment group, baseline EDSS (as a continuous variable), change in EDSS from baseline to the tentative progression and presence (or absence) of a relapse within the last 29-days of the tentative progression. On average, 20 subjects in the IFN β -1a group and 9 subjects in the DAC HYP group were imputed with confirmed PD. The resulting hazard ratio is 0.79 (nominal p-value = 0.0469).

This reviewer conducted an additional sensitivity analysis for disability progression. In this analysis, the following assumptions/modifications were made for the tentative disability progressions that could not be confirmed because of study completion or the subject withdrawing from the study:

1. For subjects who dropped out for the reason of 'lack of efficacy', the tentative disability progressions prior to drop out is assumed confirmed.
2. The study require that a disability progression to be confirmed on the next study visit occurring at least 74 days from the initial observation. In the reviewer's analysis, the last tentative disability progressions that occurred before drop out/study completion could be confirmed at any time as long as it is not during a relapse. The 74-day requirement was removed since those tentative progressions may not have the potential to be followed up for at least 74 days.

After applying the above assumption/modification, about 50% of the tentative disability progressions in the censored subjects were assumed confirmed. The resulting hazard ratio is 0.82 and the p-value is 0.0556 (Table 8), suggesting a marginal trend toward significance.

The reviewer conducted another sensitivity analysis using log rank test. The resulting hazard ratio is 0.83 and the p-value is 0.12, suggesting that the primary analysis is robust with respect to covariates adjustment.

Sensitivity analyses excluding progressions started during a relapse yielded similar result with the primary analysis.

Table 8. Study 301: Reviewer’s sensitivity analysis of time to 3-month sustained disability progression

	IFN beta-1a 30 mg	DAC HYP 150 mg
N	922	919
Number of subjects progressed (%)	161 (17)	133 (14)
Estimated proportion progressed at 144 weeks	0.225	0.179
Hazard ratio (DAC HYP/ IFN beta-1a) and 95% CI		0.80 (0.63, 1.01)
p-value		0.0556

Source: FDA reviewer.

Proportion of Relapsing Subjects

The Kaplan-Meier estimate for relapse-free subjects in the IFN β -1a and DAC HYP groups was 50.8% and 67.3% respectively at 144 weeks. The hazard ratio (DAC HYP/IFN β -1a) for the risk of relapse was 0.59, indicating that the risk of relapse was reduced by 41% in the DAC HYP group compared to IFN β -1a. As the difference between treatments in the primary analysis of 12-week confirmed disability progression was not statistically significant, the testing of lower-ranked secondary endpoints was stopped within the closed testing procedure. The nominal $p < 0.0001$.

Table 9. Study 301: Proportion of subjects Relapse Free

	IFN beta-1a 30 mg	DAC HYP 150 mg
N	922	919
Number of subjects who did not have a relapse (%)	530 (57)	659 (72)
KM estimate of proportion of subjects relapse-free at 144 weeks	0.508	0.673
Hazard ratio for risk of relapse (95% CI)		0.59 (0.50, 0.69)
p-value		<0.0001

Source: Study 301 CSR Table 34, confirmed by FDA reviewer.

Proportion of Subjects With a ≥ 7.5 -Point Worsening From Baseline in MSIS-29 Physical Impact Score at Week 96

At 96 weeks, 213 subjects (23%) in the IFN β -1a group had a ≥ 7.5 -point worsening from baseline compared with 171 subjects (19%) in the DAC HYP treatment group. The odds ratio (DAC HYP/IFN- β 1a) was 0.76 (nominal $p = 0.0176$), indicating that the risk of a clinically meaningful worsening on the subject-reported physical impact of MS was reduced by 24% in the DAC HYP group compared with the IFN β -1a group.

Table 10. Proportion of Subjects With a ≥ 7.5 -Point Worsening From Baseline in the Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score at Week 96

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922	919
Number of subjects included in analysis (a)	912 (100)	906 (100)
Number of subjects with worsening MSIS-29 physical score at Week 96		
No	699 (77)	735 (81)
Yes	213 (23)	171 (19)
Odds ratio (DAC HYP/ IFN beta-1a) (95% CI) (b)		0.76 (0.60, 0.95)
p-value vs IFN beta-1a (b)		0.0176

Source: Study 301 CSR Table 35.

