

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
103471

MEDICAL REVIEW

MEMORANDUM

DATE: May 28, 1993

FROM: Russell Katz, M.D.

TO: File, PLA 92-0495

SUBJECT: Supervisory Clinical Review of Product Licensing Application (PLA) 92-0495 for Betaseron for the Treatment of Patients with Exacerbating-Relmitting Multiple Sclerosis

BACKGROUND

This PLA was submitted to the Center for Biologic Evaluation and Research (CBER) on ~~July 23~~ ^{July 23} 1992 by Chiron Corporation/Berlex Laboratories for the use of Betaseron (interferon-beta 1b) in patients with relapsing-remitting Multiple Sclerosis. Under a recently articulated Agency policy, appropriate Divisions in the Center for Drug Evaluation and Research (CDER) are to serve as the primary clinical review teams for applications for biological products submitted to CBER with indications that fall in the area of expertise of these CDER divisions. For this reason, our division is functioning as the primary clinical review unit responsible for the clinical review of this product. However, the Division's role is largely advisory; ultimately, the staff of CBER has primary responsibility for deciding whether or not the application is approvable. The PLA for Betaseron represents the first so-called "collaborative review" effort between the 2 centers to reach this stage of consideration.

I would like to point out that Dr. Leber and I have had extensive discussions about this application, and the scientific/regulatory issues arising from it. As a result, many of the same issues and concerns are raised in our individual memos, which are being written concurrently.

CLINICAL OVERVIEW

EFFICACY

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The sponsor has submitted the results of a single double blind, parallel group, fixed dose placebo controlled trial in patients with Exacerbating-Relapsing MS. This trial was performed at several centers in the US and Canada. All the centers in Canada conducted the trial under Protocol TB01-35886, and all the centers in the US conducted the trial under Protocol TB01-35686. These 2 protocols were identical, and each stated prospectively that the results from both studies were to be pooled, and analyzed as a single study. Although the sponsor did present the results for each protocol separately, they presented the pooled data as the primary analysis, as called for in the protocols.

Patients were enrolled into this trial who had clinically definite relapsing-remitting MS by the criteria of Poser et al. Patients must have had objective neurologic dysfunction primarily of the white matter, and at least 2 exacerbations in the 2 years prior to the study. Patients must have been stable for at least 1 month prior to the study, and have an EDSS score of between 0 (normal) and 5.5 (last score for ambulatory patients).

Eligible patients were randomized to one of 3 treatment groups; Placebo, Betaseron 9 million International Units (mIU), or Betaseron 45 mIU. The treatment was self administered subcutaneously every other day for 2 years, with the first 7 doses being half strength. Patients were routinely evaluated at Weeks 5 and 7, then every 6 weeks through Week 37, and then every 12 weeks until study completion.

Patients kept daily diaries of their experience. They were to contact the clinic immediately should symptoms suggestive of an exacerbation occur, and they were to be seen by the investigator within 24 hours, and no later than 72 hours, after the onset of the presumed exacerbation. Subsequent follow-up during the attack was at the discretion of the investigator. At the visit, the investigator was to evaluate the severity of the attack by means of the Functional Neurologic Status Scale, EDSS, and Scripps Scale (copies of which are appended to Dr. Rouzer-Kammeyer's review).

The primary efficacy measures described in the protocol were:

- 1) Reduction in frequency of exacerbations per subject, and
- 2) Proportion of exacerbation-free subjects.

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Secondary Measures were to include Severity and Duration of exacerbations, Time to First Exacerbation, size and number of lesions as visualized on MRI, EDSS, Scripps Neurologic Rating Score, and Functional Neurologic Status.

The sponsor planned 2 Intent-to-Treat analyses; the primary one excluded data collected on subjects after they had terminated, and the second included all data, including that collected after the patients had terminated treatment. Also, they proposed an Evaluable Patient analysis, with criteria to be developed prior to blind breaking. The protocol was silent regarding other issues; e.g., whether the primary analysis would consider pairwise comparisons between each dose and placebo, whether a dose response analysis would be primary, etc., although they did propose primarily non-parametric tests.

An interim analysis was planned to look at the first 338 subjects at the completion of one year of treatment. An O'Brien-Fleming strategy was to be used, so that at the final analysis (when this cohort completed 2 years of treatment), statistical significance would be declared on the basis of a 2 sided p-value of 0.048.

RESULTS

A total of 338 patients were enrolled in the combined trial (Placebo-112, 9 mlU-111, 45 mlU-115). In the Canadian Study, 4 centers enrolled 131 patients (Pla-43, 9mlU-42, 45mlU-46). In the US Study, 7 centers enrolled 207 patients (Pla-69, 9 mlU-69, 45 mlU-69).

In this cohort, a total of 681 exacerbations were recorded. However, only 545/681 (80%) of these exacerbations were documented according to protocol. That is, for 136/681 (20%) of the exacerbations, patients were not evaluated by the investigator within the 72 hours of onset as required by the protocol. In these cases, the determination that an exacerbation had occurred was made retrospectively, by the investigator, based on the patients' diaries, histories, etc., when the patient was ultimately seen. In some cases, patients were seen only at their next scheduled visit, which could have been weeks to months since the onset of an exacerbation. Because of this relatively large number, we analyzed the data with and without these "unverified" exacerbations.

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In addition, the sponsor employed a blinded review committee which recommended that data from 30 patients be excluded from the analysis because of various violations, etc. Because there was little difference between the results of this "Evaluable" Patient and Intent-to-Treat Analyses, I will restrict my comments to the latter.

The following results were obtained for the Primary Variables:

PROPORTION OF EXACERBATION-FREE SUBJECTS

<u>POPULATION</u>	<u>PLACEBO</u>	<u>9 MIU</u>	<u>45 MIU</u>
All Exacerbations	18 (16.1%)	23 (20.7%)	36 (31.3%)
Only Verified	28 (25.0%)	31 (27.9%)	40 (34.8%)

For the analysis including All Exacerbations, Fisher's Exact Test yielded a 2 sided p-value of 0.008 for the 45 miU vs Placebo contrast. No other pairwise contrast (between drug and placebo or between doses) reached nominal significance for either population.

As Dr. Tiwari points out in his Statistical Review, an examination of the data for the 3 treatment arms on this variable reveals that 8 patients in the 45 miU group were considered exacerbation-free, but were in the study for less than 6 months. This was true for 6 patients in the 9 miU arm, but only for 2 of the Placebo exacerbation-free patients. As he notes, the average patient in the trial had 3.5 exacerbations for the 2 years prior to the trial, giving an average attack rate of 1 attack every 6-7 months. Given this, it is possible that patients would not be expected to have an attack before 6 months had elapsed. For this reason, he performed 2 exploratory analyses. First, he excluded the patients who were in the trial for fewer than 6 months; this yielded a 45 miU vs Placebo difference of 10.1% (26.2% vs 16.1%). Analysis of this difference yields a 2 sided p-value of 0.071. Further, he considered the 8 Betaseron patients as having an exacerbation (worst case scenario). This resulted in a difference of 8.2% (24.3% vs 16.1%), corresponding to a 2 sided p-value of 0.139.

Appears This Way
On Original

FREQUENCY OF EXACERBATIONS PER SUBJECT

NUMBER OF EXACERBATIONS PER SUBJECT

	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5+</u>
Placebo: All Exacer.	18	30	18	16	11	19
	16%	27%	16%	14%	10%	17%
Placebo: Verified	28	33	18	10	13	10
	25%	30%	16%	9%	12%	9%
	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5+</u>
9 mIU: All Exacer.	23	28	23	15	6	16
	21%	25%	21%	14%	5%	14%
9 mIU: Verified	31	30	20	15	6	9
	28%	27%	18%	14%	5%	8%
	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5+</u>
45 mIU: All Exacerb.	36	35	19	10	8	7
	31%	30%	17%	9%	7%	6%
45 mIU: Verified	40	37	22	5	9	2
	35%	32%	19%	4%	8%	2%

Analyses using the Wilcoxon Rank Sum Test yielded the following p-values:

All Exacerbations P-Value

Pbo vs 9 mIU 0.291
Pbo vs 45 mIU 0.0004
9 mIU vs 45 mIU 0.011

Verified

Pbo vs 9 mIU 0.593
Pbo vs 45 mIU 0.012
9 mIU vs 45 mIU 0.045

Secondary Variables

Because there were a number of dropouts in the trial (23, 18, and 24 for Pla, 9 mIU, and 45 mIU respectively), it appeared useful to perform Kaplan-Meier survival analysis to the Time to First Exacerbation. When this is done, the time to first exacerbation for All Exacerbations is statistically

significantly increased in the 45 mlU group compared to the Placebo group (median time 153 days vs 295 days, 2 sided p-value of 0.015). However, when done only for Verified Exacerbations, the median time is increased to 370 days for the 45 mlU group compared to 226 days for Placebo, a difference that is not statistically significant.

No other statistically significant differences were demonstrated on the other secondary clinical measures. Specifically, the following results are illustrative:

MEAN EDSS

	<u>PLA</u>	<u>9 mlU</u>	<u>45 mlU</u>
<u>Baseline</u>	2.9	2.9	3.0
<u>Endpoint</u>	3.0	2.8	2.9

These data yield an overall P-Value of 0.190.

In general, analyses of the Canadian and US studies individually revealed trends in favor of Betaseron 45 mlU vs Placebo as seen in the pooled analysis, but without reaching statistical significance.

MRI Data

Size and number of lesions seen on MRI were considered secondary outcome measures by protocol. Patients were to be scanned at baseline, at 1 year, and at the end of the study. In addition, patients at the University of British Columbia were scanned every 6 weeks. All scans done at all centers were sent to the University of British Columbia to be read in a blinded fashion.

It was agreed at the initiation of the Agency review of the PLA that CBER would obtain expert outside consultation to review the MRI data. They contacted _____

_____ He submitted a memo to CBER which outlined his concerns about the MRI data. Most of his concerns relate to the technology employed at the University of British Columbia, but his review did not contain specific analyses of the data. As far as I am aware, there is no written, detailed review of the MRI data.

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The sponsor maintained in its submission that there were statistically significant differences in the number of lesions and the total lesion area as measured by MRI favoring high dose Betaseron compared to placebo. Specifically, for example, patients in the high dose group had a median **decrease** in the total lesion area at the end of 2 years of 7.1% compared to baseline, as opposed to a median **increase** in the total lesion area in the placebo patients at 2 years of 18.0% compared to baseline, a between treatment difference significant at a p-value of <0.005.

SAFETY

Betaseron has been studied in a wide variety of illnesses, by multiple routes of administration, and at varying dose. The total number of patients who have received Betaseron as of July 31, 1991 is 2296. A total of 1440 patients have received Betaseron via routes and in doses relevant to the MS experience (others have received the drug in what are considered routes of administration that are not relevant for the determination of safety for the MS population; e.g., intracerebral, topical, intranasal, intravesicular, etc.). In this cohort, 277 patients have received Betaseron in MS studies, and 1163 have received Betaseron in studies of other illnesses, including HIV (464), Solid tumors (587), Hematologic Malignancies (66), and Condyloma (46). Of the 1440 patients in this cohort, 877 have received the drug outside of controlled clinical trials; controlled trials have been performed only in MS, HIV, and Condyloma populations.

