AFFIDAVIT

State of Maryland, Montgomery County

I, Marlene S. Bobka, under oath, hereby depose and state as follows:

1. I am the president of F.O.I., Inc. d/b/a FOI Services, Inc. ("FOI Services").

2. FOI Services is a privately-held corporation organized and operating under the laws of the State of Maryland, with its principal place of business at 704 Quince Orchard Road, Suite 275, Gaithersburg, Maryland 20878-1770, U.S.A.

3. FOI Services specializes in United States Food & Drug Administration ("FDA") information and maintains a private library of over 150,000 FDA documents obtained under the Freedom of Information Act ("FOIA") in all categories of products regulated by FDA, including drugs, biologics, veterinary products, foods and medical devices. These documents are sold individually; the copies we maintain and sell are faithful reproductions of the original documents supplied to us by FDA and, except for cover sheets, are not altered in any way. Many U.S. courts have accepted our documents as true copies of official FDA documents.

4. The document attached, FOI Document Number 146008, titled "Peripheral and Central Nervous System Drug Advisory Committee Meeting 9/19/1996" was in the possession of FOI Services, and therefore publicly available from FDA, and was provided by FOI Services to a third party at least as early as December 14, 2001.

5. The record was kept in the course of our regularly conducted business activity.

6. Making the record was a regular practice of our business activities.

THE FOREGOING IS TRUE

Marlene S. Bobka

Jan 6, 2015
Date

SUBSCRIBED AND SWORN before me this 6, day of [Month], [Year]

Notary Public

My commission expires: 7/21/2017

EXHIBIT A

Agenda

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE
Meeting #44

Food and Drug Administration
Center for Drug Evaluation and Research
Gaithersburg, Maryland

OPEN SESSION
Thursday, September 19, 1996
Gaithersburg Holiday Inn
8:30 a.m. to Conclusion

I.	8:30 a.m.	Call to Order: Welcome and Information	Sid Gilman, M.D. Chairperson
		Conflict of Interest Statement	Ermona McGoodwin Executive Secretary
II.	To Follow:	Open Session	
	NDA 20-622	COPAXONE® (Copolymer-1 for Injection): Safety and Effectiveness in use for Relapsing-Remitting Multiple Sclerosis	
IIa.	FDA Introductory Remarks:		Paul Leber, M.D. Division Director, DNDP
			Russell Katz, M.D. Deputy Division Director, DNDP
IIb.	Sponsor Presentations TEVA Pharmaceuticals, USA		
		Introduction:	Carole S. Ben-Maimon, M.D. Senior Vice President TEVA Pharmaceuticals, USA
		Multiple Sclerosis:	Kenneth P. Johnson, M.D. Professor and Chair Department of Neurology University of Maryland School of Medicine
		Safety and Efficacy:	Carole S. Ben-Maimon, M.D.

IIb. Sponsor Presentations: (continued)

Medical Perspective: Jerry Wolinsky, M.D.
Professor of Neurology, Director
Multiple Sclerosis Research Group
University of Texas
Health Sciences Center

IIc. FDA Response: FDA Staff

III. Committee Discussion

IV. OPEN PUBLIC HEARING

V. Committee Recommendation(s)

VI. Closing Remarks-Information and Followup

NOTE:
There will be a BREAK and/or LUNCH BREAK at the discretion of the Chair.

File Copy

FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM
DRUGS ADVISORY COMMITTEE
Meeting #44
September 19, 1996
COPAXONE®

TAB A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date September 3, 1996

From Ermona McGoodwin
Executive Secretary (HFD-21)

Subject **COMMITTEE MAILING:** COPAXONE® (Copolymer-1, TEVA Pharmaceuticals USA) NDA 20-622

To Peripheral & Central Nervous System Drugs Advisory Committee Members

The enclosed information is provided for your review for the September 19 meeting of the PCNS Advisory Committee. The meeting will be held at the Gaithersburg Holiday Inn (see attached directions).

TAB A: Cover Memo and Directions.
TAB B: Draft Agenda and Questions, Committee Roster.
TAB C: FDA Overview of NDA 20-622, Copolymer-1 Injection for Patients with Exacerbating-Remitting Multiple Sclerosis - Russ Katz, M.D.
TAB D: Efficacy Review - Janeth Rouzer-Kammeyer, M.D.
TAB E: Safety Review - John Balian, M.D.
TAB F: Statistical Review - David Hoberman, Ph.D.

I look forward to seeing you on Thursday, September 19. If you have any questions please call me.

Ermona McGoodwin

Ermona McGoodwin
Executive Secretary

Phone: 301-443-5455
FAX: 301-443-0699
e-mail: mcgoodwin@cder.fda.gov

)irections to: **Gaithersburg Holiday Inn**
2 Montgomery Village Avenue
Gaithersburg, MD 20879

Phone: 301-948-8900
FAX: 301-258-1940

From D.C./Maryland/Virginia

Take Interstate 270 North to Exit 11 - Montgomery Village Exit.
Go short distance to intersection of Route 355 (Frederick Ave),
Holiday Inn is cater-corner on the left.