3.2.2 Study 201

Study 201 was initiated on February 15, 2008 and completed on August 30, 2011. After the trial was started, the protocol was amended twice. The amendment dated November 20, 2008 includes substantial changes but was implemented early during the trial. The final protocol was dated October 22, 2010 and includes minor changes from the previous version.

The initial SAP was signed on the same day but prior to the unblinded futility analysis on July 20, 2009. The second/final version was signed on June 16, 2011 prior to unblinding of the study. The major updates that were made to the original SAP are as follows:

1. The covariates in the analysis of the primary endpoint and key secondary endpoints were pre-specified, instead of based on a backward selection procedure. In addition the definition of baseline EDSS group and age group were changed.
2. During the trial a study site in the study was closed after it was found that unblinded pharmacist dosed all 21 subjects with DAC HYP rather than their appropriate treatment assignments. The final SAP excluded the 21 subjects from the intent-to-treat population.
3. The final SAP changed the imputation method for the MSIS-29 physical scale from using the mean change from baseline in subjects in the same treatment group to using a random effects model.
4. In the final version of the SAP text was modified to state that EDSS assessments up to Week 20 (original Week 8) in the extension study would be used to confirm tentative progressions that began at Week 48 or Week 52.

3.2.2.1 Study Design and Statistical Methodology

Study 201 was a double-blind, placebo-controlled, dose-ranging study to determine the safety and efficacy of DAC HYP as a monotherapy treatment in subjects with Relapsing-Remitting Multiple Sclerosis. A total of 621 subjects were randomized at 78 sites in 9 countries worldwide. Subjects were randomized in a 1:1:1 ratio to receive placebo, DAC HYP 150 mg or 300 mg administered by SC injection once every 4 weeks. The study consisted of screening, a 52-week double-blind, placebo-controlled treatment phase; followed by a 20-week double-blind, follow-up phase or a double-blind extension study. Subjects were allowed to use interferon-beta after week 24 as long as they have experienced a protocol-defined clinical relapse. EDSS were done every 12 weeks and at the time of a relapse. MRI scan was done at weeks 24, 36 and 52 for all patients and every 4 weeks to week 24 in a subset of patients.

An interim futility analysis was performed after 150 subjects had completed the Week 24 visit. Sponsor personnel involved with study management received a summary recommendation of whether to continue the trial. Any sponsor personnel who were unblinded to evaluate the data at the time of the futility analysis were not involved in the management of the study after unblinding.

Analysis Sets

The intent-to-treat (ITT) population was the primary efficacy population and included all randomized subjects who received at least 1 dose of study medication. Twenty-one subjects from 1 site in Study 201 (Site 903) were excluded from the ITT population because the site was closed for dosing violations.

MRI-intensive cohort (the first 307 subjects enrolled in the study) was the primary population for the analysis of the number of new Gd-enhancing lesions. In this cohort, the MRI assessments were performed every 4 weeks between baseline and Week 24, in addition to those conducted at baseline and at Weeks 24, 36, and 52.

Efficacy Endpoints

Primary Endpoint was annualized relapse rate.

Secondary endpoints (rank ordered) included:

1. the number of new Gd+ lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24
2. the number of new or newly enlarging T2 hyperintense lesions at Week 52
3. the proportion of subjects relapsed between baseline and Week 52
4. change in MSIS-29 physical score at Week 52 compared to baseline.

Confirmed disability progression was included as one of the tertiary endpoints.

Multiplicity Adjustment

A sequential closed testing procedure was employed in the order listed in “Efficacy endpoints”. For each of the secondary endpoints, a sequential testing procedure was used to first compare the DAC HYP 300 mg group vs. placebo and then the DAC HYP 150 mg group vs. placebo. Disability progression was not included in the testing procedure.

Efficacy analyses

Analysis of Relapse

The primary analysis of relapse rate was based on INEC-confirmed relapses and it included data from all subjects in the ITT population until either the end of the treatment period, a switch to alternative MS medication, or withdrawal from the study.

Comparisons between treatment groups were based on a negative binomial regression model, adjusted for the baseline relapse rate (number of relapses in the 1 year prior to study entry, baseline EDSS (EDSS \leq 2.5 vs. EDSS $>$ 2.5), and baseline age (age \leq 35 vs. age $>$ 35). The logarithmic transformation of the number of years in the study was included in the model as the “offset” parameter.

