

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

103471

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

May 20, 1993

PLA #: 92-0495

APPLICANT: Chiron Corporation

NAME OF PRODUCT: Betaseron (Interferon Beta-1b)

DOCUMENT REVIEWED: Summary of the efficacy analysis of the Third-Year clinical data.
1. Two submissions dated 4-21-93 and 4-30-93
2. Data listing dated 4-21-93..

REQUESTER: PLA Review Committee

REVIEWER: Jawahar Tiwari, Ph.D.

This review was completed after the discussion of the clinical issues with Dr. Janet Woodcock (HFM-500), Dr. Jay Siegel (HFM-570), Dr. Theresa Gerrard (HFM-505), and Dr. Andrew Larner (HFM-508).

BACKGROUND

The clinical efficacy and safety data included in this submission were collected under prospectively developed protocols and are essentially the third year follow-up data on most of the patients enrolled in the Phase III trial. These studies were conducted under two separate but identical protocols: TB01-3103 for U.S. centers and TB01-3104 for Canadian centers.

The subjects enrolled in the Phase III efficacy trial were given the option of continuing their treatment, in a blinded fashion, under these two new protocols. The majority of

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the patients chose to enroll in this follow-up study. The procedures for collecting the safety and efficacy data (exacerbation frequencies, MRI and other clinical variables) were similar to those used in the Phase III trial.

The subjects were to remain on study for 48 weeks or until July 1, 1992, whichever occurred first. Amendment # 4 extended the studies for a total of 96 weeks. Another amendment (# 5) extended the studies for a total of 156 weeks.

The cut-off date for this analysis was July 15, 1992.

REVIEWER'S COMMENTS

I. Extent of Dropouts/Exclusions *After the Completion of Two-Year Phase III Trial*

The number of patients included in the Two-Year study and this analysis are given in Table 1. Since 18% of all the patients included in the Phase III trial dropped out or were excluded from this analysis, these three groups may not be homogenous and comparable at the baseline (i.e., at the end of the second year). Nevertheless, the groups can be analyzed to examine the trends in the key efficacy variables.

Table 1. Extent of dropouts/exclusions during the third-year follow-up study.

	Two-Year Study	Third Year Follow-up	% Dropouts/Exclusions During Third Year
Placebo	112	90	20%
9 mlU	111	94	15%
45 mlU	115	94	18%
TOTAL	<u>338</u>	<u>278</u>	<u>18%</u>

II. Baseline Characteristics

The baseline for the follow-up study is the end of the second year of the Phase III study. The sponsor (Berlex Laboratories, Dr. S.S. Verjee, Director, Biostatistics and Data Management)) was requested by this reviewer to provide an analysis of the baseline characteristics of the three groups.

The Sponsor's analysis (submission dated May 11, 1993; copy attached with this review), shows that, at the end of the second year, there were no significant differences between the three groups with respect to 10 demographic and baseline disease characteristics of the patients. These same 10 baseline parameters were also compared in the Phase III study.

[The baseline comparability issue was also discussed with Dr. Janeth Rouzer-Kammeyer (HFD-120) on 5-20-93 and she was in agreement with this analysis.]

III. Primary Endpoint I: The Frequency of Exacerbation-free Subjects

There were **11 exacerbation-free patients with less than 24 weeks on the study treatment** (3 in Placebo, 6 in 9 mIU, 2 in 45 mIU). These patients are **not included** in this analysis (see Table 2). [A similar "rule" was adopted for the analysis of the Phase III efficacy data.]

Furthermore, there were **8 additional patients with at least one exacerbation and with less than 24 weeks on the study treatments**. These 8 patients are **included** in the analysis and the total number of patients given in Table 2.

The Frequencies of exacerbation-free subjects in the three arms of the study and the P-values associated with the Fisher's Exact Test and Wilcoxon Test are given at the bottom of Table 2. The observed 13% difference between the placebo and 45 mIU groups is in favor of 45 mIU treated patients. The P-value associated with this comparison is 0.1.

Also, the frequencies of exacerbation free subjects in the three groups of patients show a dose-response relationship. A similar relationship was also seen in the data from the Phase III study. The P-values associated with these two comparisons are given at the bottom of Table 2.