TAB B

DRAFT DRAFT

Agenda

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE
Meeting #44

Food and Drug Administration
Center for Drug Evaluation and Research
Gaithersburg, Maryland

OPEN SESSION
Thursday, September 19, 1996
Gaithersburg Holiday Inn
8:30 a.m. to Conclusion

I.	8:30 a.m.	Call to Order: Welcome and Information	Sid Gilman, M.D. Chairperson
		Conflict of Interest Statement	Ermona McGoodwin Executive Secretary
I.	To Follow:	Open Session	
	NDA 20-627	COPAXONE® (Copolymer-1 for Injection): Safety and Effectiveness in use for Relapsing-Remitting Multiple Sclerosis	
IIa.	FDA Introductory Remarks:		To be Announced
IIb.	Sponsor Presentations: TEVA Pharmaceuticals, USA		
		Introduction:	Carole S. Ben-Maimon, M.D. Senior Vice President TEVA Pharmaceuticals, USA
		Multiple Sclerosis:	Kenneth P. Johnson, M.D. Professor and Chair Department of Neurology University of Maryland School of Medicine
		Safety and Efficacy:	Carole S. Ben-Maimon, M.D.
		Medical Perspective:	Jerry Wolinsky, M.D. Professor of Neurology, Director Multiple Sclerosis Research Group University of Texas Health Sciences Center

IIC. FDA Response: To Be Announced

III. Committee Discussion

IV. OPEN PUBLIC HEARING

V. Committee Recommendation(s)

VI. Closing Remarks-Information and Followup

There will be a BREAK and/or LUNCH BREAK at the discretion of the Chair.

FOOD AND DRUG ADMINISTRATION

QUESTION LIST

PCNS ADVISORY COMMITTEE MEETING

SEPTEMBER 19, 1996

COPAXONE® (COPOLYMER-1); NDA 20-622, Evaluation of Safety and Efficacy in use.

The Division of Neuropharmacological Drug Products has reviewed the New Drug Application (NDA) submitted by Teva Pharmaceuticals USA for COPAXONE® and before forwarding a recommendation to the Office of Drug Evaluation I, the Division seeks the Committee's advice on the following questions:

1. Teva Pharmaceuticals has provided results of two controlled clinical investigations of Copolymer-1's effectiveness in Exacerbating Remitting Multiple Sclerosis. Are these studies adequate and well controlled clinical investigations and does each provide evidence that would allow an expert, knowledgeable and experienced in the management of patients with MS, to conclude that Copolymer-1 is an effective treatment for MS?

2. Has the sponsor provided evidence that Copolymer-1 is safe when used in the treatment of MS?

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE
CENTER FOR DRUG EVALUATION AND RESEARCH

CHAIRPERSON

Gilman, Sid, M.D. 1/31/00
Professor and Chair
Department of Neurology
University of Michigan Medical Center
1500 E. Michigan Center Drive
Ann Arbor, Michigan 48109

EXECUTIVE SECRETARY

McGoodwin, Ermona
Advisors and Consultants Staff
Center for Drug Evaluation and Research
Food and Drug Administration (HFD-120)
5600 Fishers Lane
Rockville, Maryland 20857
301/443-4695 FAX 301/443-0699
E-mail: mcgoodwin@cder.fda.gov

MEMBERS

Copple, Peggy J., M.D. 1/31/97
Professor of Pediatrics and Neurology
Department of Pediatrics
University of Arizona Health Sciences Center
1501 N. Campbell Avenue
Tucson, Arizona 85724

Snead, Orlando Carter III, M.D. 1/31/97
Head, Division of Neurology
The Hospital for Sick Children, Room 6544
Gerrard Wing, 6th Floor
555 University Avenue
Toronto, Ontario, Canada M5G1X8

Coyle, Patricia K., M.D. 1/31/98
Professor of Neurology
Department of Neurology
Health Sciences Center
State University of New York at Stony Brook
Stony Brook, New York 11790

Gennings, Chris, Ph.D. 1/31/98
Assistant Professor
Department of Biostatistics
Medical College of Virginia
Virginia Commonwealth University
Box 32, MCV Station
Richmond, Virginia 23298-0032

Phillips, Ellyn C., B.A., M.S 1/31/99
President, Amyotropic Lateral Sclerosis
Association (ALS), Philadelphia Chapter
980 Harvest Drive, Suite 105
Blue Bell, Pennsylvania 19422-1961

Zivin, Justin A., M.D., Ph.D. 1/31/99
Professor of Neurosciences
Department of Neurosciences 0624
University of California, San Diego
9500 Gilman Drive
La Jolla, California 92093-0624

Adams, Harold P. Jr., M.D. 1/31/00
Professor, Department of Neurology
The University of Iowa
200 Hawkins Drive #2007 RCP
Iowa City, Iowa 52242-1053

Drachman, David A., M.D. 1/31/00
Professor and Chair
Department of Neurology
University of Massachusetts Medical School
Room S5-753
55 Lake Avenue, N.
Worcester, Massachusetts 01655

Kawas, Claudia H., M.D. 1/31/00
Associate Professor of Neurology
Department of Geriatric Neurology
Johns Hopkins University School of Medicine
5501 Hopkins Bayview Circle
Asthma and Allergy Building, Room 1B82
Baltimore, Maryland 21224

Khachaturian, Zaven S., Ph.D. 1/31/00
President
Khachaturian, Radebaugh and Associates, Inc.
8912 Copenhaver Drive
Potomac, Maryland 20854-3009

TAB C

MEMORANDUM

DATE: August 12, 1996

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Members, Peripheral and Central Nervous Systems Advisory Committee

SUBJECT: Background Material for September 19, 1996 Advisory Committee Meeting to Discuss NDA 20-622, Copolymer-1 Injection for Patients With Exacerbating-Remitting Multiple Sclerosis

Overview

As you know, the PCNS Advisory Committee will meet on September 19, 1996 to discuss NDA 20-622, Copolymer-1, submitted by Teva Pharmaceuticals, for use in patients with Exacerbating Remitting Multiple Sclerosis (ER MS). This memo will give an overview of the safety and effectiveness data included in the NDA, which will provide the background for your discussions and deliberations. The package also contains the detailed reviews of the effectiveness and safety data, performed by Drs. Janeth Rouzer-Kammeyer and John Balian, respectively, of the Division, as well as 2 reviews of the effectiveness data performed by Dr. David Hoberman, mathematical statistician.