A number of sensitivity analyses were planned including

1. a Poisson regression model;
2. a negative regression model adjusted only for number of relapses in the 1 year prior to study entry;
3. a negative binomial regression model excluding relapses after study drug discontinuation;
4. a negative binomial regression model including all relapses that occur after starting alternative medication;
5. a negative binomial regression model excluding relapses occurred after adding IFN-beta.

The proportion of subjects relapsed at 52 weeks was analyzed using a Cox proportional hazards model adjusted for baseline relapse rate (number of relapses in the past year, baseline EDSS (EDSS \leq 2.5 vs. EDSS $>$ 2.5), and baseline age (age \leq 35 vs. age $>$ 35).

Analysis of the number of new Gd-enhancing lesions

Treatment differences between groups in the number of new Gd-enhancing lesions were tested using a negative binomial regression model adjusting for the baseline number of Gd-enhancing lesions. If a subject is missing only 1 or 2 consecutive post-baseline scans, then the last valid non-missing, non-baseline observation will be carried forward to impute the missing value. However, if there are no values to be carried forward or if the subject is missing more than 2 consecutive scans, then the mean number of lesions from subjects in the same treatment group at the same visit will be used as the imputed value. Baseline MRI results will not be imputed. MRI data obtained after subjects take alternative medication for MS during the study will be set to missing and an imputed value will be used instead.

Analysis of the number of new or newly-enlarging T2 hyperintense lesions

The primary analysis is a negative binomial regression model, adjusted for the baseline number of T2 lesions. Missing values will be imputed using the mean from subjects from the same treatment group in the same visit. MRI data measured after subjects took alternative MS medication will be set to missing and will be imputed.

Analysis of MSIS-29 physical score

An ANCOVA model adjusting for the baseline MSIS-29 physical score will be used to compare the change from baseline between treatment groups at Week 52. If a subject is missing data for less than 10 of the 20 items that make up the physical score, then the mean of the non-missing items will be used for the missing items. If the patient is missing 10 or more of the 20 items, or if the data is missing for any other reason, then a random effects model will be used to estimate the missing MSIS-29 physical score.

Analysis of Confirmed Disability Progression on EDSS

Confirmed disability progression was defined the same as in Study 301. Confirmatory visits were allowed up to week 20 of the open label extension or to week 60 for those who did not enter the extension study. The difference between treatment groups in confirmed disability progression was assessed using a Cox proportional hazards model, adjusted for baseline EDSS (EDSS ≤ 2.5 versus EDSS >2.5) and baseline age (age ≤ 35 versus age >35 years). In Study 201, the censor date was the date of the last EDSS assessment on or prior to the Week 52 assessment. For subjects with a tentative progression that could not be confirmed, the censor date was the date of the EDSS assessment prior to the tentative progression.

3.2.2.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 621 subjects were randomized and most subjects in all treatment groups completed treatment (Table 11). All subjects were from outside the US and Canada.

Table 11. Study 201: Subject Disposition

	Placebo	150 mg DAC HYP	300 mg DAC HYP	Total
Number of subjects randomized	204 (100)	208 (100)	209 (100)	621 (100)
Number of subjects dosed	204 (100)	208 (100)	209 (100)	621 (100)
Number of subjects who completed treatment	186 (91)	189 (91)	192 (92)	567 (91)
Number of subjects who discontinued study drug	18 (9)	19 (9)	17 (8)	54 (9)
Lost to follow-up	0	1 (<1)	0	1 (<1)
Adverse event	2 (<1)	6 (3)	9 (4)	17 (3)
Investigator decision	1 (<1)	0	0	1 (<1)
Consent withdrawn	11 (5)	9 (4)	5 (2)	25 (4)
Subject non-compliance	2 (<1)	0	1 (<1)	3 (<1)

Source: Study 201 CSR Table 14.

Demographic characteristics are similar across the 3 groups (Table 12). Overall, the mean age was 36 years, and most were White (96%), female (65%).

Table 12. Study 201: Demographic Characteristics

	Placebo	150 mg DAC HYP	300 mg DAC HYP	Total
Number of subjects randomized	204 (100)	208 (100)	209 (100)	621 (100)
Age (yrs)				
Mean	36.6	35.3	35.2	35.7
SD	9.02	8.94	8.67	8.88
Sex				
Female	128 (63)	140 (67)	134 (64)	402 (65)
Male	76 (37)	68 (33)	75 (36)	219 (35)
Race				
White	197 (97)	202 (97)	200 (96)	599 (96)
Asian	7 (3)	6 (3)	9 (4)	22 (4)
Black or African American	0	0	0	0
American Indian or Alaska native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	0	0	0	0

Source: Study 201 CSR Table 15.