IV. Primary Endpoint II: The Frequency of Exacerbation Per Subject

The frequencies (from 0 to 5+) of exacerbation per subject are also given in Table 2. Again, these results are similar to those seen in the Phase III trial. These frequencies are lower in the patients treated with 45 mIU of Betaseron as compared with those receiving the placebo (P = 0.074).

The exacerbation rates during the third year are 0.93 in placebo, 0.82 in 9 mIU, and 0.67 in 45 mIU patients. The placebo vs 45 mIU comparison is of borderline significance (P=0.065)

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Table 2. Frequency of Exacerbation Per subject Observed During the Third Year in the Total Enrolled Population (U.S. + Canada)

Number of Exacerbation Per Subject	PLACEBO N=87	9 mIU N=88	45 mIU N=92
0	40 (46%)	43 (49%)	54 (59%)
1	26 (30%)	32 (36%)	23 (25%)
2	17 (19%)	8 (9%)	13 (14%)
3	4 (5%)	4 (5%)	2 (2%)
4	0	0	0
5+	0	1 (1%)	0
EXACERBATION RATE			
	0.93	0.82	0.67

COMPARISONS

I. Proportion of Exacerbation-free subjects	P (Fisher's Exact Test)
Placebo vs 45 m IU	0.10
Placebo vs 9 mIU	0.763
9 mIU vs 45 mIU	0.186
II. Frequency of Exacerbation per Subject	P (Wilcoxon Test)
Placebo vs 45 mIU	0.074
Placebo vs 9 mIU	0.421
9 mIU vs 45 mIU	0.291
III. Exacerbation Rate	
Placebo vs 45 mIU	0.065

V. Time to First Exacerbation

The Median time to first exacerbation cannot be calculated due to insufficient data. However, 40th percentile of the time to first exacerbation for all three groups is given in Table 3. The trend is in favor of 45 mIU group.

Table 3. Time (Days) to First Exacerbation in Three Groups of Patients

	PLACEBO	9 mIU	45 mIU
Two-Year Phase III Study			
MEDIAN	153	180	295
Third-Year Follow-up Study			
40th PERCENTILE	210	233	286

VI. MRI Data

The MRI data are available for only 79% (220/278) of the patients in this study. This MRI subgroup would represent only 65% of the original 338 patients included in the Phase III trial. The distribution of patients with respect to the time (week) of MRI evaluation during the third year is given in Table 4a.

These data indicate that, during the third year, the MRI of 96% (211/220) of the patients was performed after 40 weeks on study treatments.

The change in the MRI lesion area (after 40 weeks of treatment) shows a small trend in favor of 45 mIU group. The median change in the lesion area was -5.5% in placebo and -9.1% in 45 mIU patients (P=0.48, Table 4b).

In contrast, the MRI from the Phase III study showed a significant (P < 0.005) change in the total lesion area at the end of the second year (Table 4b).

Table 4a. Distribution of Patients in MRI Analysis by Weeks on Study

Weeks On Study At the Time of MRI	PLACEBO	9 mIU	45 mIU
16 - 24	0	2	0
25 - 32	1	0	0
33 - 40	2	3	1
41 - 48	42	39	40
49 - 56	30	27	33
TOTAL	75	71	74

Table 4b. Change in the MRI Lesion Area in Phase III and the Third-Year Follow-up Studies

Median Change in MRI Lesion Area	PLACEBO	9 mIU	45 mIU	P-Value Placebo vs 45 mIU
From Baseline to Year 1	9.1%	5.7%	-7.1%	<0.005
From Baseline to Year 2	18.0%	11.4%	-0.5%	<0.005
From Year 2 to Year 3	-5.5%	-13.1%	-9.1%	<0.48

CONCLUSION

1. The third-year follow-up data on the primary efficacy variables - proportion of exacerbation-free subjects and frequency of exacerbation per subject - show trends in favor of patients treated with 45 mIU of Betaseron. These results are consistent with the Phase III study.
2. Time to first exacerbation also shows trend consistent with the Phase III results.
3. The MRI results show a small trend in favor of 45 mIU Betaseron. However, the patient population on which the third year MRI was performed, represents only 65% of the patient population in Phase III efficacy trial.