Of the 1163 relevant patients not in MS studies, doses of Betaseron were considered to have been in 4 groups: Low (<45 mIU), Medium (45-89 mIU), High (90-179 mIU), and Ultra High (>180 mIU). We do not, at this time, have detailed dose and duration data on this population.

DEATHS

There were no deaths in the MS Controlled trials. The only other large placebo controlled trial performed in the 1163 patient cohort was in HIV patients with advanced disease. In this study, the incidence of death was slightly higher in the placebo patients compared to the treated patients (6.0 vs 5.0%). There were a total of 90 deaths in the cohort of 1163;

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16/464 (3%) of HIV patients, and 74/653 (11%) of patients with cancer.

DROPOUTS

In the 1163 non-MS patients, withdrawals secondary to adverse events ranged from 19% (Solid tumor patients) to 2.7% (HIV patients), with the exception of Condyloma patients (4%). Most of these withdrawals were related to common adverse effects of the drug (to be described below), or to the underlying disease process.

In the MS controlled trial, 10/115 (9%) of the 45 mIU group, 5/111 (4.5%) of the 9 mIU, and 1/112 (0.9%) of the Placebo patients withdrew due to adverse reactions. Flu-like symptoms, including fatigue and headache, account for over 40% of the drug related dropouts.

ADVERSE EVENTS

In the MS Controlled trials, the following chart lists those Adverse Events seen more frequently in the high dose Betaseron group compared to the Placebo group:

<u>EVENT</u>	<u>Placebo (N=112)</u>	<u>9 mIU (N=111)</u>	<u>45 mIU (N=115)</u>
Injection Site Reaction	37 (33%)	89 (80%)	96 (83%)
Fever	38 (34%)	44 (40%)	67 (58%)
Chills	20 (18%)	22 (20%)	51 (44%)
Myalgia	27 (24%)	27 (24%)	47 (41%)
Sweating	10 (9%)	11 (10%)	22 (19%)
Malaise	4 (4%)	9 (8%)	17 (15%)

Perhaps importantly, 5 patients have attempted suicide while on treatment; 1 HIV patient, and 4 MS patients.

LABORATORY ABNORMALITIES

In the MS studies, lymphopenia was the most common laboratory abnormality associated with Betaseron use. A total of 50/115 (43.5%) of high dose patients had counts of 500-999 lymphs/cu mm compared to 26/112 (23.2%) patients on placebo during the trials (baseline rates

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approximately 30% in both groups). Other abnormalities associated with Betaseron included elevated liver enzymes (5 people), decreased absolute neutrophil counts, decreased WBC, and decreased platelets. The vast majority of these changes were mild and not clinically significant. Most were transient, resolved with continued treatment, and no patient discontinued treatment because of a laboratory abnormality.

ADVISORY COMMITTEE MEETING

On March 19, 1993, the PLA was presented to the Peripheral and Central Nervous Systems Advisory Committee. In addition to the usual members, in attendance were Dr. Frederick R. Applebaum of the Fred Hutchinson Cancer Research Center in Seattle, Washington, an expert in the use of interferons and a member of the Biologic Response Modifiers Advisory Committee (CBER), and Dr. Henry McFarland, Acting Chief of the Neuroimmunology Branch of the NINDS.

At this meeting, while the Agency presented the results of the clinical trial, the sponsor presented the results of the MRI data. As noted earlier, the Agency had not formally reviewed this data prior to the meeting. A number of points became clear at the meeting.

There was considerable discussion about the standards the Committee was to apply in arriving at a recommendation to approve the drug for licensure. They were informed that, while the standard for NDA approval ordinarily requires data from more than one adequate and well-controlled trial, this was not necessarily the case for PLA approval, since there is no such legal requirement for data from more than one trial for biologics. However, the Committee was made aware (and, I believe, clearly understood) that they were not compelled to approve the PLA on the basis of one trial, and that they were free to consider whether the current data base in toto contained sufficient evidence of safety and effectiveness to support licensure, in their judgment.

Further, it was also clear that the Committee as a whole placed great weight on the MRI findings in their deliberations. Specifically, although the clinical benefit, as measured by the proportion of exacerbation-free patients and exacerbation frequency, was considered real and of value

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clinically, the Committee considered the size of the treatment effect relatively small.

However, it was obvious that great emphasis was placed on the MRI findings. Specifically, the Committee appeared convinced by the firm's presentation that the drug had an important effect on the underlying pathology as measured by total lesion area as seen on MRI. The statistically significant decrease in the total lesion area in the high dose group as compared to placebo patients over the course of the study that the sponsor claimed was demonstrated was interpreted by the Committee, in my view, as powerful support for the conclusion that the drug was having an important effect on the underlying disease process. While the Committee stopped short of declaring that the data proved that the drug had an effect on the progression of the disease, I believe it is fair to characterize their view with a quote, made at the meeting, by Dr. McFarland, who said at one point, that, while the sponsor had not proved that the drug had an effect on the course of the disease, "I would be amazed if it didn't change the course of disease.". A number of Committee members explicitly referred to Dr. McFarland's comments in this regard when explaining their votes.

The Committee did vote 7-2 that the sponsor has provided sufficient evidence in patients with mild to moderate relapsing-remitting MS that Betaseron is effective in decreasing exacerbations in patients with this form of the disease (while the 2 members who voted against approval agreed that the study provided evidence of effectiveness, they felt that the data, taken in its totality, was insufficient to warrant approval). Further, they voted (7 yes, 2 abstentions) that the sponsor has provided evidence that Betaseron is safe when used in the treatment of MS.

Finally, there appeared to be general agreement by the Committee members that the trial was, in fact, one clinical trial, not two, but that the totality of the evidence was sufficient to declare the drug safe and effective.

THREE YEAR DATA

On July 5, 1990, as the first patients were completing the controlled trial, the sponsor submitted an amendment to allow for a third year of blinded treatment. In this amendment, completers were permitted to

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continue to receive, in a blinded way, the therapy to which they had been randomized. Patients who had not completed the initial 2 years and patients not choosing to continue beyond 2 years were followed off drug. The design of this extension was essentially the same as the initial 2 year portion, but the primary variables were now considered to be the change from baseline to Year 3 in the EDSS, and the time to a confirmed (i.e., sustained over several visits) increase of at least 1 point on the EDSS (considered a measure of disease progression). The other variables measured in the first 2 years were also measured in the third year.

The results of this data were received after the Advisory Committee met. Medical and Statistical reviews of this data have only very recently been completed, and a decision about the effectiveness of the drug does not depend upon this data. Dr. Tiwari, in his review dated May 20, 1993, calculates p-values for the variables that were considered primary in the 2 year study, namely Frequency of Exacerbations/Subject, Proportion of Exacerbation-Free Subjects, and Exacerbation Rate. These parameters were evaluated for the third year only; that is, these values are not calculated for the entire 3 years, but only for the third year. P-values for these variables for the high dose-placebo comparison are 0.07, 0.10, and 0.065, respectively. It should be pointed out that 18% of the 338 patients included in the 2 year analysis were not included in the 3 year analysis (N=278).

With respect to the MRI data for the third year, data from only 65% of the original 338 patients (N=220) was available. In this subset, at the end of the third year, patients in the high dose group had a median decrease in total lesion area of 9.1% (as compared to their status at the end of Year 2), compared to a median decrease of 5.5% in the placebo patients. This between treatment difference was not significant, yielding a p-value of 0.48.

COMMENTS

A number of factors complicate the Division's role in this process. Because the Division served primarily as the clinical review team, our role was limited to questions of safety and efficacy. In particular, I would make a distinction between making a statement to CBER about the safety and effectiveness of the treatment, and making a recommendation about approvability. In order for us to make the latter, we would have to

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consider other, non-clinical issues. For example, I am under the impression that the sponsor has not submitted the results of in-vivo carcinogenicity studies, chronic toxicity studies, or pre-clinical reproduction studies. Since these and other issues must be considered in reaching a decision about the approvability of the application, and since we have not been involved at any level in these issues, I find it only reasonable to restrict my comments to the question of the safety and effectiveness of the treatment. Indeed, in early discussions with the staff of CBER, it was made clear that the Division would render an opinion about the safety and effectiveness of the treatment, but would not offer a recommendation about ultimate licensure.

In light of the Division's relatively restricted role, then, I believe the following comments can fairly be made.

First, it is clear that a majority of the PCNS Advisory Committee (7 for, 2 against) believes that this PLA should be approved. This, in light of the fact that there was general agreement that the PLA contained only one adequate and well-controlled trial in this population. Again, while the Committee ordinarily would only recommend approval if an application contained at least 2 such studies (the requirement for NDA approval with which the Committee usually is faced), review of the considerable discussion about the specific requirements for approval of this PLA reveals that the Committee was convinced that Betaseron is safe and effective for the proposed indication, and that it should be approved for marketing. I also believe that review of the discussion reveals that their view of the results of the analyses of the MRI data played a critical role in their reasoning. That is, given the relatively minimal amount of data (i.e., one study), and the relatively minor degree of clinical benefit seen, the MRI findings provided critical information that, taken in concert with the clinical data, allowed the Committee to feel comfortable concluding that the data supported marketing. Specifically, the general view was that the MRI data provided strong evidence that Betaseron slowed the underlying pathologic processes (and, hence, the course) of the disease. That is, it appears clear that the Committee felt that the MRI results not only were consistent with the clinical benefit observed (that is, the changes seen corresponded to the exacerbation rate data at a given point in time), but that they could be relied upon to accurately "predict" patients' future courses. In other words, the MRI data were considered, for all intents and purposes, as a surrogate marker for disease

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progression (see Dr. Leber's detailed discussion of this issue in his memo of 5/28/93). Though there was explicit acknowledgment that this had not been proven, I believe the Committee considered this to be so, and voted accordingly. (Incidentally, while the Committee did not explicitly address the issue of marketing in its vote, it is evident that they believe the data support licensure.)

In any event, I agree that the data, taken as a whole, demonstrate that Betaseron is effective in decreasing the frequency of exacerbations in patients with mild-moderate relapsing-remitting MS. While the PLA does not contain the results of more than one adequate and well-controlled trial, I believe that the clinical and MRI data taken together are sufficient to support a conclusion that the regulatory burden of proof of effectiveness has been met. Specifically, although the 2 protocols were to be combined as a single study, the trends in the results in each of the Canadian and US protocols provide reassurance about the reproducibility and consistency of the findings. Further, the relative robustness of the results with respect to the various analyses performed on the various data sets (e.g., validated vs. unvalidated exacerbations, etc.) provides additional support for this conclusion. I should point out that I also agree that the MRI data, while encouraging, certainly cannot be considered, at this time, to be a validated surrogate marker for disease progression in this population. Additional studies correlating longitudinal changes in MRI and clinical status over relatively long periods of time are still necessary before MRI can be considered an established surrogate. In this regard, it is interesting to note that at the end of third year of the study, the MRI scans in the placebo patients actually showed improvement compared to the scans taken at the end of the second year.

