DEPARTMENT OF HEALTH & HUMAN SERVICES

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Memorandum

Division of Clinical Trial Design and Analysis
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From: Cynthia A. Rask, M.D.

Subject: STN 103628/5021

Through: Marc K. Walton, M.D., Ph.D

To: Melanie Hartsough, Ph.D., sBLA review committee chair
BLA STN 103628/5021 study file

I have reviewed the clinical study report for Biogen's study C980844.

Assessment and Conclusions:
The overall safety profile for the liquid HSA-free Avonex® formulation administered in Biogen Study C94-844 is not substantially or meaningfully different from that reported with the use of the commercially available lyophilized Avonex® used in previous clinical studies and in clinical practice. This conclusion is based on the current package insert for Avonex® along with pre- and post-marketing safety reports, taking into account the different patient populations in which the two formulations have been used, the varying durations of exposure to the drug, and the frequency of ascertainment of adverse reactions and serum neutralizing antibodies.

Attached is my review.

Interim Study Report on C98-844

Study Overview

This ongoing study is a multi-center, single-arm, open-label study to determine the, pharmacokinetics, pharmacodynamics, safety and antigenicity of liquid HSA-free Avonex® administered intramuscularly (IM) to subjects with relapsing multiple sclerosis (MS). Subjects received liquid HSA-free Avonex® at 30 µg administered as one IM injection once per week (QW). The duration of subject participation was to be 24 months, where each month was defined as 4 weeks.

Approximately 150 subjects were to be enrolled into the study. Subjects were allowed to self-inject study drug or choose another person to administer the injections.
For the first 24 weeks of study-drug dosing, all subjects were instructed to take acetaminophen (paracetamol), ibuprofen, or naproxen for the prophylaxis of flu-like symptoms. Subjects were allowed to take aspirin only if the above medications were not tolerated. They were allowed additional doses of acetaminophen (paracetamol), ibuprofen, naproxen, or aspirin within any 24-hour period as necessary for relief of interferon-related flu-like symptoms.

Safety parameters assessed for this report included adverse events, physical examinations (including vital signs), assessment of injection site, pregnancy tests, and clinical (chemistry and hematology) laboratory tests.

The presence of binding antibodies to human interferon beta-1a was determined by enzyme linked immunosorbent assay (ELISA), and the presence and titer of neutralizing antibodies was determined by an antiviral cytopathic effect (CPE) assay (Rudick *et al*, 1998).

Subjects were assessed at screening, baseline, and Months 3, 6, 9, 12, 15, 18, 21, and 24. Subjects were considered to have completed the study if they completed 24 months (96 weeks) of treatment.

The interim clinical study report contained in this submission presents the results of an analysis performed on 153 subjects enrolled in this study from data collected through 27 February 2002. At the time of this report 124 subjects were actively participating in the study.

Rationale for Study Design

The Applicant stated that they believed that a multi-center, single arm, open-label study in which all subjects received liquid HSA-free Avonex® was an appropriate study design because the they consider the safety and antigenicity of the currently approved lyophilized product to be well established. Thus, the Applicant thought a control arm of lyophilized Avonex® or placebo was not necessary for this study. Results obtained from C98-844 were to be compared back to historical data regarding adverse reactions and rates of development of neutralizing antibodies.

Safety Assessments Performed

The following clinical safety assessments were performed:

- a complete physical examination at screening and at study completion, or within 2 weeks from premature discontinuation,
- measurement of vital signs at screening, Day 1 (baseline), and at Months 3, 6, 9, 12, 15, 18, 21, and 24, and
- clinician (physician, physician assistant, or nurse) assessment of the injection site at Day 1 (baseline), and at Months 3, 6, 9, 12, 15, 18, 21, and 24.

The following laboratory safety assessments were performed:

- hematology: complete blood count (CBC) with differential and platelet count, as well PT and aPTT at screening, Day 1 (baseline), and at Months 3, 6, 12, 18, and 24;
- blood chemistry: sodium, potassium, chloride, carbon dioxide, blood urea nitrogen (BUN), creatinine, uric acid, calcium, phosphorus, albumin, total protein, alkaline phosphatase, total bilirubin, ALT, AST, lactic dehydrogenase (LDH), and glucose at screening, Day 1 (baseline), and at Months 3, 6, 12, 18, and 24; and
- serum pregnancy test for female subjects who were not postmenopausal or surgically sterile at screening, and at Months 3, 6, 9, 12, 15, 18, 21, and 24.

The following product-specific safety assessments were performed:

- antibody testing. Serum was tested for the presence of binding antibodies to interferon beta-1a using an ELISA, and for the presence and titer of neutralizing antibodies to interferon beta-1a using an antiviral CPE assay at baseline, and at Months 3, 6, 9, 12, 15, 18, 21, and 24.