Under separate cover, we are also forwarding a briefing document prepared by the sponsor.

BACKGROUND OF THE NDA

NDA 20-622, for the use of Copolymer-1 (Cop 1), a 4 amino acid copolymer of fixed proportion but random order to be injected subcutaneously, was submitted by Teva Pharmaceuticals, USA on October 11, 1995. The sponsor proposes that it be approved as a treatment for patients with exacerbating-remitting Multiple Sclerosis. As support for this proposed

claim, they have submitted reports of 2 adequate and well controlled trials in patients with this condition.

and is not part of this application. The drug is presumed to exert its anti-MS effect via the activation of T-cells at the site of injection, which, in turn, are distributed widely to produce systemic effects.

The first controlled trial was performed as a single center trial by Dr. Murray Bornstein at the Albert Einstein College of Medicine in the Bronx, New York. The results of this trial were published in the New England Journal of Medicine on August 13, 1987 (a copy of which is included in the sponsor's briefing package). On the basis of this study, and the fact that a second trial (a multi-center study conducted by the sponsor) was on-going, Teva submitted a Treatment IND request to the Agency on December 4, 1992. The Treatment IND was granted on 1/5/93.

At the time of submission of the NDA, the routinely required life-time *in vivo* carcinogenicity studies in 2 animal species had not been completed (they are still on-going). In multiple discussions (taking place over years) with the sponsor prior to the submission of the NDA, the Division repeatedly informed the sponsor that these studies would be required for approval. The sponsor made a number of arguments to support their view that such studies should not be required (including the fact that Betaseron, the first approved treatment for MS, which was approved in CBER, had not had such studies performed), but these arguments were never felt to be compelling by the Division. While it was ultimately decided (based on discussions with Drs. Temple and Woodcock) that the application would be filed without this information available, Agency staff agreed that whether or not the application could be approved before the results of these studies were available would depend upon the robustness of the clinical data.

BORNSTEIN STUDY

This study was performed by Dr. Murray Bornstein (who is, unfortunately, recently deceased) and colleagues of the Albert Einstein College of

Medicine in New York under Dr. Bornstein's IND. Teva had no involvement in either the design or conduct of the study, and acquired the data after the study was completed. As a result, the records for this study were gathered retrospectively, and the sponsor's study report was written on the basis of the records that could be recovered. While CRFs were obtained, the document that the sponsor has submitted as the protocol is in fact a portion of a grant application, dated 10/1/82, that Dr. Bornstein completed **after the study was initiated** (for example, a statement in this "protocol" notes that 16 pairs of patients are receiving drug and that many of them are completing their 2 year participation in the near future). According to Drs. Scheindlin and Ben-Naiman of Teva, Dr. Bornstein submitted numerous grant applications for this study, and, again, according to the sponsor, the actual original protocol from which Dr. Bornstein worked, assuming there is such a written document, was unavailable to them. The sponsor asserts that the document that they have submitted as the protocol contains the most explicit details of the trial and its analysis plan as it was intended to be conducted.

There are, however, some points of interest related to the document, beyond the fact that it was written long after the trial had begun. For example, it describes the establishment of an External Committee composed of 3 people (named in the document) who are unaffiliated with the study whose role was to review the data regarding adverse effects. However, the document also states that they may stop the study not only for toxicity, but also "...because of an overwhelming beneficial effect". Because this statement permitted the inference that a formal interim analysis was (to be) done, we called the sponsor, who told us that, indeed, another grant application dated 2/1/81 contained the results of an interim analysis of the effectiveness data on 26 patients. Ostensibly, nominally significant results were obtained on several measures of effectiveness. Dr. Bornstein does state, in this grant application, the following:

> (In this regard, I must call attention to the conditions imposed by its being a blinded study. It is obviously necessary to disclose the data to the site visit team and The Committee in order to permit a proper consideration of this proposal. The details of this report must, however, be treated in strict confidence to avoid jeopardizing

the blinded nature of the study itself).

The sponsor assures us that Dr. Aaron Miller, the neurologist responsible for rating the patients, and who was blinded, had no knowledge of the results of the interim analysis. Dr. Bornstein, was, of course, unblinded, and knew the results of the interim analysis (as did the other trial planners-statisticians, etc.), but he apparently was not involved in the actual conduct of the trial, according to the sponsor.

We have recently recovered a document from Dr. Leber's files signed by Dr. Bornstein on February 1, 1980. In a cover letter to his IND dated 8/21/87, Dr. Bornstein states that it was this 2/1/80 protocol that was followed in the trial reported in the NEJM. The protocol appears, again, to be a portion of a grant application. The date of the protocol would appear to be consistent with Dr. Bornstein's statement in the 2/1/81 grant application that the trial began in March, 1980. The 1980 protocol is largely similar to that described in the 1982 document, with one important difference. The sample size called for in the earlier document is 40 patients total, as compared to 50 in the latter document. The 2/1/80 protocol does not included a sample size calculation, nor does it describe plans for an interim analysis.