With regard to safety, the exposure in the MS population at the high dose is quite minimal. While the entire data base represents exposure in over 1400 patients who received Betaseron parenterally at 45 mlU or greater, an exact distribution of experience by duration and dose has not been supplied by the sponsor. The vast majority of this cohort had serious illnesses other than MS (e.g., HIV, solid tumors, hematologic malignancies, etc.), and have not been in controlled trials. The Advisory Committee concluded that these safety data were sufficient to permit marketing.

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I see nothing in the safety data base that raises a particular alarm. However, since the data base in the MS population is exceedingly small, the question of the appropriateness of the safety data generated in these other populations must be asked. While the majority of those patients in these other data bases were undoubtedly more acutely ill than the MS patients, it is difficult to be certain that this is comforting. For example, while there may have been more frequent reports of ADRs in these sicker populations due to either an interaction of the drug with the underlying disease or as a result of the underlying disease itself, (with the resultant conclusion that the absence of serious reactions is particularly encouraging), it may also be the case that clinical events thought secondary to the underlying illness were reported less frequently, despite the fact that they may have been, in reality, related to treatment with Betaseron. In addition, we have not seen a detailed breakdown of the entire experience by dose and duration. The sponsor did state, at the Advisory Committee meeting, that the median duration of exposure in this cohort was approximately 2.5 months, but detailed data beyond this was unavailable then, and I have not seen any additional data since. Nonetheless, I believe that the current safety data base supports the conclusion that Betaseron can be considered safe, although I believe the Agency should urge the sponsor to conduct prospective Phase 4 studies to better define the potential toxicity of the drug.

RECOMMENDATIONS

I believe that sponsor has submitted sufficient clinical data to support the conclusion that Betaseron 8 mIU, given subcutaneously every other day, is safe and effective for decreasing exacerbations in patients with mild-moderate relapsing remitting Multiple Sclerosis, and this conclusion should be conveyed to CBER.

Further, in an attempt to better define the utility of MRI scanning to serve as a surrogate for disease progression in this population, the sponsor should be strongly urged to undertake a trial to correlate MRI findings with clinical status, the design of which to be negotiated. Finally, because the safety data base in the MS population is small, they should also be urged to conduct prospective Phase 4 studies designed to further define the toxic profile of the drug.

Finally, the draft of the clinical portions of the labeling that we have

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included with this package (and which has been discussed with the sponsor in some detail) should be forwarded to CBER to be sent to the firm.



Russell Katz, M.D.

cc:

PLA 92-0495

HFD-120

HFD-120/Katz/Leber/Rouzer-Kammeyer/Fitzgerald

rk/5/28/93

betaseron

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Memorandum**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

DATE: May 28, 1993

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products, ODE 1, CDER
HFD-120

SUBJECT: Betaseron® PLA [PLA 92-0495] Collaborative Review

Through: Robert Temple, M. D.
Director,
Office of Drug Evaluation I, CDER
HFD-100

To: Janet Woodcock, M.D.
Director,
Office of Therapeutics Research and Review, CBER
HFM-500

1.0. Introduction

DNDP's review of the clinical evidence bearing on the safety and effectiveness of the biologic product Betaseron® (interferon beta-1b) has been carried out under the recently promulgated Collaborative Review Policy.

This memorandum summarizes the findings of DNDP's review, explicates the basis for its views, explaining, when appropriate, how and why these differ from those of its advisors, and offers some suggestions for product labeling should CBER reach the conclusion that Chiron's PLA for Betaseron can be approved.

A substantial fraction of the points offered in this supervisory overview were developed in the course of discussions between myself and Dr. Russell Katz. Accordingly, there is a degree of unavoidable redundancy in the content and thrust of the memoranda that he and I have written¹.

¹ The redundancy is regrettable, but is an inevitable consequence of the concurrent development of supervisory memoranda.

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2.0. Evidence bearing on Betaseron's Effectiveness considered by the Collaborative Review Team

Study TB01-35[6/8]86², a two year long, parallel, randomized, controlled multiclinic clinical trial comparing placebo, and two doses of Betaseron in 372 mildly to moderately ill ambulatory patients {EDSS \leq 5.5} with relapsing remitting MS is the sole³ source of controlled trial evidence that speaks to the effectiveness of Betaseron.

The original protocol for the Study TB01-35[6/8]86 called for outcome to be assessed on a number of clinically assessable and/or clinically derived variables (e.g., number and severity of exacerbations, level of disability, neurological findings, etc.). The protocol also called for counts of the number and size of CNS lesions detectable on Magnetic Resonance Imaging [MRI] scans to be obtained at baseline and at the end of the first and second years of the study. The protocol identified two of the clinical outcome variables as primary: 1) the proportion of exacerbation free patients and 2) the

² The sponsor, in reporting the results of this study, described the evidence (both in the PLA and in its presentation to the PCNS) as arising from two independently planned studies, one conducted in the US (7 sites), TB01-35686, the other in Canada (4 sites), TB01-35886, both using the identical protocol. As was pointed out during discussion at the PCNS AC by Dr. Shoulson, the power calculations used to determine the number of clinics and their sample sizes reveal that it was the intent of the study's planers to test the study's hypotheses using combined data from Canadian and US sites. Accordingly, it seems fair to conclude that the study was designed as a single, multiclinic investigation despite the sponsor's post hoc division of its component clinics into two groups based on their national origins. Thus, throughout this memorandum, I refer to the combined study as TB01-35[6/8]86.

³ A small (N = 31) randomized, balanced, parallel design pilot study (TB01-1648) was initiated in June of 1986 that compared placebo, 4.5, 22.5, 45 and 90 mIU of Betaseron administered on a 3 times a week schedule. An interim analysis of the study showed an overall combined drug vs placebo trend in exacerbation rate favorable to Betaseron. The rate, however, was not consistently predicted by dose. The sponsor did not provide a formal statistical analysis of the data, stating the study was planned only to assess safety and tolerance.

[difference] in average frequency of exacerbations per patient⁴.

The Collaborative Team⁵ focused its efforts, accordingly, on assuring the integrity, validity, and between clinic consistency of the results reported on the two primary clinical endpoints. Based upon their joint effort, the statistical and clinical members of the team concluded that the between treatment differences detected in Study TB01-35[6/8]86 on its two primary outcome variables provided statistically significant evidence that MS patients treated every other day for an interval of two years with subcutaneous injections of 45 mIU ⁶ of interferon beta - 1b suffer fewer and/or less severe clinically symptomatic exacerbations than MS patients randomized to a vehicle control or to a 9 IU dose of the drug.

Supervisors from CBER and CDER jointly decided that the Rouzer/Tiwari team would not attempt a review of the MRI scan results which were designated, by protocol, as secondary outcome measures. CBER did agree, as the 'Lead' Center, to recruit a suitably qualified outside expert to conduct, on the behalf of the agency, a comprehensive review of the MRI findings. It is noteworthy, considering the central role they played in the sponsor's presentations to the PCNS AC, that the MRI findings ⁷ were not emphasized in

⁴ Expressed in exacerbations/year and adjusted for time at risk.

⁵ DNDP's reviewer, Dr. Janeth Rouzer-Kammeyer, working in consultation with Dr. Jawahal Tiwari, the CBER statistician assigned to the Betaseron Collaborative review project.

⁶ The scale of International Units used to describe the potency of Betaseron has changed since the conduct of the study. The high dose of 45 mIU employed in the reports of the study in the PLA is equivalent to 8 mIU in the new International Unit system.

⁷ The original PLA submission contained at most a few pages of descriptive text of the MRI findings, and 3 summary tables providing means and standard errors for lesion areas and counts by treatment groups at baseline, and at the end of the first and second years of the study. In November of 1992, Chiron submitted additional information about group of 52 patients at the British Columbia site who had been scanned at 6 weeks intervals.

the original PLA submission.

3.0 Evidence Bearing on the clinical Safety of Betaseron in MS Patients considered by the Clinical reviewer.

3.0.1 Clinical Experience

Dr. Rouzer-Kammeyer reviewed reports of adverse clinical experiences and laboratory findings recorded in the course of clinical studies conducted with Betaseron in MS patients. She confirmed the sponsor's findings that injection site reactions and a flu-like syndrome are the two most common clinical adverse phenomenon associated with the use of Betaseron in this patient population. Lymphopenia was the most common single laboratory abnormality; it is not reported to be associated with any serious sequelae.

The warrant of safety in use provided by clinical experience with Betaseron in MS, however, is limited by the fact that only 277 MS patients have been treated with the Betaseron subcutaneously in clinical trials. Of these, according to Dr. Rouzer-Kammeyer's 3/5/93 review, more than 45% (N =130) were exposed to doses lower than the 45 mIU dose that would be recommended if the PLA were approved under the conditions of use proposed by Chiron.

Almost 2700 human subjects suffering from other diseases (HIV infection, various types of cancer) have been exposed to Betaseron by a number of different routes of administration. The sponsor was asked to provide an enumeration, by time, dose of exposure, and indication for use, of the number of individuals exposed by the subcutaneous and/or intravenous routes. To my knowledge, the request has not been honored.

3.0.2 Pre-Clinical Experience [CBER]

Results of preclinical studies of the sort ordinarily employed to evaluate the carcinogenic and teratogenic potential of new drug products have not been provided for Betaseron. Under the Collaborative Review arrangements, CBER retains responsibility for assessing the adequacy and the findings of the preclinical assessments that have been conducted.

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4.0 DNDP's assessment of Betaseron's effectiveness as a treatment of MS

The between group differences observed on the two primary, clinically assessed, outcome variables, taken together with the favorable results on the secondary outcome variables, (including the MRI results) provide reasonably compelling support for a conclusion that Betaseron has a clinically meaningful, beneficial effect on MS patients of the type enrolled in Study TB01-35[6/8]86 (i.e., Relapsing-Remitting patients early in the course of their illness with little or no physical disability {EDSS \leq 5.5}).

5.0: The PCNS AC's assessment of Betaseron's effectiveness

The PCNS AC's official evaluation of Betaseron's effectiveness in MS is not dissimilar from the Division's. Specifically, by a vote of 7 to 2, it agreed that there was "sufficient evidence in patients with mild to moderate relapsing remitting multiple sclerosis to support the conclusion that Betaseron is effective in decreasing exacerbations in patients with [this type of] multiple sclerosis.⁸"

The two dissenting members of the Committee, importantly, cast their negative votes not because they disagreed with the majority's conclusions about the findings of Study TB01-35[6/8]86, but because they believed, as a matter of epistemologic principle, that valid scientific conclusions require independent confirmation/corroboration. Specifically, they did not agree, as did the majority of the Committee, that the strength and consistency of the evidence adduced in Study TB01-35[6/8]86 were a sufficient basis to conclude that Betaseron was effective⁹.

⁸ Transcript of PCNS AC meeting, page 284

⁹ The Committee's discussion of the necessity for the independent corroboration of experimental results was confounded by concerns among some Committee members that a decision to declare Betaseron effective on the basis of a single study was inconsistent with the standard of evidence the Committee ordinarily applied to the evaluation of the effectiveness of new drug products. Although aware that the requirements of approval of a PLA under the Public Health Service Act differ from those set for a drug product under the Federal Food, Drug and Cosmetic Act, several members asserted

6.0 Is Betaseron a breakthrough treatment for MS?

Despite the relatively conservative tone of the Committee's formal resolution, many of its members were clearly more sanguine than are DNDP staff about the strength of the evidence adduced in Study TB01-35[6/8]86. The difference in viewpoint is explained by the very different weights and meanings the two groups have attached to the Magnetic Resonance Imaging Scan results.