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HFD-120/Dr. Rouzer-Kammeyer
HFM-210/Chron
FILE: OT-5.7, Betaseron (Interferon Beta-1b) for Multiple sclerosis,
Chiron Corp.

Tiwari/Disk File: PL920495.2/May 20, 1993

STATISTICAL REVIEW AND EVALUATION

Date: 3-1-93

PLA #: 92-0495

APPLICANT: Chiron Corporation

NAME OF PRODUCT: Betaseron (Interferon Beta)

DOCUMENT REVIEWED: Volumes 50, 51, & 77, dated 5-22-92

BACKGROUND

The data presented in this PLA were collected under two identical study protocols: one for 7 U.S. centers and the other for 4 Canadian centers. The study protocol proposed to pool the data from both studies and analyze as a single study.

The trial was designed as randomized, double-blind and placebo controlled study to evaluate the safety and efficacy of Betaseron in the treatment of patients with relapsing-remitting MS. The eligible patients were randomized to placebo and two doses of Betaseron - 9 million IU and 45 million IU. A subcutaneous injection of the assigned medication was to be given on alternate days for 104 weeks.

The protocols proposed that **the primary efficacy evaluations** will be based on reduction in frequency of exacerbations per subject and proportion of exacerbation-free subjects.

The protocol emphasized that "Patients will be instructed to contact the study center immediately should any symptoms suggestive of an exacerbation appear. The study center will evaluate these patients within 24 hours." This time was amended to 72 hours.

The secondary endpoints were:

- Severity and duration of exacerbations
- Time to first exacerbation
- Sequelae of exacerbations
- Size and number of lesions as determined by annual Magnetic Resonance Imaging (MRI)
- Kurtzke Neurologic Ratings
- Scraps Neurologic Rating Scores
- Functional Neurologic Status

The statistical section of the protocol was very general. It specified that "Statistical significance will be assessed by Chi-square test or Fisher's exact test for proportions without stratification, by Mantel-Haenszel test for proportions with stratification, and by analysis of variance (ANOVA) of ranks for ordered and continuous variables. For comparison without covariates, the ANOVA of ranks is the same as the two-sample Wilcoxon test."

One interim analysis was performed after one year of subject experience for the first 338 subjects.

REVIEWER'S COMMENTS

There are several major issues in the review and evaluation of the clinical data from this trial.

- (1). The analysis and interpretation of the primary and the key secondary efficacy endpoints on the basis of the study protocol.
- (2). The effect of early dropouts (due to adverse events) from Betaseron groups on the efficacy. These dropouts were exacerbation-free but participated in the trial for less than six months. In the intent-to-treat analysis, they were counted as "success". They could also be counted as "treatment failures".
- (3). The effect of the protocol violations on the the clinical evaluation and measurements of the exacerbation, the primary endpoint variable. Thus, the efficacy data and the analysis presented by the Sponsor in the PLA may be subject to some degree of bias.
- (4). The effect of these protocol violations on the key secondary efficacy variables - time to first and second exacerbations and, severity of disease.

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As noted in the previous section, the protocol specified (and indeed emphasized) that all patients will be instructed to report immediately any symptom(s) suggestive of an exacerbation and the study center will evaluate these patients within 24 hours. However, during the early phase of the review, it appeared that exacerbations of a number of patients were not verified (documented). Thus, Dr. Rouzer-Kammeyer and this reviewer requested Chiron Corporation to provide the analysis of the primary and the key secondary endpoints by using only the verified (documented) exacerbations.

These data show that only 80% (545/681) of all exacerbations reported in the study were verified. These 136 (or 20%) of the unverified exacerbations were from 89 of the 338 (or 26.3%) patients in the trial.

Also, during the CBER's inspection of the clinical centers, it was found that exacerbations of many patients were evaluated several days or weeks after they were reported to the study centers.

We will evaluate the efficacy of Betaseron two ways: by analyzing all reported exacerbations and by analyzing only verified exacerbations.

I. The Primary Endpoint I: Proportion of Exacerbation-Free Subjects

(a). All Exacerbations

The proportions of exacerbation-free subjects in the three arms of the study are given in Table 1. If we consider all reported exacerbations, 18 of the 112 placebo patients (16.1%) and 36 of the 115 45 mIU Betaseron patients (31.3%) were exacerbation-free. This difference was significant at $P = 0.008$ (see lower portion of Table 1). The 9 mIU Betaseron Group was not significantly different from placebo and 45 mIU groups.