These matters take on some importance because it is not clear when the actual sample size for the study was calculated. In the 10/1/82 document submitted as the protocol, it states that 50 patients (25 matched pairs) would give reasonable power and would be the final number of patients enrolled. The outcome variable used to calculate sample size, proportion of patients exacerbation-free for 2 years, was one of the variables analyzed and found to be nominally significant ($p=0.021$) in the interim analysis. As noted above, the 2/1/80 document, described by Dr. Bornstein in 1987 as the protocol used for the trial, calls for 40 patients (explicitly describing 20 matched pairs). The sequence of documents in our possession as of this date would permit the suggestion that the sample size could have been increased based on the results of the interim analysis reported in 2/1/81. We have also just recently retrieved Dr. Bornstein's original IND application. The original submission (received in January, 1978) proposed a small, open, uncontrolled trial of Cop 1. I cannot find in the file a detailed protocol for the double blind, placebo

controlled trial ultimately performed. However, Dr. Bornstein did submit an amendment to the IND dated November 19, 1979, in which he described a randomized, double blind, placebo controlled trial of IM Cop 1, to enroll "approximately 30-40 patients equally divided between the chronic progressive and the exacerbating and remitting types.".

The description of the protocol given below, however, is taken from the 10/1/82 grant application. Again, the 2/1/80 document is essentially the same, with the already described differences in sample size and lack of sample size calculations.

This was a single center, double blind, randomized trial comparing Cop 1, 20 mg SC, given daily, to placebo in patients with exacerbating-remitting MS, as defined by usual criteria. Patients must have had at least 2 well-defined attacks a year for the 2 years prior to entry, and must have had a Kurtzke score of no greater than 6 (this disability scale ranges from 0-Normal to 10-death due to MS; a score of 6 means the patient can walk with assistance; a 7 means the patient is restricted to wheelchair).

Patients were to be evaluated at 4 weeks after randomization, and then every 3 months for 2 years. In addition, whenever an exacerbation occurred, patients were to be seen by the evaluating neurologist who was to document that an objective neurologic deficit was present. There was no specific definition in the protocol of how an exacerbation was to be determined. However, in the description of exacerbations for purposes of inclusion into the trial, the protocol suggests that an exacerbation must be a new neurologic deficit, of greater than 24 hours duration (changed at some unknown point during the trial to the requirement for 48 hours duration), primarily related to a lesion in the white matter, with no other identifiable cause.

At each evaluation (routine or exacerbation), various assessments were made. These included:

1) **Kurtzke Scale**-described above

2) **Functional Status**-8 scales covering:

a. Pyramidal tract functions-(0-normal-5-paraplegia,hemiplegia, marked quadriparesis

b. Cerebellar functions-0-normal-5-unable to perform coordinated movements due to ataxia

c. Brainstem functions-0-normal-5-inability to swallow or speak

d. Sensory Functions-0-normal-6-analgesia and anaesthesia to neck

e. Bowel and bladder functions-0-normal-5-loss of bladder and bowel control

f. Visual functions-0-6

g. Mental functions-0-normal-5-dementia, incompetent

h. Other functions-0-none-1 specify any other findings

3) **Ambulatory Index**

4) **Incapacity Scale**-16 functions graded as normal, without aid, with mechanical aid, with human aid, not able to do.

Other measures and derived measures included:

5) **Total Severity Score**-each exacerbation is ranked from 1-3, with 3 being most severe;scores for all exacerbations during the 2 years will be added together

6) **Mean Severity Score**-the mean score will be calculated

7) **Total Time in Exacerbation**-the total number of weeks spent during exacerbations over the 2 years

8) **Severity-Duration Index**-A combined score of duration and severity will be calculated for each bout and "summarized" for each patient.

Prospective patients were to be extensively screened by Dr. Bornstein and Dr. Miller, as well as a social worker, who were to ensure that the patient was an appropriate candidate for the study.

Patients were to be "matched" according to age, sex, duration of illness and frequency of attacks. Specifically, a given patient was randomized, and the next patient who "matched" this patient on the 4 mentioned criteria was automatically assigned the alternate therapy (there was a certain amount of variability permitted in the matching maneuver; for example, when matching on the Kurtzke, patients were categorized into 3 groups; 0-2,3-4, and 5-6). Clearly, it was anticipated that the second member of a pair could be enrolled into the study considerably later in time than the first member.

The protocol lists 3 outcome measures on which "major analyses" will be performed (the 1980 and 1982 documents differ in the order in which these 3 are listed):

1) Frequency of attacks per year
2) Change in the number of attacks in the study years compared to the number of attacks in the 2 years prior to study
3) The number of patients in each group having attacks.

Both documents state that the "first outcome measure to be evaluated will be the occurrence or absence of exacerbations", and, as noted earlier, the sample size calculations in the 1982 document were based on the proportion of patients exacerbation free. This apparent primary outcome was to be analyzed using McNemar's test with Edward's corrective factor.

The 1980 document goes on to say that the "second phase of analysis" will examine the frequency of exacerbations, while the "third phase" will look at the change in frequency in a patient compared to his or her previous attack rate. The 1982 document states that, after the primary outcome, they will examine the change in attack rate, and, in the text of the Statistical Analysis section, does not explicitly discuss in detail the analysis of the frequency of attacks.

RESULTS

Approximately 1000 patients were screened prior to enrollment. A total of 50 patients, however, were actually enrolled into the trial, with 25 randomized to each treatment. There were a total of 24 matched pairs, with 1 additional unmatched patient randomized to each treatment.