For DNDP, the MRI scans results, which showed that the patients randomized to treatment with 45 mlU of Betaseron had a reduced number, size [area], and persistence of 'lesions' compared to those randomized to placebo,¹⁰ represented a finding on a secondary outcome variable that was entirely consistent with the results reported on the study's primary outcome measures. Specifically, it did not (and does not now) seem improbable, given the reported association between clinical exacerbations and MRI lesion number and size in MS patients, that a drug reducing the incidence of clinical exacerbations might be associated with a corresponding reduction in MRI lesion count and area, etc.

A more sanguine, albeit speculative, interpretation of this same evidence is possible, however. If the lesions detected on MRI are taken to be a better index of the 'activity' of the pathologic process than are clinical manifestations of MS, (a not unreasonable possibility given the knowledge that lesions detected on MRI may be unaccompanied by clinical signs/symptoms when they occur in so-called 'silent' regions of the CNS) and if the rate of clinical progression of MS (in the sense of increasing physical disability) is a positive function of the 'activity' of that pathologic process,

their belief that the standards of efficacy assessment used by the Committee ought to be the same for therapeutic agents regardless of their classification by the agency as drugs or biologics.

¹⁰ MRI scans had been obtained on all subjects at baseline, at 49 weeks and at the end of Study TB01-35686. In addition, serial MRI scans had been obtained at 6 week intervals on the subset of MS patients enrolled at the University of British Columbia site of the study.

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it follows logically that any drug suppressing this 'activity' 'must'¹¹ have some beneficial effect on the progression of MS (as manifest by increasing physical disability). Although the clinical evidence collected¹² in Study TB01-35[6/8]86 does not provide convincing affirmative support for this hypothesis, that does not necessarily undercut its appeal or its psychological impact on those asked to render an opinion about the 'therapeutic potential' of Betaseron.

During the PCNS meeting, the sponsor's representatives, several members of the Committee and, in particular, Dr. Henry McFarland, who was attending the meeting as the agency's expert consultant on neuro-imaging and MS, espoused the hypothesis just described. Although virtually all proponents of this hypothesis acknowledged that the link between MRI lesion frequency/intensity/area and subsequent outcome (progression in level of physical disability) in MS was not proven, almost all affirmed that they would be very surprised if the link was not eventually demonstrated. Thus, for many experts, the number and area of lesions detected on MRI are tantamount to a 'surrogate' endpoint that predicts disease progression in MS.

It is important to emphasize, however, that the validity of MRI lesions as surrogate measures for progression is undocumented; as noted earlier, the findings of Study TB01-35[6/8]86 fail to show that MRI lesion activity

¹¹ 'Must' appears in quotations as a reminder of prior occasions in the history of therapeutics where perfectly logical extrapolations based on beliefs about the pathophysiology of a disease and the postulated mechanism of a drug's action have led experts to reach totally incorrect conclusions about the promise of a particular drug (e.g., CAST: the suppression of ventricular ectopy 'must' save lives.)

¹² In their report of the study, the sponsor asserts that the correlation between EDSS disability scores and MRI lesion areas detected at both baseline ($r = 0.169$) and at the end of year two ($r = 0.2$) establishes that MRI 'burden' predicts disability (EDSS score). Although these statements are correct in a statistical sense, the correlation does not tell us what we really seek to learn: whether a treatment reducing the extent of MRI area increase over time will reduce the extent of clinical worsening, as judged by EDSS, over the same interval or in a future one.

predicts disability outcome in MS ¹³. Moreover, among patients in Study TB01-35[6/8]86 who elected to remain on the treatments to which they were randomized during a year long extension to the study, no between treatment differences in MRI lesion area change were detected over the interval of that year. Thus, even if changes in MRI lesion area and/or number predict long term outcome in MS, Betaseron's ability to affect the surrogate endpoint may not persist.

5.0.2 The Committee's consideration of Betaseron's Safety

Although relatively little substantive discussion was devoted to this topic during the PCNS AC meeting, the Committee, by a vote of 7 in favor, 2 abstaining, concluded that Chiron's PLA provided "evidence that Betaseron is safe when used in the treatment of multiple sclerosis." ¹⁴

6.0 Discussion of Risk/Benefit

It is widely recognized that regulatory licensing approval decisions turn on judgments that weigh simultaneously the probable risks and benefits associated with the use of a product under the conditions of use that will obtain if it is marketed and used as recommended in its approved labeling. Such judgments involve, beyond objective evidence of effectiveness adduced in controlled experiments, and information about the number and kind of reported risks, sentiments and beliefs about the disease, the nature of the population being treated, the kind of risks patients with the disease might reasonably take to gain the expected benefits of treatment, etc. Thus, risk benefit considerations often turn on personal values and beliefs as much as objective evidence and professional judgment. Consequently, what is a close decision for one person may be an unequivocally persuasive one for another

¹³ In fairness, Study TB01-35[6/8]86 serves as a poor medium in which to evaluate Betaseron's potential effects on progression. It enrolled ambulatory, mildly ill patients who, as the recent report on the changes during year 3 of the study continues to show, exhibit little tendency to disease progression. Consequently, if Betaseron were actually acting to slow the rate of disease progression in these patients, they might have to be followed for many years before the effect became evident.

¹⁴ Transcript of PCNS AC pages 285-287

So it is with Betaseron. If the MRI lesion data are interpreted as compelling evidence that treatment with Betaseron alters the long term course of MS, nothing within (or absent from) the PLA administrative file of which I am currently aware could reasonably be deemed to militate against the immediate approval of the PLA. This, I believe, more or less captures the viewpoint of the 7 members of the PCNS AC who voted in favor of Betaseron's marketing.

However, if MRI lesion data are viewed only as confirmation of the trial's clinical findings on exacerbation rate, the expected benefits associated with the use of Betaseron are considerably more modest, necessitating, in turn, a much closer consideration of the risks that might be associated with its use in a young, predominantly female population that suffers from a disease that has a highly variable, and often benign, course.

As noted previously, results of the preclinical tests that would ordinarily be used to assess the carcinogenic and teratogenic potential of a new drug intended for use in a population of the sort just described are not available.

I am not especially concerned about the latter, however, because the issue of Betaseron's incompletely tested potential to cause terata can be reasonably dealt with by the imposition of Phase IV testing requirements (if feasible) and appropriate labeling statements warning about the drug's use in pregnancy or females seeking to become pregnant (Betaseron has been shown to be an abortifacient in Rhesus Monkeys; this action could well reflect an undocumented teratogenic effect of the drug.).

Betaseron's potential to cause tumors in animals is unevaluated; were it a drug product, it seems likely that we would at a minimum, if approval were being contemplated, impose a Phase IV requirements for in-vivo lifetime testing as a condition of approval. I am reluctant to make a specific suggestion/recommendation here, however, because there is as yet no clear agency policy regarding the value and/or feasibility of doing in-vivo lifetime testing of biologic substances such as interferons for their carcinogenic potential.

Finally, the warrant of safety in use provided by clinical experience with Betaseron in MS patients at the dose of Betaseron to be recommended derives from no more than 140 or so patients. Although this experience provides no pattern of adverse clinical or laboratory findings that raise concerns about

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the safety of Betaseron, its represents a relatively meager experience, one that would ordinarily be viewed as inadequate on its own to support the approval of a new chemical entity. Betaseron, of course, has been used widely in a number of other clinical populations (Cancer, HIV, etc.), a fact that may well mitigate the lack of clinical experience at appropriate doses in the MS population. It certainly seems as if it should serve that purpose. Nonetheless, there are theoretical concerns; for example, might adverse events caused by Betaseron in a population of cancer patients be systematically under-estimated (i.e., incorrectly attributed to the disease and not reported as drug related)? Unfortunately, these are not questions that experts in the Division are competent to answer; indeed, the individuals best able to estimate the warrant of safety provided by experience with Betaseron in non-MS populations probably reside in CBER.

In sum, the risk to benefit analysis of Betaseron is strongly affected by the interpretation of the MRI scan results and the assessment of the warrant of safety in use provided by clinical experience in non-MS populations.

7.0 DNDP's Conclusions concerning the Clinical evidence:

1- The data derived from the 372 subjects entered in Study TB01-35[6/8]86 show that treatment with Betaseron (at a subcutaneous dose of 45×10^6 mIU every other day) reduces the incidence and severity of clinical exacerbations in a relatively mildly ill population of ambulatory MS patients for periods of two and perhaps as long as three years.

2- There is no empirical basis to conclude that Betaseron has an effect on the course of MS. When the clinical status of patients under the 3 treatment arms of Study TB01-35[6/8]86 are compared on the EDSS, no statistically significant differences were detected at the protocol defined endpoint of two years. The failure to find a difference in outcome may well be attributable to the relatively mild/moderate disease state of the patients studied, however.

3- The MRI data collected over the first two years of Study TB01-35[6/8]86, assuming they actually represent the phenomena that are the anatomical manifestations of disease activity in MS, can be used to argue that Betaseron may have an ameliorating effect on the pathogenic process. This effect, incidentally, is not sustained during the third year extension of the study. The truth of this hypothesis, in any case, remains to be

demonstrated.

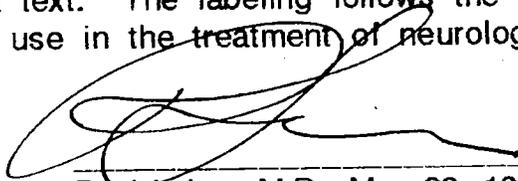
4 - The evidence gained from clinical experience with MS patients does not show Betaseron to pose any degree of unacceptable risk. The value of this conclusion is undercut by:

a) the limited amount of clinical information available that is directly relevant to the use of Betaseron in the population for whom it would be recommended under the conditions of use recommended if the PLA were to be approved ¹⁵.

b) the lack of the usual preclinical teratogenicity, reproductive performance, and carcinogenicity studies in appropriate animal species.¹⁶

8.0 DNDP's Consultative Recommendations:

Although I am confident that DNDP has a clear and sound understanding of the clinical evidence that has been gained with Betaseron in MS patients, the Division and its staff are inadequately informed about other elements critical to the formulation of the risk benefit assessment that must underlie any decision regarding Betaseron's suitability for marketing. Consequently, the Division will not offer a recommendation regarding the approval of the PLA; we trust, however, that CBER staff will be willing to consider the suggestions that we have for the structure and text of the Betaseron's labeling in the event that it does elect to approve the PLA. These suggestions are presented in the form of a draft text. The labeling follows the format used for drug products intended for use in the treatment of neurological conditions.



Paul Leber, M.D., May 28, 1993

¹⁵ As noted, CBER would appear to be in a better position than DNDP to determine whether clinical experience gained with Betaseron in non-MS populations is sufficient to discount this limitation.