It is possible, by calculating Mann-Whitney U statistic, to get an estimate of the probability of a better response to Betaseron therapy than to placebo (Moses et al, N Engl J Med 1984; 311:442-448). Based on the data in Table 1, we could say that the probability of a better response on 45 mIU Betaseron therapy is 58%.

If the effects of placebo and Betaseron were the same then this probability would be 50%. Note that in this data the probability

of 58% is significantly different from 50% (P=0.007).

(b). Only Verified Exacerbations

In case of only verified exacerbations (Table 1), the placebo group had 28 exacerbation-free subjects (25%) as compared with 40 (34.8%) in the 45 mIU group. This 9.8% difference, although still favoring Betaseron, was not significant.

Here, the probability of a better response is 55% and is not significantly different from 50%.

It should be noted that in the placebo group the percent of exacerbation-free subjects has increased from 16.1 to 25.0 (a difference of 8.9%). However, in the 9 mIU group this increase was from 20.7% to 27.9% (7.9% difference) and in the 45 mIU group, from 31.3% to 34.8% (a difference of only 3.5%). It appears that disproportionately large percentage of exacerbations in the placebo group were not verified.

(c). Separate Analysis of U.S. and Canadian Centers

There were 7 U.S and 4 Canadian centers participating in the trial. The proportion of exacerbation-free subjects in the placebo and Betaseron groups were compared separately for U.S. and Canadian centers. These results are given in Tables 2 and 3. The analysis was performed for all exacerbations and also for only verified exacerbations.

The results for individual country are not significant. However, they are consistent with the overall pooled analysis. The proportions of exacerbation-free subjects in both U.S. and Canadian data are higher in Betaseron as compared with the placebo group.

We also see in these two tables, as in the pooled analysis given in Table 1, that a disproportionately large percentage of exacerbations in the placebo group were not verified.

(d). Exacerbation-free Subjects With Less than 6 Months On Study Treatments

A comparison of all exacerbation-free subjects in the three arms of the trial showed that 8 patients receiving 45 mIU of Betaseron

had spent less than 6 months on the treatment (Table 4a). Similarly, 6 patients receiving 9 mIU were in the trial for less than 6 months. On the other hand, all but two patients in the placebo group had spent approximately 2 years on the treatment (the other two were in the study for 51.1 (Patient #246) and 52.1 weeks (Patient #480).

Chiron Corporation explained (after a written request from Drs. Rouzer-Kammeyer and Tiwari) that these early drop-outs from the Betaseron arms of the study were related to adverse events.

The average number of exacerbations experienced by the trial patients during the last two years (baseline) was approximately 3.5. It appears that at the baseline, an "average patient" was experiencing, on the average, one exacerbation every 6 or 7 months. Thus it could be argued that an exacerbation-free patient with less than 6 months on the study treatment has not been observed for a reasonable time interval during which an exacerbation could develop. Inclusion of these patients in the intent-to-treat analysis as "success" (i.e., exacerbation-free) due to Betaseron therapy will clearly introduce bias in favor of Betaseron. In fact, these early drop-outs have occurred exclusively in the Betaseron arms due to adverse events and they can be classified as treatment "failures".

In an exploratory analysis, the proportion of exacerbation-free subjects in the placebo and Betaseron groups were compared after excluding all patients who have spent less than 6 months on the study treatments. These results are given in Table 4b. Here, the difference between the 45 mIU and the placebo arms is 10.1% (26.2% vs 16.1%) and still favors Betaseron (P = 0.071).

If we include these 8 patients in the group "with exacerbation" (a penalty against Betaseron), then the difference between the 45 mIU and the placebo groups is 8.2% (24.3% vs 16.1%) with a P-value of 0.139.

II. The Primary Endpoint II: Frequency of Exacerbation Per Subject

The second primary endpoint, prospectively specified in the protocol, was the frequency of exacerbation per subject. These frequency data are given in Table 5. Again, we have compared the frequencies of ALL EXACERBATIONS and also of ONLY VERIFIED EXACERBATIONS.