In the NEJM publication, the authors excluded 2 patients from the efficacy analysis. They were both placebo patients, who did not complete the 2 years of treatment, and they were excluded because the authors considered them unevaluable for psychogenic reasons. These exclusions resulted in 22 matched pairs and 4 unmatched patients (3 Cop I, 1 Placebo) having been included in the analysis reported in the NEJM. In this memo, I will report the results of analyses that include all 50 patients.

A total of 7 patients (3 Cop 1, 4 Pbo) did not complete the full 2 years of treatment. Two (2) Cop 1 patients withdrew because of ADRs, and 1 withdrew for unspecified reasons. Two (2) placebo patients were terminated by the investigator (see above) and 1 each left for hospitalization due to a relapse and patient decision.

The following describes the results of the analysis of what appears to have been the primary outcome; namely, the proportion of exacerbation-free patients.

	N	% Exacerbation Free	P-value
Cop 1	25	14/25 (56%)	
Pbo	25	8/25 (32%)	0.18

The p-value reported in the NEJM article for this comparison was 0.039; however, this analysis was based on 48 patients. The p-value reported here is the result of an analysis performed by the sponsor (and confirmed by Dr. Hoberman) that included all 50 patients.

The following chart displays the results of an analysis of exacerbation frequency. It should be kept in mind that in this analysis, for patients

who did not complete the full 2 years of treatment, exacerbation frequency was calculated as # of exacerbations/2 years. The following results were obtained:

	N	Mean Exacerbation Frequency	P-value
Cop 1	25	(16/25) 0.6	
Pbo	25	(59/25) 2.4	0.004

Again, this P-value represents the result of a Fisher's Exact Test performed by the sponsor. Dr. Hoberman, in his supplementary review dated 8/1/96, suggests that a more appropriate analysis would take into account the fact that randomization was performed within pairs. As such, he performed an analysis that examined only the 24 matched pairs; this analysis yielded a similar P-value of 0.005. It is interesting to note, as Dr. Hoberman points out on page 5 of his 12/22/95 review and illustrates with Figure 1, only in the placebo group are there patients who had 4 or more relapses (maximum 8). Inspection of the individual patient data reveals that this does not represent a marked increase in the number of episodes in these placebo patients compared to their previous 2 year rates.

The following chart displays the results of the third of the "major"endpoints described in the protocol; namely, the change in relapse rate on treatment compared to the rate in the 2 years prior to enrollment in the trial:

	N	Baseline Rate	Treatment Rate	Change	P-value
Cop 1	25	3.8	0.6	3.2	
Pbo	25	4.0	2.4	1.6	0.025

The p-value obtained was the result of a sign rank test performed by Dr. Hoberman.

Other outcomes were examined in this study as well, as noted in the description of the protocol. Results of some of these are presented below.

	Median Time to First Relapse	P-value
Cop 1	>700 days	
Pbo	150 days	0.03 (log rank)

Time to Progression

Only 5/25 Cop 1 patients progressed (defined as an increase of at least 1 point on the Kurtzke that persisted for 3 months; the time to progression was the time from treatment onset to the time a persistent change was first noted). during the trial, compared to 12/25 Placebo patients who progressed. The p-value for the comparison between the 2 groups on this measure was 0.023.

Proportion of Patients With Change From Baseline on Kurtzke

A comparison of the proportion of patients who worsened as measured by the Kurtzke (see Figure 2 of Dr. Hoberman's 12/22/95 review) yielded a p-value of 0.13. A comparison of the proportion of patients who improved on the Kurtzke yielded a p-value of .2.

As noted above in the description of the protocol, at some point in the conduct of the trial (it is not clear to us when), the duration of persistence of a new neurologic deficit necessary to declare this new deficit an exacerbation changed from 24 to 48 hours. The records of patients who had had an exacerbation declared under the 24 hour rule were reviewed after the fact and were to have been re-classified as an exacerbation if the records showed that the new deficit had, in fact, persisted for at least 48 hours. The sponsor claims that all episodes classified as exacerbations under the 24 hour rule also were classified as exacerbations when the 48 hour rule was applied.

The retrospective nature of the re-classification raised one issue. Specifically, the protocol required that patients be seen by the study neurologist as soon as possible after the onset of a new deficit, so that the neurologist could document objective neurologic signs (one criterion

necessary to call the deficit an exacerbation). If this visit occurred less than 48 hours after the onset of the deficit, and objective signs were present, the event could rightly be classified as an exacerbation by the 24 hour rule, but not by the 48 hour rule. Given this, we asked the sponsor to document that all re-classified exacerbations had, in fact, had a visit occurring in proximity to the onset of the deficit but at least 48 hours after its onset, so that we could be assured that all of the "24 hour exacerbations" were truly also exacerbations by the new rule. The sponsor was unable to produce such documentation.

STUDY 9001

This was a multi-center, randomized, double blind, placebo controlled trial comparing Copolymer 1, given as 20 mg subcutaneously, to placebo in patients with exacerbating remitting MS.

Two hundred forty (240) patients similar to those enrolled in the Bornstein study were to be enrolled into the trial. The primary outcome was to be the "...number of relapses during a fixed period of treatment.". The primary analysis of this primary outcome was to be performed on the evaluable patient subset, defined as those patients who do not violate the protocol and who completed the full treatment period. Although the primary analysis was to be based on the evaluable subset, the protocol did state that an analysis of the intent to treat population would also be performed.

The protocol called for an interim analysis to be performed on the primary outcome for the evaluable subset when all patients either completed 12 months in study or prematurely discontinued treatment. The stopping rule for effectiveness was to be based on the method of Lan and DeMets.