Assessment of Antigenicity

The assessment of antigenicity was conducted in a two-step assay, as follows: An ELISA assay was performed to screen for the presence of binding antibodies. If the ELISA results were negative (i.e., <20), no further tests were performed. If the ELISA results were positive, the antiviral CPE assay was performed to screen for the presence of neutralizing antibodies (NAB). The neutralizing titer value was calculated automatically, as a part of the antigenicity bioassay, only if the antiviral CPE assay showed positive sample results.

For analysis purposes, for negative ELISA results, neutralizing antibodies were assumed not present, and the neutralizing titer value was set to zero. Also, for antiviral CPE assays indicating that the sample was negative for neutralizing antibodies, the neutralizing titer value was set to zero. For cases with no titer values, the following specifications were utilized to determine titer values.

- If titer is not missing, then the calculated titer = titer value.
- If the titer is missing and the titer screen is negative then the calculated titer = 0.
- If the titer is missing and the titer screening is missing and ELISA is negative then the calculated titer = 0.
- For all other conditions, the calculated titer is missing.

Determination of Antibody Presence
An antibody positive subject was defined as a subject with a neutralizing titer value greater than or equal to a specified threshold value at any scheduled visit. Scheduled visits were at baseline, Month 3, 6, 9, 12, 15, 18, 21, and 24. The pre-specified neutralizing titer threshold values were 0, 5, and 20.

Changes in the Conduct of Study That May Affect Amount of Drug Delivered
At the start of the trial, liquid HSA-free AVONEX® was supplied to study subjects in a tray containing a pre-filled syringe and a separate 23 Gauge x 1¼ " ——— needle. This presentation required subjects to ——————————— prior to injection. In September 2000, the study medication delivery system was changed to a pre-filled syringe with a 23 Gauge x 1¼" ——— needle, which eliminated the need to ——————————————————However, in April 2001, the study reverted back to the use of the ——— needle and syringe based on study subjects' preference for this method of drug delivery.

Study Results

Subject Accountability
One hundred fifty-three (153) subjects were enrolled in this study at 16 investigational sites in North America and Europe. Six investigators in the United States enrolled 67 subjects, six investigators in Canada enrolled 44 subjects, and four investigators in Europe enrolled 42 subjects. Twelve investigators each had enrolled at least five subjects; collectively, the subjects of these twelve investigators accounted for 94% of the total subject enrollment.

Four sites each enrolled fewer than five subjects.

The first subject received their first dose on January 31, 2000, and the last subject included in this interim report received their first dose on June 26, 2000. Among the 153 subjects enrolled in the study, 124 remained in the trial and 29 (19%) had withdrawn from the study at the time of this report.

Twelve (8%) subjects withdrew from the study due to adverse events, 6 (4%) withdrew due to worsening of disease, 4 (3%) withdrew due to lack of tolerability to study drug (presumed also to represent adverse events), 3 (2%) withdrew due to subject request/voluntary withdrawal, 3 (2%) withdrew due to other reasons (two were pregnancies), and 1 (1%) was lost to follow up.

Duration of Exposure
A total of 134 subjects (88% of those dosed) had received study drug for at least 48 weeks. One hundred and forty-two subjects (93%) had received study drug for at least 26 weeks and 91 subjects (59%) had received study drug for at least 78 weeks. (Note that the duration of the study is 96 weeks, and that no data are provided for this duration of exposure.)

Antigenicity Results

At the time of this interim report, 134 Avonex®-treated subjects had at least one sample drawn for binding antibody testing. At Month 12, 13.6% of subjects had binding antibodies to interferon beta and at Month 21, 23.1% of subjects had binding antibodies to interferon beta. At the time of this interim report, 150 Avonex®-treated subjects had at least one sample drawn for neutralizing antibody testing. Of these 150 subjects, 8 (5.3%) had titers >0 for anti-interferon beta serum neutralizing activity at some time during the course of the study. Of these 8 subjects, 5 subjects (3.3%) had titers that were ≥20 (and therefore, also ≥5). Three subjects had titers between 5 and 20. The percentage of subjects testing positive for neutralizing antibodies did not change substantially after Month 15 through Month 21, consistent with perhaps having reached a plateau in the incidence of neutralizing antibodies. However, the numbers of subjects tested at Months 18 and 21 were much smaller than the numbers tested prior to that time, and the incidence of binding antibodies continued to increase at Month 21 as compared to Month 12. Antibody results beyond Month 21 are not contained in this report. The results of the assays for neutralizing antibodies are summarized below in Table.1.