¹⁶ Again, CBER, given its wide experience with interferons, is in a better position to judge the importance of these limitations than DNDP.

cc:

PLA 92-0495

HFD-100

Dr. Robert Temple

HFD-120

Dr. Russell Katz

Dr. Janeth Rouzer-Kammeyer

Mr. Jack Purvis

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**COLLABORATIVE
REVIEW AND EVALUATION OF CLINICAL DATA**

Original PLA: Vol. 1.1-1.172
Amendments

Sponsor: Berlex Laboratories\Chiron Corporation

Drug: Betaseron®
(Recombinant Human Interferon Beta₁₇)

Indication: Relapsing-remitting multiple sclerosis

Date Submission: May 22, 1992

Date Review Completed: March 18, 1993

Related INDs: BB-IND 1846

Statistical Reviewer: Jawahal Tiwari, Ph.D (HFM-215)

Relevant Issues Discussed in this Review:

1. Definition of Exacerbation
2. Number of Invalidated Exacerbations
3. Potential for Unblinding

1.0 Introduction

The clinical development program of Betaseron in MS consist of three double-blind studies which provide safety and efficacy data for 277 MS subjects. Those three studies consist of a pilot dose-finding study, a Phase III efficacy trial conducted under identical protocol in the U.S. and Canada, and an extension study which was limited to subjects previously enrolled in the Phase III efficacy trial. All studies were double-blind and placebo-controlled, and Betaseron was administered subcutaneously. Doses ranged from 4.5 to 90 million IU, and were self-administered every other day or three times weekly.

1986: (Protocol TB01-16468) Phase I placebo-controlled pilot study

This was a 3 year dose-ranging study in 31 relapsing-remitting MS patients who were randomized to dose levels (4.5, 22.5, 45, 90 million IU). The study was amended to allow a fourth year of open-label treatment (placebo subjects were crossed over to receive 45 mIU). 23 patients completed the two year study, 19 completed up to 4 years as of March of 1990.

Dose selection was made from this trial (Study TB01-16486) where 7 of 24 Betaseron-treated subjects remained exacerbation-free for 3 years as compared to one of seven subjects in the placebo group.

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1988: Phase III randomized, double-blind placebo-controlled multicenter trial N=338. U.S. sites: Protocol TB01-35686; Canadian sites: Protocol TB01-35886

The primary evidence of efficacy of this application derives from the final analyses of pooled data from a multicenter Phase III efficacy study. Berlex conducted two identical double-blind, placebo-controlled, multicentered Phase III studies, one in the U.S. (Study TB01-35686) and one in Canada (Study TB01-35886), from which data were to be pooled for analysis. Subjects in each center within a study were to be randomly allocated to one of three parallel treatment groups: placebo, 9 or 45 mIU of Betaseron. Assigned treatment was administered subcutaneously, every other day, for two years. Primary efficacy evaluations was based on reduction in frequency of exacerbations per subject and proportion of exacerbation-free subjects. Efficacy and safety results represented are based on the final report for these studies and represent all data for the first 338 subjects enrolled.

1989: Phase III Extension Trial-U.S. TB01-3103 and Canada TB01-3104

In January 1989, Berlex initiated protocols for an additional Phase III extension study with enrollment limited to participants in the initial Phase III trial. Studies TB01-3103 and TB01-3104 each provide for two cohorts. Group A subjects continue treatment as assigned in either Study TB01-35686 or Study TB01-35886. Group B consists of subjects who either withdrew from the efficacy studies before 104 weeks or completed 104 weeks and chose not to continue treatment in the follow-on studies. Subjects in Group A were to continue receiving blinded study drug and be followed for at least 48 weeks. At completion of 48 weeks, they may elect to continue dosing and follow-up for another year. Those in Group B will be followed without study therapy for 48 weeks and then terminate.

311 subjects who completed the efficacy trials elected to participate in the extension studies: 278 in the treatment group and 33 in the non-treatment follow-up group.

2.0 Efficacy Trials: TB01-35686 (U.S.)\TB01-35886 (Canada)

Design

Trial design consisted of two identical, multicenter, double-blind, placebo-controlled studies, with three parallel treatment groups (placebo, 9 and 45 mIU Betaseron). Study treatments were self-administered subcutaneously every other day for approximately 104 weeks (2 years). The protocols provided for an interim analysis of the data collected through the first year on study.

All subjects were to have an MRI scan at baseline, week 49, and withdrawal. MRI scans were conducted every 6 weeks at the University of British Columbia.

Subject Population

Inclusion criteria for the 338 subjects included:

- Clinically definite relapsing-remitting MS as defined by Poser criteria
- Objective neurologic dysfunction reflecting primarily the white matter
- History of clearly defined relapse and remission, with at least two exacerbations in the 2 years preceding study entry.
- Stable disease for at least 1 month at time of screen & baseline evaluation
- EDSS score of 0 (normal)-5.5 (ambulatory)

Exclusion criteria included prior treatment with interferon or cytotoxic immunosuppression, or steroid/ACTH therapy within 30 days of study entry

Withdrawal criteria included:

- Interruption of scheduled dosing for more than 2 weeks, except for resolution of study drug toxicity or exacerbations.
- intolerable side effects
- phase of increasing disability that progresses unremittingly for 6 consecutive months
- violation of concomitant therapy restrictions, including corticosteroid use for exacerbations (no more than 3 courses, each 28 days or less in a 12-month period)

Study Medication

Supplies of Betaseron and placebo were provided in refrigerated vials containing a sterile lyophilized cake of assigned study medication to be reconstituted by the patient with 1.3 mL sterile diluent.

Randomization Procedure

A central randomization schedule assigned two subject numbers, from a block of six sequential numbers, to each of the three treatment groups. To ensure treatment group balance at each site, subject numbers were sent to the sites in blocks of six.

Blinding Procedure

Sponsor's analysis were prepared by the project statisticians and a small group of supporting statistical staff, who were the only Berlex staff members un-blinded to treatment assignment other than staff involved in drug labelling and shipping. All other Berlex staff, study investigators and staff, study site pharmacy staff, and study subjects remain blinded.

At study sites, all investigators, study and pharmacy staff, and subjects were blinded to treatment assignment. Neurologic and adverse event evaluations were conducted by two different physicians-one for neurological exams, the other for evaluating adverse events and symptoms and managing overall patient care. Also, the initial seven on-study injections were given at half dose to mitigate known interferon side effects with the intention of reducing the likelihood of subject unblinding to treatment assignment.

Acetaminophen could be given concomitantly with test drug for relief of fever and/or myalgias. All such use was to be documented on the CRF.

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Also, a nurse could assist with the evaluation of possible adverse experiences. Patients were to be asked in a consistent manner about presence or absence of symptoms known to be associated with interferon therapy such as fever or malaise.

Primary Endpoints

- (1) Frequency of exacerbation per subject.
 - (2) Proportion of exacerbation-free subjects.
- The protocol did not specify whether one and/or both outcomes were sufficient to win.

Definition of Exacerbation

- Appearance of a new neurologic abnormality or
- Reappearance of a neurologic abnormality any time after initial attack
- Must last at least 24 hours
- Must be immediately preceded by a stable or improving neurologic state in the 30 days before deterioration.

Verification of Exacerbation

According to protocol, subjects were instructed to contact the clinic immediately should symptoms suggestive of an exacerbation appear and were then to be evaluated at the clinic within 24 hours, but no later than 72 h after contact . At the exacerbation visit, the examining physician noted the probable location of the lesion or lesions responsible for the new clinical findings and evaluated neurologic status and disability by means of the Functional Neurologic Status scale, EDSS, and Scripps scale. Subjects were then followed throughout the course of the attack at the investigator's discretion.

When, in the investigator's opinion, the exacerbation had begun to remit, the investigator was to assess the global severity of the exacerbation at its worst point as either mild, moderate, or severe. This evaluation was to be based on the investigator's clinical judgement of the severity of the event at its worst point, to be completed in addition to the evaluation based on the Scripps Score. This severity designation and the date of the assessment will be entered on the exacerbation case report form. This assessment was added to the protocols by a later amendment and data are not available for all exacerbations.

For each exacerbation, the difference between the first Scripps score taken while the exacerbation was ongoing and the last previous stable score was calculated. A decrease in score of 7 points or less was defined as mild, a decrease of 8 to 14 points as moderate, and a decrease of 15 or more as severe. If a Scripps score was not obtained while the exacerbation was ongoing, change from previous status and severity could not be determined, and the severity of the exacerbation was classified as unknown.

However, the study data and FDA inspection indicate:

- A large number of exacerbations (approximately 20%) were not verified
- A large number of exacerbations were not verified on time

Therefore, a major issue for this study is the effect of verification/non verification on the evaluation of efficacy.

Evaluation of Exacerbations

The two primary efficacy endpoints reflect incidence of exacerbations. Individual subject exacerbation rates were calculated using the number of exacerbations divided by the time on study for that subject. These rates were used for the primary efficacy analyses. Overall exacerbation rates for each group were annualized by dividing the total number of exacerbations for the group by total group time on study (in years) to derive an exacerbation rate per subject year.

To assess the effects of Betaseron treatment on exacerbation rates over time, annual exacerbation rates were examined for three different intervals: 0-6 months, 7-12 months, and 13-24 months.

Secondary Endpoints

- (1) Time to first exacerbation
- (2) Exacerbation severity as measured by the Scripps Scale
- (3) Exacerbation duration
- (4) Disability as measured by EDSS and Scripps score
- (5) Disease burden as measured by MRI

For assessment of exacerbation-free interval, time to first exacerbation was defined as the number of days from start of dosing to the onset of the initial on-study attack. Time to second exacerbation was defined in two ways: as the number of days from start of dosing to the onset of the second exacerbation and, for the group of subjects with at least one attack, the number of days from the onset of the first attack to the onset of the second.

For calculations of exacerbation duration, duration was defined as the number of days from the onset to resolution of the attack. If the exacerbation never resolved or resolved after study completion, the study completion date was used for the duration calculation.

The Scripps scoring system (Appendix I, Table 3) was used to determine exacerbation severity. In this scale, a score of 100 is normal and the score decreases to reflect increasing disability. For each exacerbation, the difference between the first Scripps score taken while the exacerbation was ongoing and the last previous stable score was calculated. A decrease in score of 7 points or less was defined as mild, a decrease of 8 to 14 points as moderate, and a decrease of 15 or more as severe. If a Scripps score was not obtained while the exacerbation was ongoing, change from previous status and severity could not be determined, and the severity of the exacerbation was classified as unknown. The occurrence of exacerbations for which severity was unknown were assumed to be independent of the treatment group and degree of severity.

Study Conduct

The pivotal trial was conducted in neurologic clinics at academic institutions in the U.S. and Canada. Beginning on Day 1, subjects self-

injected the study medication subcutaneously on an every other day schedule. Subjects received the first three injections of drug at the study center. The first seven injections were given at half volume (0.5 mL: PBO or 4.5 or 22.5 mIU Betaseron) to minimize tell-tale side effects of interferon. On Day 15, injections were increased to full volume (1 mL). Additional clinic visits were made at weeks 5 and 7; thereafter, every 6 weeks through week 37 and then every 12 weeks through study completion.