In this trial, a relapse (exacerbation) was defined as the appearance of one or more new neurologic deficits or the re-appearance of one or more previously observed abnormalities, persisting for at least 48 hours. The deficit must have been preceded by a stable or improving neurologic condition for the 30 days prior to the onset, and must have been documented by objective signs. The objective change must have been

accompanied by an increase of at least 0.5 on the Kurtzke or an increase of at least one grade in at least 2 of the Functional Systems (FS) or 2 grades in at least 1 FS.

Patients were to be assessed using the Kurtzke, FS, Ambulation Index, a Neuropsychological Profile, and other laboratory tests. Patients were to be seen every 3 months, at which the first 3 tests listed above were performed, and at the 12 and 24 month evaluations the Neuropsychological Profile was administered, as well as additional assessments, including a Quality of Life questionnaire. Patients were to be seen at these times by a blinded Examining Neurologist who was to evaluate the patient without verbal communication regarding symptoms and who did not have access to prior evaluations. They were also seen by a blinded Treatment Neurologist who was to assess adverse events and make treatment decisions (e.g., acute treatments for a relapse). Patients who discontinued were to be seen at specified intervals after discontinuation. In addition, patients were to be seen within 7 days of a suspected relapse; at this visit, the neurologic exam was performed (not including the neuropsychological profile).

The sample size was calculated in order to provide 85% power to detect a "meaningful difference" for all primary and secondary outcomes, the most conservative being proportion of patients experiencing a relapse.

As noted, the primary variable was to be the number of relapses during "...the prescribed period of treatment (12 months for the interim analysis and 24 months for the final analysis).". The primary method of analysis of this variable was to be analysis of variance on the evaluable cohort. Pretreatment measures were to be considered as possible covariates. Specifically, baseline Kurtzke, sex, and number of relapses during the prior 2 years (factors employed in the randomization process), were to be particular candidates. The protocol also states that a non-parametric analysis of ranks will be performed, as well as an appropriate non-parametric analysis of the distribution of the number of relapses. In particular, an analysis of the proportion of relapse free patients was to be performed. The protocol states that if any differences between these 3 analyses, or differences between the results of these analyses on the

evaluable vs. Intent to treat cohorts, emerge, these differences will be explained.

Secondary analyses included analyses of time to first relapse and time to progression, (defined as the onset of an increase of at least 1 Kurtzke unit that persists for 3 months), the proportion of patients with progression, and changes from baseline in the Kurtzke, Ambulation Index, and Neuropsychological Profile.

A protocol amendment extended double blind treatment to a maximum of 35 months, in order to maintain the blind until all patients either completed 24 months or discontinued treatment.

A revised statistical plan was developed after the trial was completed, but before the blind was broken. The important aspects of that plan were:

1) A statement that *no interim* analysis had been performed.

2) The definition of an evaluable patient was changed somewhat.

3) The primary analysis was changed to a last observation carried forward (LOCF) analysis. Specifically, a patient who discontinued prior to 24 months of treatment was assigned a number of relapses using the following rule:

> a) if in the study for at least 6 months, the number of relapses reported for that patient were to be adjusted to account for a 24 month period
>
> b) if in the study for less than 6 months, the patient will be assigned a number of relapses equal to the greater of either:
>
> > i) the actual number of relapses, or
> > ii) the overall average, calculated by dividing the total number of relapses in all patients divided by the total number of patient-months of treatment, multiplied by 24

4) Various other analyses of the secondary measures were more explicitly

defined.

RESULTS

A total of 251 patients were randomized to treatment (125 Cop1, 126 Pbo) at 11 centers, with enrollment at the centers ranging from 6-16. The following chart provides a brief description of patient flow during the trial:

	Randomized	Completed	Treated at Least 6 Months
Cop 1	125	106 (85%)	119 (95%)
Pbo	126	109 (87%)	119 (95%)

Patients were well matched at baseline, although the following differences were noted:

	Cop 1	Pbo
Mean Kurtzke	2.8	2.4
Mean FS	6.2	5.3
Mean Duration of Illness (yrs)	7.3	6.6

Primary Outcome-Relapse Rate

The sponsor reports the results of a covariate adjusted analysis without the treatment by center interaction term (a term which the protocol states would be included even if the interaction was not significant) of this primary outcome as yielding a p-value of 0.007. While a covariate adjusted analysis was described in the protocol, the Division feels that the methodology utilized to incorporate these covariates (a retrospective choice of covariates not prospectively designated which, in this case, resulted in the use of baseline Kurtzke and prior relapse rate) cannot be relied upon to maintain the overall experiment wise Type 1 error rate at the traditional 0.05. For this reason, analyses using a simple model

including treatment, center, and center by treatment interaction terms were performed on the intent to treat cohort. These analyses were performed by 1) using a simple LOCF rule, 2) using the sponsor's bifid LOCF rule, referred to as spLOCF and defined above, 3) applying the sponsor's criteria for calculating relapse rate in patients in the trial for greater than 6 months to all patients, referred to as $spLOCF_1$, and 4) applying the sponsor's rule for calculating relapse rate in patients in the trial for fewer than 6 months to all patients, referred to as $spLOCF_2$:

	Cop 1 (N=125)	Pbo (N=126)	P-Value
1) LOCF			
Mean	1.19	1.68	0.055
2) spLOCF			
Mean	1.38	1.73	0.09
3) $spLOCF_1$			
Mean	1.42	1.91	0.037
4) $spLOCF_2$			
Mean	2.02	2.25	0.084

Various other simple analyses performed by Dr. Hoberman yield P-values in the range of 0.02-0.04 for this primary outcome.