Baseline MS history and the baseline MRI evaluation are summarized in Table 13. The mean EDSS score at baseline was 2.7. The mean time since diagnose was 4.1 years and the mean number of relapses in the 12 months before study inclusion was 1.4. The mean number of Gd lesions on baseline MRI was 1.8. The number of prior relapses and MRI-defined lesions was numerically higher in the DAC HYP 150 mg group compared to the other groups.

Table 13. Study 201: Baseline Disease Characteristics and MRI Evaluation

	Placebo	150 mg DAC HYP	300 mg DAC HYP	Total
Number of subjects randomized	204 (100)	208 (100)	209 (100)	621 (100)
EDSS score				
Mean	2.7	2.8	2.7	2.7
SD	1.17	1.15	1.21	1.17
Time since diagnosis (Years)				
n	204	208	209	621
Mean	4.1	4.5	3.7	4.1
SD	5.26	4.96	4.00	4.77
Median	2.0	3.0	3.0	2.0
Min, Max	0, 26	0, 23	0, 21	0, 26
Number of relapse during the past 12 months				
0	4 (2)	7 (3)	1 (<1)	12 (2)
1	136 (67)	129 (62)	150 (72)	415 (67)
2	56 (27)	62 (30)	46 (22)	164 (26)
3	7 (3)	8 (4)	10 (5)	25 (4)
>=4	1 (<1)	2 (<1)	2 (<1)	5 (<1)
n	204	208	209	621
Mean	1.3	1.4	1.3	1.4
SD	0.60	0.73	0.68	0.67
Median	1.0	1.0	1.0	1.0
Min, Max	0, 4	0, 6	0, 6	0, 6
Number of T2 hyperintense lesions				
n	203	206	206	615
Mean	39.5	44.6	35.9	40.0
SD	32.17	34.71	30.63	32.69
Number of Gd-enhancing lesions				
n	203	206	206	615
Mean	2.0	2.1	1.4	1.8
SD	4.48	3.47	3.26	3.78

Source: Study 201 CSR Table 16, 17, 44 & 46.

3.2.2.3 Results and Conclusions

Annualized relapse rate

The adjusted annualized relapse rate in the placebo group was 0.458 compared to 0.211 in the DAC HYP 150 mg group and 0.230 in the DAC HYP 300 mg group. The annualized relapse rate ratio was 0.461 and 0.503 for DAC HYP 150 mg and DAC HYP 300 mg versus placebo, respectively, indicating that the annualized relapse rate was reduced by 54% in the DAC HYP 150 mg group ($p < 0.0001$) and by 50% ($p = 0.0002$) in the DAC HYP 300 mg group, compared with placebo (Table 14).

Table 14. Study 201: Analysis Result of annualized relapse rate

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Number of relapses			
0	127 (65)	163 (81)	163 (80)
1	52 (27)	33 (16)	34 (17)
2	15 (8)	5 (2)	5 (2)
3	2 (1)	0	1 (<1)
>= 4	0	0	0
Adjusted relapse rate (95% CI) (b)	0.458 (0.370,0.566)	0.211 (0.155,0.287)	0.230 (0.172,0.308)
Rate ratio (95% CI) (b)		0.461 (0.318,0.668)	0.503 (0.352,0.721)
p-value vs placebo		<0.0001	0.0002

Source: Study 201 CSR Table 21, confirmed by FDA reviewer.

The results of all planned sensitivity analyses were similar to the primary analysis. Post-hoc sensitivity analyses were also conducted using a negative binomial regression model that includes all relapses that met the protocol-defined objective relapse criteria (INEC confirmed or not), and a negative binomial regression model that includes the 21 subjects from Site 903 who had been excluded from the ITT population. The results also supported the primary analysis.

This reviewer conducted an analysis using the definition of baseline EDSS group and age group in the original SAP dated prior to the unblinded futility analysis. The result is similar to that of the primary analysis.