Between visits, subjects were to maintain diaries, in which they recorded the date of each injection, any adverse experiences or intercurrent medical events, and concomitant medications. At the next scheduled visit, pertinent data were transcribed onto the case report forms by the clinic data manager under the supervision of the investigator.

A study center nurse or data manager was to telephone the patient during the exacerbation at weekly intervals to inquire about the patient's clinical status. The information was to be recorded in the Case Report Forms.

In the event of grade 3 or 4 toxicity (Clinical Scale for Interferon Toxicity), dosing was to be interrupted. When the toxicity level had fallen to grade 2 or less, therapy could be reinstated at a 50% reduction for each subsequent dose unless toxicity occurs during doses 1-7 (i.e., patient is terminated from the study). Dosing was to remain at the 50% level unless toxicity increases to Grade 3 or 4 again, at which time the patient must be terminated from the study. Dosage reescalation may not occur following dosage reduction.

Remission is defined as the complete disappearance or significant decrease in severity followed by stability for at least 1 month of a neurologic abnormality that had lasted for at least 24 hours.

Potential for Unblinding

Clinic scheduling procedures varied. Some clinics reserved certain days for evaluation of subjects participating in clinical trials. Other clinics scheduled clinical trial subjects intermixed with regular MS patients throughout the week.

The sponsor reviewed the database and reports that for 42% of study visits, only one subject was seen at the site for the day; for 78% of visits, no more than three subjects were seen. Because enrollment at most sites extended over a year or more, it is likely that subjects who were seen on the same day were at different points in the study.

Statistical Methodology

The trial was designed based on a power calculation assuming a placebo rate of 0.4 exacerbations per year and a 50% reduction in exacerbations at a two-sided alpha level of 0.05.

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Three datasets were employed in the efficacy analyses: two intent-to-treat datasets and one evaluable dataset. The primary intent-to-treat dataset included all pre-withdrawal data for the 338 subjects; the second intent-to-treat analysis used all available pre- and post-withdrawal efficacy data for the 338 subjects; the third dataset included all subjects and data considered evaluable by an evaluation committee blinded to treatment assignment.

The primary intent-to-treat dataset was used for all the analyses by the sponsor. The secondary and evaluable datasets were used to analyze exacerbation rates, proportion of exacerbation-free subjects, and time to first exacerbation.

The main analyses were based on the pair-wise comparisons of PBO with the 9 mIU (low-dose) and 45 mIU (high dose) arms. The O'Brien-Fleming sequential rule was used to specify the significance level. For the high-dose-v. PBO and low-dose v. PBO pairwise comparisons, the significance level of $\alpha=0.048$ was adjusted by the Bonferroni technique. The Student-Newman-Keuls technique, incorporating the $\alpha=0.048$ was used to adjust for the multiple pair-wise comparisons between treatment arms. Two-sided significance level of $\alpha=.05$ was used for testing the null hypothesis.

The proportion of subjects free of exacerbations and the distribution of the numbers of exacerbations per subject were tested using the CMH test stratified for study site. The comparison of exacerbation rates across treatment groups was performed using the ANOVA Model 1 on the rank-transformed subject data.

The protocol specified for an analysis stratified by baseline EDSS (less than or equal to 3.0 compared with baseline EDSS greater than 3.0) to determine if disability at entry influenced exacerbation rate. Subjects with a baseline EDSS less than or equal to 3.0 (the study population median value) were compared with those with baseline EDSS greater than 3.0.

EDSS and Scripps values for the three treatment groups were compared for change in neurological status at 12 and 18 months and at last visit. EDSS scores were also used to define change from baseline in neurologic status, categorizing as improved (>1 point decrease), stable ($+0.5$ points), or worsened (>1 point increase) at endpoint. The analysis was repeated with subjects stratified for baseline EDSS <3 or >3 .

By amendment, an interim analysis of pooled data for these two studies was performed based on data collected for subject visits occurring through July 31, 1990 (at least 1 year of subject experience for the first 338 subjects). The amendment was finalized with CBER consultation to use the O'Brien-Fleming rule to confirm statistically significant results. In addition, an "administrative" interim was performed in August 1989 to determine whether exacerbation rates were increased in the Betaseron-treated groups. This analysis was completed after enrollment of the 338

subjects was complete and the results were censored to preserve study blind. The firm states it did not adjust the alpha spending function for the administrative analysis since it "did not carry a risk of prematurely terminating the trial for efficacy reasons".

Extension Studies

At study completion, subjects from these studies could choose to continue treatment in a blinded fashion in the ongoing protocols TB01-3103, conducted in the U.S., and TB01-3104, conducted in Canada. Only subjects previously enrolled in either Study TB01-35686 or Study TB01-35886 are eligible to enroll in these additional studies. Studies TB01-3103 and TB01-3104 provide for two cohorts. Group A subjects continue treatment as assigned in either Study TB01-35686 or Study TB01-35886. Group B consists of subjects who either withdrew from the pivotal studies before 104 weeks or completed 104 weeks and chose not to continue treatment on Studies TB01-3103 and TB01-3104. Subjects in Group A are to continue receiving study drug and be followed for at least 48 weeks. At completion of 48 weeks, they may elect to continue dosing and follow-up for another year. Those in Group B will be followed without study therapy for 48 weeks, then terminate from study.

3.0 Results

Subject Disposition and Baseline Comparison

TB01-35686: 207 subjects (69 subjects in each of the three treatment groups).

TB01-35886: 131 subjects (placebo:43, 9 mIU:42, 45 mIU:46).

By treatment group, there were 112 subjects on the placebo arm, 111 on the 9 mIU arm (low-dose), and 115 on the 45 mIU arm (high-dose). Of these subjects, 69% were female and 93% were Caucasian (Appendix I, Tables 5 and 6, and Appendix III, Listings 1 and 2).

The trial was conducted in neurologic clinics at academic institutions in the U.S. and Canada. The following table displays enrollment by site for the two studies.

**Appears This Way
On Original**

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ENROLLMENT BY STUDY AND SITE					
BETASERON					
STUDY	SITE	PLACEBO	9 mIU	45 mIU	TOTAL
TB01-35686 (U.S.)	Temple U	9	9	9	27
	Thomas Jefferson	9	9	10	28
	UCSF	10	10	10	30
	U Alabama	4	4	4	12
	U Arizona	11	12	11	34
	U Chicago	16	16	16	48
	U Maryland	10	9	9	28
	TOTAL				
TB01-35886 (CANADA)	Hosp de Notre Dame	11	11	12	34
	Montreal Neurologic	8	6	8	22
	U British Columbia	11	10	10	31
	U Hospital	13	15	16	44
	TOTAL				
TOTAL		112	111	115	338

The contribution of subjects by each center was roughly comparable.

The three treatment groups were comparable for basic demographic factors and baseline disease characteristics, including number of exacerbations in the preceding two years (see Attachment 1). There were statistically significant differences but not clinically meaningful between groups for age at diagnosis and disease duration at baseline. Baseline demographics define a young population (age 32) with relatively minimal disease as indicated by EDSS score of 2.9.

Subject Evaluability

000394

A blinded data review committee composed of Berlex staff (physician, clinical research monitor, statistician and clinical data coordinator) was convened to establish criteria for data exclusion before analysis of the study data. The committee's task was to review subject data to identify those subjects with protocol deviations that make their experience inevaluable for efficacy. When this review was complete, the committee was disbanded.

The committee identified the following protocol deviations considered to potentially impact efficacy analysis:

- potentially unblinding events (9 subjects)
- >3 courses corticosteroids in a 12- month period (14 subjects)
- more than 30 doses missed per year (2 subjects)
- only 1 exacerbation in 2 years before study entry (2 subjects)
- wrong subject's drug dispensed (1 subject)
- ongoing exacerbation at baseline (1 subject)
- subject psychologically unstable (1 subject)

There were no exclusions from the primary intent-to-treat dataset. As a result of committee review, complete or partial data for these 30 subjects itemized in the previous paragraph (14 PBO, 8 low-dose, 8 high-dose) were excluded from the evaluable subject dataset. No substantive differences were noted between the results of the intent-to-treat and evaluable dataset analyses.

58 subjects were entered who did not meet one or more entry criteria, most commonly regarding duration of interval for time from resolution of last exacerbation to first study dose. None of these subjects were excluded by the firm.

Analysis of Discontinuations

Sixty-five subjects (19%) either withdrew or were withdrawn from treatment (Appendix I, Table 9 and Appendix III, Listing 11) for reasons other than study completion: 23, 18, 24, respectively in the PBO, 9, and 45 mIU arms. Median subject exposure to study drug was 23.9 months. Time on study was comparable for all three treatment groups.

Withdrawals due to adverse events suggested a dose-response effect with one, five, and ten withdrawals, respectively, for the placebo, low-dose group and high-dose groups. Only four adverse event withdrawals were required by the protocol; all others were subject initiated.

Dose Reductions

13/338 (4%) subjects experienced a dose-limiting event (Appendix I, Table 10). 10/13 completed study without further incident; the other 3 were withdrawn, 2 for recurring toxicity despite dose reduction and one by subject and investigator choice following a dose reduction.

Concomitant Medications

000395

Almost all subjects used acetaminophen at some time, but incidence was comparable across groups. Ibuprofen was used equally across groups and indomethacin was used by only two subjects.

Ingredient	Placebo (N=112)	Betaseron		Total	(%)
		9 mIU (N=111)	45 mIU (N=115)		
Acetaminophen	91	94	98	283	(84)
Pseudoephedrine hydrochloride	44	39	41	124	(37)
Prednisone	46	37	35	118	(35)
Codeine phosphate	32	47	34	113	(33)
Chlorpheniramine maleate	36	31	38	105	(31)
Phenylpropanolamine hydrochloride	37	29	30	96	(28)
Baclofen	24	26	26	76	(22)
Amitriptyline hydrochloride	20	26	26	72	(21)
Aspirin	18	19	18	55	(16)

The difference between PBO and high-dose groups for number of subjects using steroids was significant ($P=.021$). Also, as compared to PBO, the high-dose group has significantly fewer days of steroid use ($P=.001$). The proportion of subjects withdrawing from study for use of steroids beyond protocol limits was also significantly larger in the PBO group, as compared to the Betaseron groups.

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Glucocorticoid Use			
	Placebo (N=112)	Betaseron	
		9 mIU (N=111)	45 mIU (N=115)
No. subjects using glucocorticoids	56	48	41
Mean days of use	64.6	46.5	46.7
Std err	8.1	6.4	6.4
No. withdrawn for >3 steroid courses in a 12-month period	10	1	1

Sponsor's Efficacy Analysis Exacerbation Rates

Summary of the primary efficacy results are displayed following. The annual exacerbation rates were 1.27, 1.17, and 0.84 for the placebo, low-dose and high-dose groups, respectively, which represents a 34% reduction in the high dose rate as compared to placebo. As shown by pair-wise (t-test) comparisons of the least square means, the exacerbation rate for the high-dose group as compared to both the placebo and low-dose groups was highly significant ($p=.0001$ and $p=.0086$, respectively).