Table 1: Incidence of Neutralizing Antibodies

	Number of Subjects Tested (a)	Titer > 0	Titer >= 5	Titer >= 20
Baseline	150	0 (0.0)	0 (0.0)	0 (0.0)
Month 3	137	0 (0.0)	0 (0.0)	0 (0.0)
Month 6	129	0 (0.0)	0 (0.0)	0 (0.0)
Month 9	124	1 (0.8)	0 (0.0)	0 (0.0)
Month 12	127	2 (1.6)	2 (1.6)	1 (0.8)
Month 15	121	4 (3.3)	3 (2.5)	3 (2.5)
Month 18	115	5 (4.3)	4 (3.5)	3 (2.6)
Month 21	79	3 (3.8)	3 (3.8)	2 (2.5)
Maximum through Month 6 (b)	150	0 (0.0)	0 (0.0)	0 (0.0)
Maximum through Month 12 (b)	150	3 (2.0)	2 (1.3)	1 (0.7)
Maximum through Month 15 (b)	150	5 (3.3)	3 (2.0)	3 (2.0)
Maximum through Month 18 (b)	150	8 (5.3)	5 (3.3)	5 (3.3)
Maximum through Month 21 (b)	150	8 (5.3)	5 (3.3)	5 (3.3)

NOTE: Numbers in parentheses are percentages. Percentages are base on the total number of subjects tested.

(a) Includes subjects who tested negative at baseline and had data at any post-baseline visits.

(b) Subjects who tested negative at baseline and had at least one positive post-baseline visit are included.

Assessment of Antigenicity Results

In C98-844, the incidence of binding (vs. neutralizing, which are shown above) antibodies to liquid HSA-free Avonex® was 13.6% at Month 12 and 23.1% at Month 21. In study C94-801, in which patients received lyophilized Avonex®, the incidence of binding antibodies in patients with no prior exposure to interferon beta was 17% at Month 12 and 28% at Month 21 All these results are not substantially different, despite the fact that they were studied in different groups of patients.

Similarly, in C98-844, the incidence of neutralizing antibodies measured in patients treated with liquid HSA-free Avonex® administered with pre-filled syringes is not substantially different from the incidences reported following treatment with lyophilized Avonex® in clinical studies. At the time of this interim study report for C98-844, 3.3% of subjects had neutralizing antibody titers ≥20 at some time during the course of the study using liquid HAS-free Avonex® pre-filled syringes.

Study C95-812 was a double-blind, randomized study to determine if the currently approved lyophilized Avonex® was beneficial in delaying the diagnosis of clinically definite MS in subjects who experienced a first and recent onset of a demyelinating and who were at high risk of developing MS based on the presence of multiple brain MRI abnormalities (Jacobs 2000). Subjects received 30 mcg of AVONEX® IM once weekly for up to 36 months. No subjects were reported to test positive for neutralizing antibodies at baseline. In this study, the incidence of subjects developing NAB titers ≥5 was reported to be 3.4%; with titers ≥20 the incidence was reported to be 1.7%. Again, one can conclude from these reports that the incidence of the occurrence of neutralizing antibodies after receiving liquid HSA-free Avonex® and the commercially available lyophilized product are not substantially different, taking into account the differences in the patient populations studied, the numbers of patients tested in each study, the varying durations of exposure, and the numbers of samples analyzed.

A theoretical concern with neutralizing antibody formation is allergic reactions and injection site reactions. The incidence of adverse events in relationship to antibody status is presented in Table 2. Overall, the incidence of adverse events in neutralizing antibody-positive subjects is not different compared to neutralizing antibody-negative subjects.

Adverse Events Considered Likely Related to Administration of Avonex®

Table 2 displays the adverse events occurring in ≥2% of subjects considered likely or definitely related to study drug. Ninety three percent (93%) of subjects experienced an adverse event considered by the investigator to be likely or definitely related to study drug.

The adverse event considered likely or definitely related to study drug with the highest incidence was flu syndrome (86%). Additional adverse events considered likely or definitely related to study drug that occurred at an incidence of 5% or more were headache (27%), myalgia (10%), injection site pain (7%), chills (6%), asthenia (5%), fever (5%), arthralgia (5%), myasthenia (5%), hypertonia (5%), nausea (5%), and ecchymosis injection site (5%).

Table 2: Adverse Events Considered Related to Administration of Avonex®

Preferred Term	Total
Number of Subjects with a Likely or Definitely Related Event:	142 (93)
FLU SYNDROME	132 (86)
HEADACHE	41 (27)
MYALGIA	15 (10)
INJECTION SITE PAIN	11 (7)
CHILLS	9 (6)
ASTHENIA	8 (5)
FEVER	8 (5)
ARTHRALGIA	7 (5)
MYASTHENIA	7 (5)
HYPERTONIA	7 (5)
NAUSEA	7 (5)
ECCHYMOSIS INJECTION SITE	7 (5)
INJECTION SITE INFLAMMATION	6 (4)
VOMITING	5 (3)
DEPRESSION	4 (3)
INSOMNIA	4 (3)
PARESTHESIA	4 (3)
INJECTION SITE REACTION	3 (2)
PAIN	3 (2)
HYPERSTHESIA	3 (2)
DIARRHEA	3 (2)
ALOPECIA	3 (2)
RASH	3 (2)

NOTE 1: Subjects are only counted once within each event and body system. Events with missing relationships are set as 'Definitely Related'.
2: Numbers in parentheses are percentages. Percentages are based on the total number of subjects dosed.