2)	Proportion of Patients Relapse Free	P-Value
Cop 1	42/125 (33.6%)	
Pbo	34/126 (27%)	0.25

The P-value reported above is based on a simple test of proportions performed by Dr. Hoberman. The sponsor reports a p-value of 0.098, the result of a logistic regression analysis utilizing the same covariates (not pre-specified) as in their analysis of the relapse rate (i.e., baseline Kurtzke and prior 2 year relapse rate).

3)	Median Time to First Relapse (Days)	P-Value
Cop 1	287	
Pbo	198	0.23

The P-value in this chart was based on a log rank test, the test described in the protocol. The sponsor reports a p-value for this comparison of 0.097, based on an analysis not described in the protocol.

4) Time to Progression

Only about 25% of patients in each group progressed during the trial; the p-value for the comparison of the 2 groups for this outcome was therefore not significant (see below).

5)	Proportion of Patients Progression Free	P-Value
Cop 1	98/125 (78.4%)	
Pbo	95/126 (75.4%)	0.48

6)	Mean Change From Baseline in Kurtzke	P-Value
Cop 1	-.05	
Pbo	+.21	0.023

The P-value reported here is the result of the protocol specified repeated measures analysis of covariance using baseline Kurtzke as the covariate.

There were no significant differences on tests of the Ambulation Index and the Quality of Life questionnaire.

A comparison of the distribution of relapses yielded an odds ratio of 1.7, a statistically significant difference favoring Cop 1. However, the mean change from prior 2 year relapse rate for Cop1 was a decrease of 1.62,

compared to a decrease of 1.26 for the placebo patients, a difference that yielded p-values ranging from 0.10 to 0.17.

SAFETY

A total of 852 patients with Multiple Sclerosis and 49 normal volunteers have received at least one dose of Cop 1. Of this number, 779 patients have had Exacerbating-Remitting MS. The distribution of duration of treatments in this latter group is displayed below (all patients having received 20 mg subcutaneously once a day):

Duration	N
> 6 months	670
>1 year	490
>2 years	290
> 3 years	87

An additional 73 patients with chronic-progressive MS received Cop1 in 2 trials. In one trial patients received 15 mg BID, while in the other trial, they received 20 mg once a day.

DEATHS

A total of 7 patients died while receiving treatment with Cop 1. None of these deaths occurred in the controlled trials, although 2 of the deaths did occur in patients with E-R MS. The remaining 5 deaths occurred in patients with C-P MS.

As Dr. Balian reports in his safety review, there is little detailed information in the application concerning these deaths. Three (3) of the deaths appear perhaps to have had identifiable causes (tumor complications, pneumonia, colon malignancy), but for 4 others, the available information does not permit a reliable conclusion about causality. For 2 of these 4, (a 48 year old woman with CP MS receiving

treatment for 2 years and a 43 year old woman with ER MS receiving treatment for an unknown duration), there is essentially no information available.

For the remaining 2 patients who died, there are some incompletely reported data.

One patient, a 46 year old man with CP MS, had been treated with Copl for 3 years at the time of his death. After 2 years of treatment, the patient began to experience chest tightness, anxiety, and throat constriction, symptoms not uncommonly seen in Cop 1 treated patients, and categorized by the sponsor as a "systemic reaction" (more on this reaction later). This patient was reported to have become comatose approximately 2 weeks after the onset of these symptoms. While hospitalized he continued to receive Cop 1, and his family reports the occurrence of the initial symptoms periodically throughout the year that he remained hospitalized. He died during the process of changing his tracheostomy tube. It is entirely unclear how the family could have reported what are essentially subjective symptoms for a patient who was presumably comatose. The sponsor has not been able to provide additional clarifying information.

The second patient who died was a 48 year old woman with CP MS who died after about 1 1/2 years of treatment. She had presumably reported symptoms, including constriction of the throat, consistent with the systemic reaction described by the sponsor, shortly before her death. There is no other available information on this patient.

DROPOUTS

Overall, 200/844 (24%) of Cop 1 treated patients discontinued treatment. In the 2 controlled trials of patients with ER MS, 31/150 (21%) of Cop 1 and 33/151 (22%) of Placebo patients discontinued treatment. In the overall controlled trial data base, a total of 48/201 (24%) Cop 1 patients discontinued, whereas 54/206 (26%) of placebo patients withdrew.

The following chart displays the most common reasons for discontinuation in the combined controlled trial data base for ER MS patients, as well as for the total combined controlled trial database (including CP MS

patients):

Reason	ERMS		Total MS	
	Cop 1 (N=150)	Pbo (N=151)	Cop 1 (N=201)	Pbo (N=206)
Adverse Event	19 (13%)	4 (3%)	25 (12%)	5 (2%)
Patient Decision	7 (5%)	18 (12%)	11 (7%)	23 (15%)
Disease Progression	1 (0.6%)	0 (0%)	8 (4%)	13 (6%)

(The overall rate of discontinuations from treatment with Cop 1 due to an adverse event was 72/893 or 8%)

The most common Adverse Event resulting in discontinuation in the controlled trials was Injection Site Reaction, with 13/201 (6.5%) in the Cop 1 group, and 2/206 (1%) in the placebo group. The next most common Adverse Events resulting in discontinuation seen in the Cop 1 treated group in the Total MS controlled trial database were Vasodilation and Unintended Pregnancy, Depression (3 reports each); Dyspnea, Urticaria, Tachycardia, Dizziness, Tremor (2 reports each).