The top portion of Table 5 gives the observed frequencies for the placebo group. For example, there were 18 subjects (16%) with 0 exacerbation, 30 (27%) with 1, 18 (16%) with 2, 16 (14%) with 3,

11 (10%) with 4, and 19 (17%) with 5 or more exacerbations. These frequencies were compared with those of 9 mIU and 45 mIU Betaseron-treated patients by using Wilcoxon's Rank Sum Test. The P-values associated with each of the 6 comparisons are given in the bottom portion of Table 5. The outcome in the 45 mIU treated patients is significantly better than those treated with 9 mIU or placebo.

If we consider the outcomes in all six categories of exacerbations (i.e., 0, 1, 2, 3, 4, and 5+) then the probability of a better response on Betaseron therapy is 63%. It is significantly different ($P=0.0004$) from 50%.

The difference between 45 mIU Betaseron and placebo groups is also significant with respect to ONLY VERIFIED EXACERBATIONS.

It is interesting to note here that with respect to "1" and "2" exacerbation categories, patients treated with 45 mIU Betaseron are showing worse outcome than those treated with placebo.

The contribution to the statistical significance is coming primarily from "0", "3", "4", and "5+" categories. There is some indication of probable bias in the determination of exacerbation in patients experiencing 5 or more exacerbations (see below).

III. Percent Change in the Frequencies: From All Exacerbations to Only Verified Exacerbations

An interesting observation can be made if we compare the frequencies of ALL EXACERBATIONS with those of ONLY VERIFIED EXACERBATIONS given in Table 5. Let us consider the placebo group given in the top portion of Table 5. If we consider ALL EXACERBATIONS, there were 19 patients (17% of the total) with 5+ exacerbations. However, there were only 10 such patients (9% of the total) if we consider ONLY VERIFIED EXACERBATIONS. This represents a difference of 8%. The corresponding values for the 9 mIU and 45 mIU groups are 6% and 4%, respectively. A similar large shift in the positive direction has taken place for the "0 exacerbation" category.

These extreme categories with large shifts are the prime contributors towards the statistical significance.

Furthermore, as the data in the following table shows, it seems that slightly larger percentages of exacerbation were not verified in placebo group.

GROUP	Number of Subjects	Number of Exacerbations	Number of Verified Exacerbations
Placebo	112	266	207 (77.8%)
9 mIU	111	242	196 (81.0%)
45 mIU	115	173	142 (82.1%)

This is also evident in the data on the exacerbation-free subjects from the individual study centers (Table 6). As a specific example, let us examine the data for the placebo patients from Center #2. When we consider ALL EXACERBATIONS, there were 2 patients with zero exacerbations and 7 with 1 or more exacerbations. However, when ONLY VERIFIED EXACERBATIONS are considered, there are 3 patients without any exacerbations and 6 with 1 or more exacerbations. It seems that one patient's (one or more) exacerbations were not verified and for this reason this patient was added to the zero-exacerbation category. No such change has occurred in the Betaseron treated patients.

Similar changes in the placebo patients have occurred at 5 centers (marked with "\$\$\$" in Table 6). Two centers (#8 and #11) show changes in all three arms and only one center (#5) shows change in the high-dose arm of the Betaseron.

Could this higher proportion of unverified exacerbation in the placebo patients be due to the partial loss of the blind?

IV. Efficacy Analysis Based on Subgroups of Centers

The review committee, after examining the inspection reports from the Office of Compliance, decided to pool the clinical centers into three groups on the basis of their adherence to clinical protocol with respect to the verification of the exacerbations. The evidence of efficacy with respect to the frequency of

exacerbation-free subjects was examined in these three subgroups of centers (Table 7).

In each of the three subgroups, the trend was in favor of Betaseron, i.e., the frequency of exacerbation-free subjects was higher in 45 mIU Betaseron-treated subjects than in placebo-treated subjects. None of this difference was statistically significant, however.

Due to small number of subjects in each subgroup, this analysis was not performed for other categories of exacerbations (i.e., 1, 2, 3, 4, and 5+).