Proportion of Relapsing Subjects

The Kaplan-Meier estimate for the proportion of subjects who relapsed at Week 52 was 36% in the placebo group compared to 19% in the DAC HYP 150 mg and 20% in the DAC HYP 300 mg group. The hazard ratio was 0.45 for the DAC 150 mg group compared to placebo and 0.49 for the DAC 300 mg group compared to placebo. These results indicate that the proportion of relapsing subjects was reduced by 55% in the DAC HYP 150 mg group ($p < 0.0001$) and 51% ($p = 0.0003$) in the DAC HYP 300 mg group, compared to placebo.

Table 15. Study 201: Proportion of subjects who relapsed at Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196	201	203
Subject status at 52 weeks			
Relapsed	69 (35)	38 (19)	40 (20)
Censored	127 (65)	163 (81)	163 (80)
Estimated cumulative proportion of subjects relapsed at (a)			
52 weeks	0.36	0.19	0.20
Hazard Ratio and 95% CI (b)		0.45 (0.30-0.67)	0.49 (0.33-0.72)
p-value vs placebo (b)		<0.0001	0.0003

Source: Study 201 CSR Table 24, confirmed by FDA reviewer.

Number of new Gd-enhancing Lesions at Weeks 8, 12, 16, 20, and 24

Treatment group differences were evaluated using a negative binomial regression model adjusting for the baseline number of Gd-enhancing lesions. The adjusted mean numbers of new lesions from Weeks 8 to 24 were 4.79 lesions for placebo, 1.46 lesions for DAC HYP 150 mg, and 1.03 lesions for DAC HYP 300 mg. This result indicated that treatment with DAC HYP 150 mg and 300 mg reduced the number of new Gd-enhancing lesions by 69% ($p < 0.0001$) and 78.4% ($p < 0.0001$), respectively (Table 16).

Table 16. Study 201: Number of New Gd-Enhancing Lesions Between Week 8 and Week 24 - MRI Intensive Population

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of new Gd-enhancing lesions			
n	104	101	102
Mean	5.7	3.1	1.4
SD	9.98	9.21	2.99
Median	2.0	0.0	0.0
Min, Max	0, 78	0, 67	0, 17
Adjusted mean number of new Gd lesions (b)	4.79	1.46	1.03
95% CI (b)	3.56, 6.43	1.05, 2.03	0.73, 1.46
Percent reduction (b)		69.47	78.44
95% CI (b)		52.40, 80.41	65.97, 86.35
p-value vs placebo		<0.0001	<0.0001

Source: Study 201 CSR Table 22, confirmed by FDA reviewer.

Supportive analysis of the number of new Gd-enhancing lesions was conducted, which includes subjects with non-missing MRI data from baseline, Weeks 8, 12, 16, 20, and 24 who did not take prohibited alternative MS medications during the treatment period. The result was similar to the primary analysis. Additional pre-specified sensitivity analyses also supported the primary analysis.

Number of new or Newly Enlarging T2 Hyperintense Lesions at Week 52

Treatment effects on the number of new T2 lesions at Week 52 were analyzed using a negative binomial regression model adjusting for the baseline number of T2 lesions. The adjusted mean number of new or newly enlarging T2 lesions at Week 52 was 8.13 in the placebo group, 2.42 in the DAC HYP 150 mg group, and 1.73 in the DAC HYP 300 mg group. This result indicated that DAC HYP 150 mg reduced the number of new or newly enlarging T2 lesions by 70% ($p < 0.0001$) and DAC HYP 300 mg reduced it by 79% ($p < 0.0001$), respectively compared to placebo.

Table 17. Study 201: Number of New or newly-enlarging T2 hyperintense lesions at week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population in the analysis (a)	195 (100)	199 (100)	200 (100)
Adjusted mean number of new or newly enlarging T2 hyperintense lesions	8.13	2.42	1.73
95% CI (b)	6.65, 9.94	1.96, 2.99	1.39, 2.15
Percent reduction (b)		70.23	78.73
95% CI (b)		59.94, 77.88	71.33, 84.22
p-value vs placebo (c)		<0.0001	<0.0001

Source: Study 201 CSR Table 23, confirmed by FDA reviewer.

Change in MSIS-29 Physical Score at Week 52

Treatment with DAC HYP 150 mg and DAC HYP 300 mg reduced the decline in the MSIS-29 score at Week 52 relative to placebo. The results were not statistically significant for both treatment groups because the closed testing procedure required that the 300 mg dose group be tested first and achieve statistical significance before the 150 mg dose group could be tested.