SUMMARY OF PRIMARY EFFICACY RESULTS

	PLACEBO (N=112)	BETASERON		OVERALL P-VALUE
		9 MIU (N=111)	45 MIU (N=115)	
EXACERBATION RATE	1.27	1.17	0.84***,++	0.0001
NO. SUBJECTS EXACERBATION FREE	18	23	36**,+	0.019
NUMBER OF EXACERBATIONS	0	23	36	
	1	28	35	
	2	23	19	*** 0.001
	3	15	10	+
	4	6	8	
	≥5	16	7	

000397

Analysis by protocol confirmed the results obtained with pooled data. For each protocol, the high-dose groups showed significantly lower exacerbation rates than the placebo group.

Annual Exacerbation Rates by Protocol		
Treatment	TB01-35686 (United States)	TB01-35886 (Canada)
Placebo	1.10	1.55
Betaseron 9 mIU	0.97	1.48
45 mIU	0.79	0.89
Overall	p=0.034	p=0.013
Placebo vs 45 mIU	p=0.011	p=0.004
Placebo vs 9 mIU	p=0.271	p=0.081
9 mIU vs 45 mIU	p=0.092	p=0.068

According to the sponsor's analysis, the pairwise comparison for annualized exacerbation rates of 45 mIU vs. placebo was statistically significant for both protocols (p=.0040).

Exacerbation-Free Subjects

For this primary endpoint, proportion of subjects remaining exacerbation-free, the difference among the three treatment arms was significant (p=0.019). The pairwise comparison between placebo and the high dose arm was also statistically significant (p=.007). Also, the difference in proportion of exacerbation-free subjects by protocol was significantly in favor of 45 mIU as compared to placebo for Canada and approached significance for the US (see below).

Proportion Exacerbation-free Subjects by Protocol		
Treatment	TB01-35686 (United States)	TB01-35886 (Canada)

Placebo	20%	9%
Betaseron		
9 mIU	22%	19%
45 mIU	35%	26%
Overall	p=0.105	p=0.119
Placebo vs 45 mIU	p=0.063	p=0.040
Placebo vs 9 mIU	p=0.852	p=0.176
9 mIU vs 45 mIU	p=0.090	p=0.497

Secondary Endpoints

Time to First and Second Exacerbation

Survival analysis shows that the overall difference between treatment groups was significant ($P=.03$), with Kaplan-Meier curves displaying a distinct separation between the placebo and high dose groups. Betaseron 45 mIU significantly prolonged the interval to first exacerbation as compared to the PBO and 9 mIU arms ($P=.015$ and $P=.003$, respectively). The median time to first exacerbation was 295 days for the high-dose group, 180 days for the 9 mIU group, and 153 days for the PBO group.

Additional analyses showed that high-dose Betaseron significantly prolonged the time to second exacerbation when compared to PBO. Median time from baseline to second attack was 503 days for PBO, 556 days for the low-dose arm, and greater than 762 days for the high-dose group. Results were significant ($P=.015$) and similar to that for time to first attack: as compared to PBO and low-dose arms, high dose subjects had a significantly longer interval to second attack. The difference between PBO and high-dose median times was lengthened by an additional 117 days over the differences seen for time to first attack, representing a continued delay in exacerbation occurrence.

An alternate analysis of data for the subset of subjects who already had one attack compared treatment groups for the probability of remaining free of a second attack. In this comparison, time between attacks was prolonged for the high-dose group as compared to PBO; this effect was of borderline significance ($P=.059$). Median time from the onset of the first exacerbation to onset of the second was 190 days for PBO as compared to 262 days for the 45 mIU group.

Exacerbation Severity

The severity of each exacerbation was calculated by subtracting the Scripps score for the period of disease stability preceding the exacerbation from the score while the exacerbation was ongoing. A trend toward decreased exacerbation severity with high-dose Betaseron was observed.

Analyses based on a count of the worst attack for each subject showed significant differences between groups for attack severity ($p=.038$). 30%

of high-dose subjects had moderate and/or severe attacks, as compared to 45% of the PBO group. A similar, though not significant result was seen for counts of actual exacerbation ($P=.114$). In the high-dose group, 33% of exacerbations with known severity were moderate or severe as compared with 45% in the PBO group.

Exacerbation Duration

No differences were seen between treatment groups in median duration of exacerbations. Medians were 35, 32, and 35 days for the PBO, low- and high-dose groups, respectively.

Exacerbation Rates by Time

When annual exacerbation rates were calculated for different intervals (0-6 months, 7-12 months, and 13-24 months) results were consistent with overall results: the high-dose group had consistently lower rates than the placebo group (Appendix I, Table 19). Time-related effects were not evident.

Exacerbations by Baseline Disability

Exacerbation rates were not affected by degree of disability at study entry (baseline EDSS ≤ 3.0 or > 3.0). Results for groups stratified by baseline EDSS were similar to overall results (Appendix I, Table 20).

Disability

Over the interval reported here (median time on study of 23.9 months), Betaseron therapy did not significantly affect disability, as measured by EDSS and Scripps.

EDSS and Scripps scores for the three treatment groups were compared for change from baseline at 12 months, 18 months, and at last available value. For all of these analyses, the value used was that for the period of stable disease most closely preceding the analysis timepoint. No significant differences between treatment groups were found.

Treatment groups were compared for category of change (improved, stable, or worsened; see section 2.9.2) from baseline to endpoint. This analysis was repeated for subjects stratified by baseline EDSS (≤ 3.0 or > 3.0) to detect possible treatment effects on disability associated with degree of disability at start of treatment. None of these analyses showed a significant treatment group effect.

Analysis

Treatment-by-center interaction

No treatment-by-center interaction was detected for either of the two primary outcomes (Vol 51.022, 035, 049-051). The analysis of variance performed on both the ranked and the raw exacerbation rate (frequencies in protocol) data did not indicate a significant center-by-treatment interaction effect. The analysis of exacerbation-free subjects also showed no significant center-by-treatment effect. The Cochran-Mantel-

Haenzel pairwise comparisons between treatment groups did not show a significant center by treatment interaction. (Vol 51, 049-051).

Invalidated exacerbations

There were 681 exacerbations observed during the study in 338 patients over 2 years.

Extent of verification of those 681 exacerbations is depicted in the following display.

	Extent of Verification		Verified Exacerbation
	# Patients	Total Exacerbation	
Placebo	112	266	207 (77.8%)
9 mIU	111	242	196 (81.0%)
45 mIU	115	173	142 (82.1%)

There were 266 exacerbations in the placebo arm, as compared with 173 in the 45 mIU arm. However, roughly 20% of these exacerbations for each treatment arm were unverified. The distribution of exacerbations without exam (i.e., unverified) is not significant. When the primary analyses are repeated using only verified exacerbations, the results is to reduce the number of exacerbations eligible for analysis

For 545/681 attacks, subjects were evaluated at the clinic by investigators during the event. For the remaining 136 exacerbations, subjects were not examined during the attack. In these cases, the attack was recorded at the subject's next visit after verification by the investigator through history (including telephone log), post-attack neurologic findings, and subject diary review.

In these studies, EDSS, Scripps, and FNS scores were determined by neurologic exam only and were never extrapolated from subject diaries. These 136 exacerbations without neurologic exams could not be rated for severity according to the Scripps scale or scored for EDSS or FNS. Since quantitative severity according to the Scripps scale was not possible, these attacks were considered to be of "unknown" severity and were not included in the analysis of exacerbation severity. For all 681 exacerbations, duration was determined by the investigator based on the history (including telephone contact reports), neurologic findings, and by review of subject diaries.

Severity Score

The protocols were amended to include a second severity assessment made by the investigator. When an individual attack had begun to remit, the investigator was to classify the attack as mild, moderate, or severe based on a global clinical assessment of the severity of the attack at its worst point. This assessment was subjective and not grounded to any rating

scale per se. Only 134/681 were graded for severity by the investigator, thus this data was not analyzed.

The analysis of exacerbation severity is based on 545 exacerbation for which Scripps scores derived from neurological examinations performed during the exacerbation are available. These analyses are based on quantitative change in Scripps score obtained by neurologic exam while the exacerbation was ongoing.

4.0 Safety-Precis

4.1 Deaths

There were no deaths on study or within 30 days of the last dose of placebo or betaseron.

4.2 Discontinuations

Dropout rate is comparable across groups (65 [19%] Total: 23, 18, 24 PBO-9-45 mIU, respectively).

4.2 Adverse Events

Significantly associated with Betaseron treatment were injection site events (inflammation, pain, hypersensitivity, reaction) and systemic flu-like events consisting of fever, chills, malaise, myalgia complex and neutropenia.

4.3 Dose Reductions

13/338 (4%) experienced a dose-limiting event. 10/13 completed the study without further incident; the other three were withdrawn, 2 for recurring toxicity despite dose reduction and one by subject and investigator decision following a dose reduction.

5.0 Issues for Discussion

There are several issues impacting on the study results, as discussed below:

5.1 Population

The patient population recruited for the study represents the earlier stage of disease and relatively minor disability, with baseline disease duration mean 3.9-4.4 years, baseline EDSS 2.9, and history of at least one exacerbation per year in the year preceding study entry. It appears to be a representative population of early-diagnosed MS patients.

5.2 Potential Unblinding

Patients were permitted to take acetaminophen, NSAIDs, aspirin to mask potentially unblinding side effects of Betaseron. These include fever, chills, fatigue, malaise, anorexia. Acetaminophen was used by all groups. There was no differential use of these symptomatic treatments.

The systemic events significantly associated with effective Betaseron dose were the flu-like symptoms expected with interferon therapy: fever, chills, malaise, myalgia, and sweating. Although these events occurred more frequently in the 45 mIU Betaseron during the first 6 months of

treatment, after 6 to 7 months, frequency was evenly distributed across all three treatment groups.

Some types of injection site reaction (inflammation, pain, reaction, and hypersensitivity) were also significantly more frequent in subjects injecting active drug and correlated specifically with injection of the effective dose. However, injection site events also occurred in a sizable proportion (33%) of those injecting placebo.

The review committee in its analysis identified 9 subjects with potentially unblinding events, without further elaboration. These were not excluded from the primary intent-to-treat dataset.

Comment

Certainly the conditions are present for unblinding in this trial, considering the systemic and injection site reactions. At best, it is not systematic bias but equally distributed across treatment groups.

5.3 Selection of Endpoint

The identified primary outcome criteria, reduction in frequency of exacerbations and proportion of exacerbation-free subjects, are clinical criteria which we would accept as valid outcome measures in this trial.

If there is any question regarding the definition of endpoints, specifically frequency of exacerbation, then it would appear that the other primary outcome "proportion of exacerbation-free patients" is less ambiguous (U.S. $P=.08$; Canada $P=.05$).

We do not prefer the technique of "annualized" exacerbation rate, but the simple comparison of the frequency of exacerbation is still positive.

We consider that the firm performed two interim analyses. With the statistical penalty, the pooled results are still significant ($P=.048$, $P=.045$).

5.4 Treatment by Center Effect

No center by treatment interaction was noted for either of the two primary outcomes . Dr. Tiwari performed some additional analyses comparing different groupings of the centers according to percentage of unverified exacerbations and found no difference between the combinations; all fall within 5% of each other.