CONCLUSIONS AND ISSUES FOR FURTHER DISCUSSION

1. Primary Endpoint I: Proportion of Exacerbation-Free Subjects

(a). When we consider all reported exacerbations, there is a significant evidence that Betaseron therapy increases the frequency of exacerbation-free patients.

The probability of a better response on Betaseron therapy is 58%.

(b). When we consider only verified exacerbations, there is some evidence that Betaseron therapy increases the frequency of exacerbation-free patients. The difference between placebo and 45 mIU is not significant ($P=0.114$).

The statistical significance in this comparison is borderline. If 3 more patients were exacerbation-free in 45 mIU group, then the difference would be significant at $P=0.047$.

(c). If we delete 8 exacerbation-free patients who have spent less than 6 months on 45 mIU of Betaseron, the difference between Betaseron and placebo is 10.1%. It is in favor of Betaseron with a $P=0.071$. This is again of a borderline significance and could change by the addition and/or deletion one or two patients.

(d). The proportion of exacerbation-free subjects in 45 mIU group was higher than that in the placebo group in centers with "high"

as well as "low" degree of adherence (with respect to the verification of the exacerbation) to the protocol.

Similar consistency was observed in an analysis of subgroups of 7 U.S and 5 Canadian centers.

2. Primary Endpoint II: Frequency of exacerbation per subject

(a). When we consider all reported exacerbation, there is a significant evidence that Betaseron is efficacious in reducing the frequency of exacerbations.

The probability of a better response on Betaseron therapy is 63%.

(b). When we consider only verified exacerbations, there is significant evidence that Betaseron is efficacious in reducing the frequency of exacerbations.

(c). There may be some bias in this frequency data. A significant percentage of exacerbations were either not verified or verified much later than the time frame specified in the protocol.

This may introduce significant bias in the determination of the efficacy.

3. Time to First Exacerbation

(a). When we consider all exacerbations, time to first exacerbation is significantly increased in the 45 mIU Betaseron-treated patients (median time of 153 days in the placebo vs 295 days in 45 mIU group).

(b). When we consider only verified exacerbations, time to first exacerbation is increased in the 45 mIU Betaseron-treated patients median time of 226 days in the placebo vs 370 days in 45 mIU group). However, the difference is not significant.

4. Issues For Discussion

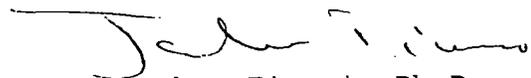
(a). Is verification (or verification within 72 hours as specified in the protocol) of exacerbation in MS patients crucial for the evaluation of efficacy?

(b). How much bias is introduced if only 80% of all exacerbations were verified?

[This constitutes one or more exacerbations of 26.3% (89/338) of the patients in the trial.]

(c). Can we consider only one primary endpoint, the frequency of exacerbation-free subjects, for the evaluation of efficacy?

This endpoint may be less affected by the issues related to the verification of exacerbations.



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HFM-570/Dr. Siegel
HFM-505/Dr. Gerrard
HFM-210/Chron
FILE: BLG-7.0 Betaseron (Interferon Beta) for
Multiple Sclerosis, Chiron Corp.

Tiwari/12-1-92/295-9094/wpPLA92-0495.1

Table 1. PRIMARY ENDPOINT I: Proportion of exacerbation-free subjects in total enrolled population (U.S. and Canada combined).

	Placebo (n=112)	9 Million IU (n=111)	45 Million IU (n=115)
0 EXACERBATION			
All	18 (16.1%)	23 (20.7%)	36 (31.3%)
Only Verified	28 (25.0%)	31 (27.9%)	40 (34.8%)
> 0 EXACERBATION			
All	94 (83.9%)	88 (79.3%)	79 (68.7%)
Only Verified	84 (75.0%)	80 (72.1%)	75 (65.2%)

COMPARISONS

All		Fisher's Exact Probability
Placebo vs 9 million IU		P = 0.392
Placebo vs 45 million IU		P = 0.008
9 million IU vs 45 million IU		P = 0.095
Only Verified		
Placebo vs 9 million IU		P = 0.651
Placebo vs 45 million IU		P = 0.114
9 million IU vs 45 million IU		P = 0.316

Table 2. PRIMARY ENDPOINT I: Proportion of Exacerbation-free subjects in population enrolled in U.S.