Table 18. Study 201: Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score Change From Baseline to Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Change from Week 0 to Week 52			
n	196	201	203
Mean	3.0	-1.0	1.4
SD	13.52	11.80	13.53
Median	2.5	0.0	0.0
Min, Max	-56, 65	-39, 38	-43, 47
p-value vs placebo (a)		0.0008	0.1284
Relative mean change (95% CI)		-4.27 (-6.76, -1.78)	-1.93 (-4.42, 0.56)

Source: Study 201 CSR Table 25.

Confirmed Disability Progression on EDSS

Progression of disability was an exploratory endpoint. The proportion of subjects with 12-week confirmed disability progression at Week 52 was 13.3% in the placebo group, 5.9% in the DAC HYP 150 mg group, and 7.8% in the DAC HYP 300 mg group. Treatment with DAC HYP 150 mg reduced 12-week confirmed disability progression by 57% relative to placebo (nominal $p = 0.0211$), and treatment with DAC HYP 300 mg reduced 12-week confirmed disability progression by 43% relative to placebo (nominal $p = 0.0905$).

3.3 Evaluation of Safety

Please see the clinical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Age, Race and Geographic Region

Results of subgroup analyses are in Table 19 and Table 20. The results of subgroup by race are not presented as most subjects are White. In both studies, a greater treatment effect on ARR was observed for DAC HYP 150 mg relative to the control across demographic subgroups. The treatment effect seemed larger for male and younger age group. For Study 301, region 1 (United States and Canada) appeared to have smaller treatment effect than European countries.

Table 19. Study 301: Analysis of the Primary Endpoint by Demographic Subgroups

	IFN beta-1a N=922	DAC HYP N=919
Gender, Male		
n	295	294
Adjusted annualized relapse rate	0.401	0.186
Rate ratio (95% CI)		0.46 (0.35, 0.62)
Gender, Female		
n	627	625
Adjusted annualized relapse rate	0.386	0.227
Rate ratio (95% CI)		0.59 (0.49, 0.71)
Baseline Age, <= 35		
n	449	451
Adjusted annualized relapse rate	0.505	0.205
Rate ratio (95% CI)		0.41 (0.32, 0.51)
Baseline Age, > 35		
n	473	468
Adjusted annualized relapse rate	0.315	0.233
Rate ratio (95% CI)		0.74 (0.59, 0.92)
Geographic Region*, Region 1		
n	118	118
Adjusted annualized relapse rate	0.321	0.227
Rate ratio (95% CI)		0.71 (0.46, 1.10)
Geographic Region, Region 2		
n	207	210
Adjusted annualized relapse rate	0.498	0.227
Rate ratio (95% CI)		0.46 (0.33, 0.64)
Geographic Region, Region3		
n	597	591
Adjusted annualized relapse rate	0.374	0.212
Rate ratio (95% CI)		0.57 (0.46, 0.69)

*Region 1: United States and Canada; Region 2: Western European countries; Region 3: Eastern European countries
Source: FDA reviewer.

Table 20. Study 201: Analysis of the Primary Endpoint by Demographic Subgroups

	Placebo N=196	150 mg DAC HYP N=201	300 mg DAC HYP N=203
Gender, Male			
n	73	65	71
Adjusted annualized relapse rate	0.43	0.13	0.18
Rate ratio (95% CI)		0.22 (0.10-0.48)	0.34 (0.17-0.66)
Gender, Female			
n	123	136	132
Adjusted annualized relapse rate	0.32	0.22	0.22
Rate ratio (95% CI)		0.66 (0.40-1.07)	0.65 (0.40-1.05)
Age <= 35			
n	90	99	106
Adjusted annualized relapse rate	0.46	0.18	0.21
Rate ratio (95% CI)		0.32 (0.18-0.56)	0.38 (0.23-0.64)
Age > 35			
n	106	102	97
Adjusted annualized relapse rate	0.28	0.20	0.19
Rate ratio (95% CI)		0.68 (0.38-1.20)	0.67 (0.37-1.20)

Source: FDA reviewer.

4.2 Other Special/Subgroup Populations

In both study, the treatment effect seemed larger in the subgroup of patients with mild disease (EDSS <= 2.5) at baseline. The randomization was stratified by prior use of IFN- β in Study 301. The subgroup of patients with prior use of IFN- β appeared to have smaller treatment effect.