Twenty-two percent (22%) of subjects experienced an adverse event related to the site of injection. Injection site pain was the most frequently experienced adverse event classified as an injection site reaction, occurring in 11% of subjects. Ecchymosis at the site of injection and inflammation at the site of injection occurred with an incidence of 9% and 4%, respectively.

There was one serious adverse event (in patient 105015) in which "myositis" occurred at the injection site. This patient was a 53-year-old female with poorly controlled diabetes mellitus at study entry (serum glucose was 727 mg/dL at screening and 348 mg/dL at baseline). She developed a warm tender area at the injection site in the left thigh, approximately one month after starting study drug. This area became swollen and was initially diagnosed as a cellulitis. The patient underwent incisional drainage and biopsy of the left thigh. The biopsy report showed an acute necrotizing myositis suggestive of an infectious process and occasional gram positive organisms were seen on the tissue section. The patient was treated with antibiotics and received physical therapy. She was hospitalized for approximately 10 days, and then was transferred to an extended care facility for approximately 2 months. She remained in the extended care facility primarily due to fluctuations in serum glucose levels that were initially noted upon entrance to the study. The event resolved without sequelae at the time of the final follow-up approximately 5 months after the start of the event. The investigator stated that the relationship between this event and study drug was "none". In addition, the investigator stated that the event was due to the patient's injection technique and poorly controlled diabetes mellitus. However, Biogen stated that the relationship between this event and study drug was "likely related" since this was a more conservative interpretation of causality. Therefore, this serious adverse event was reported as an IND safety report.

Table 3: Injection Site Reactions

Body System/ Preferred Term	Total
Total Number of Subjects Dosed	153
Number of Subjects with an Injection Site Event:	33 (22)
BODY AS A WHOLE	26 (17)
INJECTION SITE PAIN	17 (11)
INJECTION SITE INFLAMMATION	6 (4)
INJECTION SITE REACTION	4 (3)
INJECTION SITE FIBROSIS	2 (1)
INJECTION SITE ATROPHY	1 (1)
INJECTION SITE EDEMA	1 (1)
INJECTION SITE HEMORRHAGE	1 (1)
INJECTION SITE HYPERSENSITIVITY	1 (1)
HEMIC & LYMPHATIC	14 (9)
ECCHYMOSIS INJECTION SITE	14 (9)

NOTE 1: Subjects are only counted once within each event and body system.
2: Numbers in parentheses are percentages. Percentages are based on the total number of subjects dosed.

Of the 6 adverse events in which the incidence was 15% or greater, 4 (flu syndrome: 132 patients [86%]; headache: 64 [42%]; myalgia 29 [19%]; and asthenia 32 [21%]) are attributable to the flu-like syndrome associated with interferon therapy, as already identified and described in the current label. Paresthesia occurred in 31 (20%) patients and is also described in the current version of the label. "MS exacerbation" was seen in 41 (27%) patients. Exacerbations are inherent to relapsing MS, though they are not described as adverse reactions in the current package insert.

Depression, which is known to be associated with MS and potentially with interferon therapy (Vial 1994) was observed in 19 patients (12%). There were no reported suicides, suicide attempts, or suicidal tendency in this study. The incidence of depression in this study is similar to that observed in the lyophilized Avonex®-treated group in the pivotal Phase 3 (NS 26321) study (15%) but lower than that seen in the clinically isolated symptom (C95-812) study (20%). This may be due to the shorter duration of treatment in the C98-844 study (up to 2 years) compared to the C95-812 study (up to 3 years).

There were no unexpected laboratory abnormalities in this trial. Mild shifts outside of the normal range occurred with an incidence similar to that seen in previous clinical trials with lyophilized Avonex®.

The overall safety profile observed in C98-844 studying administration of liquid HAS-free Avonex® administered via pre-filled syringes is similar to that observed with the use of the commercially available lyophilized Avonex® used in previous clinical studies and marketed in the U.S. since 1996.

Assessment and Conclusions:
The overall safety profile for the liquid HSA-free Avonex® formulation administered in Biogen Study C94-844 is not substantially or meaningfully different from that reported with the use of the commercially available lyophilized Avonex® used in previous clinical studies and in clinical practice. This conclusion is based on the current package insert for Avonex® along with pre- and post-marketing safety reports, taking into account the different patient populations in which the two formulations have been used, the varying durations of exposure to the drug, and the frequency of ascertainment of adverse reactions and serum neutralizing antibodies.