	Placebo (n=69)	9 Million IU (n=69)	45 Million IU (n=69)
0 EXACERBATION			
All	14 (20.3%)	15 (21.7%)	24 (34.8%)
Only Verified	21 (30.4%)	19 (27.5%)	25 (36.2%)
>0 EXACERBATION			
All	55 (79.7%)	54 (78.3%)	45 (65.2%)
Only Verified	48 (69.6%)	50 (72.5%)	44 (63.8%)

COMPARISONS

	Fisher's Exact Probability
ALL	
Placebo vs 9 million IU	P = 1.000
Placebo vs 45 million IU	P = 0.086
9 million IU vs 45 million IU	P = 0.130
ONLY VERIFIED	
Placebo vs 9 million IU	P = 0.851
Placebo vs 45 million IU	P = 0.588
9 million IU vs 45 million IU	P = 0.361

Table 3. PRIMARY ENDPOINT I: Proportion of Exacerbation-free subjects in population enrolled in Canada.

	Placebo (n=43)	9 Million IU (n=42)	45 Million IU (n=46)
0 EXACERBATION			
All	4 (9.3%)	8 (19.0%)	12 (26.1%)
Only Verified	7 (16.3%)	12 (28.6%)	15 (32.6%)
>0 EXACERBATION			
ALL	39 (90.7%)	34 (81.0%)	34 (73.9%)
Only Verified	36 (83.7%)	30 (71.4%)	31 (67.4%)

COMPARISONS

ALL

Placebo vs 9 million IU
 Placebo vs 45 million IU
 9 million IU vs 45 million IU

Fisher's Exact
 Probability

P = 0.228
 P = 0.054
 P = 0.458

ONLY VERIFIED

Placebo vs 9 million IU
 Placebo vs 45 million IU
 9 million IU vs 45 million IU

P = 0.201
 P = 0.089
 P = 0.818

Table 4a. Patients without exacerbation who have spent less than 6 months on study treatments.

PLACEBO		IFN 9 mIU		IFN 45 mIU	
Pt. ID	Weeks On Study	Pt. ID	Weeks On Study	Pt. ID	Weeks On Study
NONE		261	24.1	223	8.3
		434	19.1	278	18.4
		441	15.3	297	4.1
		465	6.1	316	18.1
		578	0.4	347	24.4
		580	16.3	376	16.1
				388	8.1
				483	24.1

Table 4b. Comparison of exacerbation-free subjects after excluding subjects who have spent less than 6 months on the study treatments.

	Patients Without Exacerbation	Patients With Exacerbation	TOTAL
Placebo	18 (16.1%)	94 (83.9%)	112
9 mIU	17 (16.2%)	88 (83.8%)	105
45 mIU	28 (26.2%)	79 (73.8%)	107

COMPARISONS

	Fisher's Exact Probability
Placebo vs 9 mIU	1.000
Placebo vs 45 mIU	0.071
9 mIU vs 45 mIU	0.093

Table 5. Frequency of Exacerbation Per Subject in total enrolled population (U.S. + Canada).

=====						
NUMBER OF EXACERBATION PER SUBJECT						
0	1	2	3	4	5+	SUM

PLACEBO: All Exacerbations						
18	30	18	16	11	19	112
16%	27%	16%	14%	10%	17%	100%
PLACEBO: Only Verified Exacerbations						
28	33	18	10	13	10	112
25%	30%	16%	9%	12%	9%	100%
9 mIU: All Exacerbations						
23	28	23	15	6	16	111
21%	25%	21%	14%	5%	14%	100%
9 mIU: Only Verified Exacerbations						
31	30	20	15	6	9	111
28%	27%	18%	14%	5%	8%	100%
45 mIU: All Exacerbations						
36	35	19	10	8	7	115
31%	30%	17%	9%	7%	6%	100%
45 mIU: Only Verified Exacerbations						
40	37	22	5	9	2	115
35%	32%	19%	4%	8%	2%	100%
=====						

Table 5 Continued

COMPARISONS:

	Wilcoxon Rank Sum Test Probability
All Exacerbations	
Placebo vs 9 million IU	P = 0.291
Placebo vs 45 million IU	P = 0.0004
9 million IU vs 45 million IU	P = 0.011
Only Verified Exacerbations	
Placebo vs 9 million IU	P = 0.593
Placebo vs 45 million IU	P = 0.012
9 million IU vs 45 million IU	P = 0.045

**Appears This Way
On Original**

Table 6. Number of subjects WITHOUT and WITH Exacerbations at individual study centers. \$\$\$ denotes the study arms in which the numbers have changed as a result of counting only verified exacerbations.