Table 21. Study 301: Analysis of the Primary Endpoint by Baseline Disease Characteristics Subgroups

	IFN beta-1a N=922	DAC HYP N=919
Baseline EDSS <= 2.5		
n	540	562
Adjusted annualized relapse rate	0.387	0.165
Rate ratio (95% CI)		0.43 (0.34, 0.53)
Baseline EDSS > 2.5		
n	382	357
Adjusted annualized relapse rate	0.400	0.302
Rate ratio (95% CI)		0.75 (0.60, 0.94)

	IFN beta-1a N=922	DAC HYP N=919
Prior Interferon beta use, Yes		
n	311	308
Adjusted annualized relapse rate	0.483	0.308
Rate ratio (95% CI)		0.64 (0.50, 0.81)
Prior Interferon beta use, No		
n	611	611
Adjusted annualized relapse rate	0.323	0.159
Rate ratio (95% CI)		0.49 (0.40, 0.61)

Source: FDA reviewer.

Table 22. Study 201: Analysis of the Primary Endpoint by Baseline Disease Characteristics Subgroups

	Placebo N=196	150 mg DAC HYP N=201	300 mg DAC HYP N=203
Baseline EDSS <= 2.5			
n	104	93	117
Adjusted annualized relapse rate	0.39	0.14	0.20
Rate ratio (95% CI)		0.32 (0.17, 0.60)	0.46 (0.28, 0.78)
Baseline EDSS > 2.5			
n	92	108	86
Adjusted annualized relapse rate	0.33	0.23	0.20
Rate ratio (95% CI)		0.65 (0.38, 1.13)	0.57 (0.31, 1.04)

Source: FDA reviewer.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The efficacy of DAC HYP was studied in 2 pivotal trials in subjects with RMS: Study 201, a placebo-controlled study, and Study 301, an active-controlled study versus with IM IFN β -1a as comparator. Study 201 investigated two doses and results suggested that there was no additional benefit in using the DAC HYP 300 mg dose than the 150 mg dose. Study 301 only investigated the 150 mg dose. The discussion below only refers to the DAC HYP 150 mg dose unless otherwise stated.

Both Studies 201 and 301 demonstrated a statistically significant effect of DAC HYP on the reduction in MS relapse. On the primary efficacy endpoint of ARR, there was a 54% reduction

vs. placebo in Study 201 and a 45% reduction vs. IFN β -1a in Study 301 (Both $p < 0.0001$). The efficacy on ARR was robust, supported by sensitivity analyses and subgroup analyses.

Both studies also showed statistically significant treatment benefits on brain MRI measures. Analysis of the number of new or newly enlarging T2 lesions showed a 70% reduction compared to placebo over 52 weeks and a 54% reduction compared to IFN β -1a over 96 weeks (both $p < 0.0001$). Study 201 also indicated that treatment with DAC HYP reduced the number of new Gd-enhancing lesions by 69% ($p < 0.0001$).

In addition, DAC HYP treatment resulted in a numerically slowing of disability progression as measured by EDSS. In Study 301, there was a 16% reduction in 12-week confirmed disability progression ($p = 0.1575$, not statistically significant). There were a substantial number of subjects with a tentative disability progression not confirmed because of study completion or the subject withdrawing from the study. Sensitivity analyses which make reasonable assumptions regarding those unconfirmed tentative disability progressions suggested a marginal treatment effect toward statistical significance. In Study 201, disability progression was an exploratory endpoint. The result showed a 57% reduction in 12-week confirmed disability progression (nominal $p = 0.0211$) in the treatment group compared to the placebo.

In Study 301 there was a 24% reduction compared to IFN β -1a in the proportion of subjects with at least 7.5-point decline on the MSIS-29 Physical Impact scale score. In Study 201, treatment with DAC HYP appeared to reduce the decline in the MSIS-29 score at Week 52 relative to placebo. Although both nominally statistically significant, the endpoints of MSIS-29 could not be formally tested in either of study as the testing procedures were stopped because of non-significant results of a preceding comparison.

5.2 Conclusions and Recommendations

The data overall provided adequate evidence to support the efficacy of DAC HYP 150 mg as treatment of subjects with relapsing MS.

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

/s/

XIANG LING
03/18/2016

KUN JIN
03/18/2016
I concur with the review.

HSIEN MING J HUNG
03/18/2016