5.5 Inspection of Study

Inspection by Bioresearch Monitoring detected numerous protocol violations, both major and minor, occurring at all sites. Major protocol violations include lack of immediate reporting of MS symptoms by study subjects, failure of physician to validate exacerbations within 72h.

Other findings include less than weekly follow up of exacerbation cases by the Clinical Investigators, failure to assess on-study MS symptoms within the time frame specified by the protocols.

5.6 Unverified Exacerbations

Approximately 20% of the exacerbations were not verified by the investigators as called for in the protocol and were distributed equally across the three treatment arms. In discussions with the firm, the following definitions and procedures were elaborated:

An undocumented exacerbation is one in which the patient was not examined by the investigator during the exacerbation, i.e., a neurologic exam was not performed. Although CRFs pertaining to the neurologic examination were not completed, information on each of the undocumented exacerbations was noted on Exacerbation CRFs and captured in the database.

After excluding 20% of the exacerbations for which no intraexacerbation neurological examination was done, a highly significant difference between treatment groups remain: PBO v. 45 mIU group ($p=.001$) for 2 year data.

By amendment dated January 21, 1993, the firm provided a detailed characterization of the 136 unverified exacerbations (below).

Reason for Missing Scripps Score	#Exacerbations
Patient did not call or visit the clinic until after the exacerbation was over	77
Patient visited site during the exacerbation but Scripps Score is not available	3
Patient visited the clinic and had a Scripps Score the same day the exacerbation resolved (Of these, 6 called in earlier to report the exacerbation.)	13*
Patient called in to report the exacerbation but did not visit the clinic until after the resolution of the exacerbation	42
Resolution date unknown	<u>1</u>
TOTAL	136

*Since the Scripps scores were obtained the same day the exacerbation ended, it was assumed that the neurological exam was performed after the exacerbation was over. This was a conservative approach in that it resulted in these exacerbation not being classified as to severity.

For approximately 12% of all 681 exacerbations, the patient never informed the center of the event while it was ongoing; instead they chose to describe the exacerbation event at their next routine clinic visit.

The following questions and answers were developed during the review:

How did the investigator complete the required information on the CRF for an exacerbation, if he did not examine the patient during the attack?

Answer: If a patient was not seen during an exacerbation, investigators relied on a variety of sources to assist them with their evaluation:

Sources of information

- a) Patient history
- b) Family interview
- c) Medical records
- d) Phone contact, if available
- e) Patient diary
- f) Neurologic examination

After synthesizing this information, the investigator completed the Exacerbation CRF.

How was the start date established for all attacks verified or unverified? Was it based on the clinic visit date?

Answer: Unless a patient is under continuous medical observation, the exacerbation start date is always based on the physician's assessment of historical information provided by the patient. This data was recorded on the exacerbation and was not necessarily the date the patient first contacted the site nor was it the visit date following the onset of the exacerbation.

Three study centers had higher percentages of unverified exacerbations: University of British Columbia in Vancouver, University Hospital in London, Ontario, and UCSF in San Francisco. It may be hypothesized that the inconvenience of travel to a tertiary referral center explains the higher numbers of undocumented exacerbations at these sites.

	# Unverified Exac	%
Temple	4	15
Thomas Jefferson	0	0
UCSF	13	43
U Alabama	5	41
U Arizona	5	14
U Chicago	6	12
U Maryland	7	25
(CANADA)		
Hosp de Notre Dame	11	32
Montreal Neurologic	2	9
U British Columbia	16	50
U Hospital	20	40

The percentage of undocumented exacerbations ranged from 0 to 50% by center. Therefore it is important to examine the centers individually for results. No center by treatment interaction was noted for either of the two primary outcomes).

Additional Independent Analyses

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In his review, Dr. Tiwari has performed several additional analyses to further examine the database with respect to verified vs. unverified exacerbations and early dropouts. His results are tabulated here; for more detailed discussion, please refer to his review.

EFFICACY VARIABLE	RESULTS OF STATISTICAL ANALYSIS	
	ALL EXACERBATIONS	VERIFIED EXACERBATION
PROPORTION OF EXACERBATION-FREE	FISHER'S EXACT (P=.008)	FISHER'S EXACT (P=.114)
EXACERBATION-FREE EXCLUDING < 6 MONTHS	FISHER'S EXACT (P=.075)	
FREQUENCY OF EXACERBATION PER SUBJECT	WILCOXON RANK SUM (P=.0004)	WILCOXON RANK SUM (P=0.012)
TIME TO FIRST EXACERBATION	(P=.030)	NS

For the primary endpoint proportion of exacerbation-free subjects, when all exacerbations are included, the comparison of PBO v. 45 mIU remains significant at P=.008, while when only verified exacerbations are examined, the proportion of exacerbation-free subjects for the PBO v. 45 mIU comparison is no longer significant (P=.114). In a worst case scenario, excluding those subjects with less than six month data due to premature discontinuation due to adverse event, the difference between the 45 mIU and the PBO arm still favors Betaseron but the P-value is of borderline significance, P=.075.

For the primary endpoint frequency of exacerbation, the outcome in the 45 mIU group is significantly better than the 9 mIU or PBO. The difference between 45 mIU and PBO group is also significant regarding only verified exacerbations.

Regarding time to first exacerbation, when all exacerbations are considered, time to first exacerbation is significantly increased in the 45 mIU group (median time of 153 days in PBO vs 370 days in the 45 mIU group, p=.03). Considering only verified exacerbations, due to loss of power, there was a loss of significance in the pairwise comparison, although the trend is still there.

The primary analyses based on exacerbation data were repeated using only those exacerbations verified by the investigator during subject visits to

the clinic. The result of using only verified exacerbations was to reduce the number of exacerbations eligible for analysis in the following manner displayed by the sponsor:

6.0 Statistical Results

When one examines the effect of excluding the unverified exacerbations, there is a shift in score from the higher number of exacerbations to the lower, especially toward 0 (none).

For the overall frequency of exacerbation, there is a slight advantage when examining exacerbations 1 through 5, although this could be artifact due to the tail. Most of the power is contributed by the fourth or fifth exacerbation. A trend is there, but not significance. 2/3 subjects had only 1 or 2 total exacerbation, yet there is no difference overall.

Therefore, we considered that the outcome of proportion of exacerbation-free subjects to be the least ambiguous of all the primary outcomes. When one looks at the outcome of proportion of exacerbation free subjects vs all other outcomes, then the results are significant. Thirty-one (31%) of subjects receiving 45 mIU continue to be exacerbation-free at 2 years (placebo 16%).

Dr. Tiwari suggests that the data is binary, such that Betaseron only prevents exacerbations (84% in PBO vs 69% in 45 mIU); a modest difference of 15%). If exacerbation does start, then the frequency of occurrence in the treatment group is no different from that in the placebo group.

At the completion of the study, 65(19%) subjects had withdrawn from the study early: 23, 18, and 24, respectively of the placebo, 9 and 45 mIU arms. Median subject exposure to study drug was 23.9 months. Time on study was comparable for all three treatment groups.

6.0 MRI data

MRI data was collected. It will be reviewed separately by an expert in the field.

According to the sponsor's analysis, the assessment of disease burden (volume of abnormality in the brain) as measured by serial MRI shows a significant difference in the degree of disease progression in the 45 million IU group as compared to the other two groups both at 12 months ($p=0.005$) and at endpoint (24 months for over 80% of subjects, $p=.0002$). At both of these time points, treatment with 45 million IU Betaseron had halted the progression of disease burden, while continued progression was seen in both other groups. The positive effect in the 45 million IU group was also reflected by a significantly smaller percent change in lesion area and a smaller increase in the number of regions of interest. In all groups, disease burden by MRI, evaluated at endpoint, had a positive correlation with disability as measured by EDSS. This suggests that lower disease burden by MRI correlates with less severe disability as measured by EDSS.

7.0 NAB Activity

The development of neutralizing antibody (NAB) did not appear to influence response to therapy. To analyze the relationship of NAB activity and treatment response, subjects on active drug were divided, by treatment group, into those with and without NAB activity. Further analysis of those subjects who were NAB+ compared exacerbation rates for the periods before and after development of NAB activity. Neither analysis showed a significant effect of NAB on treatment response.

7.0 Summary and Conclusions

The results of this multicenter trial of Betaseron in the treatment of MS provide evidence of borderline clinical significance but great statistical consistency on the primary identified outcome of frequency of exacerbations and proportion of exacerbation-free subjects. Several of the secondary endpoints (time to first exacerbation, exacerbation duration) were also significant. Although they were not identified as secondary outcome measures, frequency of steroid use and frequency of MS-exacerbation related hospitalizations is of interest as each shows a dose-response outcome in favor of active treatment. Eleven centers enrolling 338 patients individually contribute to the overall results with trends in the same direction.

The size of effect is small. Evidence of this is provided by the findings of no concomitant change in EDSS over the two year course and two-tailed distribution of exacerbation frequency, that is, subjects with 0 exacerbations and with 4 or 5 exacerbations carry the statistical results.

The primary analyses based on exacerbation data were repeated using only those exacerbations verified by the investigator during subject visits to the clinic. Generally, the exclusion of those 20% invalidated exacerbations had little impact on the planned analyses.

There has been much discussion regarding how to treat the number of unverified exacerbations in the study. Although at first the invalidated exacerbations threatened the results of the study, at this point this reviewer feels that statistical and clinical maneuvers to look at this issue are reassuring. In fact, when one examines in detail the undocumented exacerbations, most of them may be attributed to poor patient compliance with the protocol rather than through fault of the investigator. That is, a majority of these patients (77/136) did not call or initiate a visit until after the exacerbation was over. Patient diaries are difficult to maintain in clinical trials, which makes it all the more difficult to show an effect in a randomized trial. Essentially, one may call the data both historical (those "invalidated" assigned by the investigator based on a retrospective view of the evidence) and that directly observed.

Toxicity appears to be low. There were no deaths in this two year study. The withdrawal rate was 19% (65 subjects), such that 81% of patients completed the two years of study. There was no differential dropout rate. No subgroup on this study developed rapidly progressive disease while on Betaseron. Most adverse events reported in the pivotal study were evenly

distributed across blinded groups, and thus were associated with MS itself. Hospitalization for MS-exacerbation related events showed a distribution supportive of increased drug benefit, rather than increased risk. The number of subjects whose disease worsened by an EDSS of 2 or more was less in the 45 mIU group than in the placebo group (8 vs 17) and the proportion having more than four exacerbations was substantially less in those treated at effective dose than in those on placebo (13% vs 27%).

This reviewer is impressed by the degree of consistency in the data. The safety profile that emerged in this study indicates that the majority of subjects can receive this therapy every other day for an extended period with very few subjects experiencing serious adverse events.

8.0 Recommendation

PLA for Recombinant Human Interferon Beta (Betaseron) is approvable for treatment of relapsing remitting Multiple Sclerosis.


Janeth Rouzer-Kammeyer, M.D.

cc:Orig PLA
ccHFD-120/RKatz/JRouzer-Kammeyer
4-30-93
dt:10/30/92/gt/4/5/93/gt
F:\Betaseron

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