	ALL EXACERBATIONS		VERI. EXACERBATIONS		
	Number of Patients		Number of Patients		
	Without	With	Without	With	
	-----	----	-----	----	
Center 1					
45 mIU	2	8	2	8	
9 mIU	3	6	3	6	
Placebo	3	6	3	6	
Center 2					
45 mIU	4	5	4	5	
9 mIU	3	6	3	6	
Placebo	2	7	3	6	\$\$\$
Center 3					
45 mIU	1	3	1	3	
9 mIU	0	4	0	4	
Placebo	0	4	0	4	
Center 4					
45 mIU	4	7	4	7	
9 mIU	4	8	4	8	
Placebo	2	9	4	7	\$\$\$
Center 5					
45 mIU	6	10	7	9	\$\$\$
9 mIU	2	14	3	13	\$\$\$
Placebo	4	12	4	12	

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Table 6 Continued

Center 6

45 mIU	2	7	2	7	
9 mIU	2	7	3	6	\$\$\$
Placebo	1	9	2	8	\$\$\$

Center 7

45 mIU	5	5	5	5	
9 mIU	1	9	3	7	\$\$\$
Placebo	2	8	5	5	\$\$\$

Center 8

45 mIU	2	8	3	7	\$\$\$
9 mIU	0	10	1	9	\$\$\$
Placebo	1	10	2	9	\$\$\$

Center 9

45 mIU	2	10	2	10	
9 mIU	2	9	2	9	
Placebo	1	10	1	10	

Center 10

45 mIU	4	4	4	4	
9 mIU	3	3	3	3	
Placebo	1	7	2	6	\$\$\$

Center 11

45 mIU	4	12	6	10	\$\$\$
9 mIU	3	12	6	9	\$\$\$
Placebo	1	12	2	11	\$\$\$

Table 7. PRIMARY ENDPOINT I: Proportion of exacerbation-free subjects in Total enrolled population and in three GROUPS of Center (see footnote for the definitions of GROUPS)

	Placebo	9 Million IU	45 Million IU
=====			
0 EXACERBATION			
Group 1*	5/39 (12.8%)	8/36 (22.2%)	13/39 (33.3%)
GROUP 2**	4/20 (20.0%)	2/20 (10.0%)	7/20 (35.0%)
GROUP 3***	9/53 (17.0%)	13/55 (23.6%)	16/56 (28.6%)
ALL CENTERS	18/112 (16.1%)	23/111 (20.7%)	36/115 (31.3%)
=====			
> 0 EXACERBATION			
Group 1*	34/39 (87.2%)	28/36 (77.8%)	26/39 (66.7%)
GROUP 2**	16/20 (80.0%)	18/20 (90.0%)	13/20 (65.0%)
GROUP 3***	44/53 (83.0%)	42/55 (76.4%)	40/56 (71.4%)
ALL CENTERS	94/112 (83.9%)	88/111 (79.3%)	79/115 (68.7%)
=====			

* GROUP 1 = Centers 6, 7, 9, and 10.

** GROUP 2 = Centers 3 and 5.

*** GROUP 3 = Centers 1, 2, 4, 8, and 11.

Table 7 Continued

* GROUP 1

COMPARISONS:

Placebo vs 9 million IU	P = 0.365
Placebo vs 45 million IU	P = 0.058
9 million IU vs 45 million IU	P = 0.315

** GROUP 2

COMPARISONS:

Placebo vs 9 million IU	P = 0.661
Placebo vs 45 million IU	P = 0.480
9 million IU vs 45 million IU	P = 0.127

*** GROUP 3

COMPARISONS:

Placebo vs 9 million IU	P = 0.476
Placebo vs 45 million IU	P = 0.176
9 million IU vs 45 million IU	P = 0.666

All P-Values are based on Fisher's Exact Test.