SERIOUS ADVERSE EVENTS

In the entire MS database (N=844), the incidence of patients reporting one or more serious adverse events was 55/844, or 6.5%. In the MS controlled trial database, a total of 36/201 (18%) of the Cop 1 and 23/206 (11%) of placebo patients reported one or more serious events. Dr. Balian has reviewed the available information on all these events (again, there is often little useful detail provided in the application about these events). He has, in his Appendix 13.3, attempted to classify certain of these serious adverse events, based on the consideration that there is no

compelling evidence to rule out an event's association with treatment. In this list, there appear 3 cases of syncope/loss of consciousness, and 2 cases of asthenia, and 1 case of several other events, including chest pain, serum sickness, rash, and lymphadenopathy. In his listing of serious events/hospitalizations that are likely not drug related (Appendices 13.1 and 13.2) are included several reports of depression, suicide attempt/ideation, atrial fibrillation, and asthenia.

OTHER ADVERSE EVENTS

The vast majority of patients receiving Copl reported at least 1 adverse event. However, the following chart presents those important events that were reported at an incidence on Cop 1 at least twice that on placebo for the combined MS controlled trial database (this chart is based on Dr. Balian's Tables 9.c.1,2, and 3, pages 16 and 17 of his review).

Event	Cop 1 (N=201)	Placebo (N=206)
Injection Site Reactions		
Inflammation	98 (49%)	22 (11%)
Pruritus	80 (40%)	12 (6%)
Erythema	73 (36%)	17 (8%)
Mass	52 (26%)	19 (9%)
Induration	25 (12%)	1 (0.5%)
Pain	23 (11%)	9 (4%)
Welt	22 (11%)	5 (2%)
Vasodilation	55 (27%)	21 (10%)
Chest Pain	33 (16%)	13 (6%)
Palpitation	28 (14%)	12 (6%)
Dyspnea	26 (13%)	8 (4%)
Pruritus	18 (9%)	7 (3%)
Peripheral Edema	14 (7%)	7 (3%)
Tremor	14 (7%)	7 (3%)
Syncope	8 (4%)	4 (2%)
Weight gain	7 (3%)	0 (0%)

There is little detailed description in the application about most of the adverse events listed in the chart above. Of particular concern might be the cases of chest pain, dyspnea, syncope, palpitation, and perhaps vasodilation. Unfortunately, there is little detailed information about these events. In particular, no systematic specific testing was performed on these patients to gather further information. For example, there were essentially no EKGs performed during any episodes of chest pain (they were invariably brief and occurred in the out-patient setting), no formal pulmonary function tests performed in patients reporting dyspnea, no formal evaluation of patients who reported syncope. In the case of chest pain, we do know that the episodes were brief, often multiple over time, but for most of the episodes, the time of occurrence in relation to injection is unrecorded. Some of the events listed in the chart occurred in the context of what the sponsor has characterized as a "systemic reaction".

"SYSTEMIC REACTION"

The sponsor has created a definition of a systemic reaction that attempts to explain a series of adverse events that have been seen to occur together in temporal relationship to an injection of Cop 1. Their definition of the reaction includes

> vasodilatation or chest pain with palpitations, anxiety, and/or dyspnea

Utilizing this case definition, a total of 87/844 (10%) of MS patients reported the occurrence of at least one episode of systemic reaction. Of these 87, 52 reported one episode, 17 reported 2 episodes, 11 reported 3 episodes, and fewer reported more, with one patient reporting 7 episodes. As Dr. Balian describes, in Study 9001, 19/125 (15%) of Cop 1 patients and 4/126 (3%) of Placebo patients reported at least one episode. Most of these episodes first occur several months after the initiation of treatment (interestingly, of the 33 cases of chest pain that occurred in Study 9001, only 6 were considered to have been part of a systemic reaction as defined).

Although it is possible that the adverse events considered by the sponsor

to constitute this stereotyped reaction may not be related at all, this is probably unlikely. The sponsor suggests that this reaction occurs as the result of inadvertent intravenous injection; there is no empiric evidence that this occurred in patients who experienced these events. While it is reasonable to relate the occurrence of these simultaneous events to drug administration, as Dr. Balian notes, the etiology remains a question (for example, the sponsor concludes that the reaction is not an immunologic event, although this has not been definitively demonstrated), as does whether or not the definition of this "reaction" is sufficiently comprehensive or adequate.

LABORATORY ABNORMALITIES

No important changes have been seen in routine laboratory measures (chemistry, hematology, urinalysis, vital signs) that were measured every 3 months in controlled trials, or in EKG, which was performed at baseline and at the end of the trial in Study 9001.

In Study 9001, blood was analyzed every 3 months for the appearance of anti-Cop 1 antibodies. Approximately 80% of Cop 1 treated patients developed elevations of antibodies of greater than 150% of baseline by 3-6 months, which ultimately decreased to about 50% above baseline in most of these patients. Evidence apparently suggests that the antibody was IgG. The sponsor claims that the presence of the antibody does not interfere with the clinical activity of the drug or the drug's ability to activate T cells, the presumed mechanism of action. Of interest in this regard is the finding of deposition of drug -complement complexes in the glomeruli of rat and monkey following chronic exposure. No adverse effects of these complexes were reported.

COMMENTS

The data submitted by the sponsor in support of their proposed claim that Cop 1 is a safe and effective treatment for patients with exacerbating-remitting Multiple Sclerosis raise a number of questions.

In the first place, the study performed by Dr. Bornstein was designed as a pilot study, a point made numerous times by Dr. Bornstein in his multiple

grant applications. Having said that, though, it should be stated that the study, by design, was an adequate and well controlled trial, and the fact that it was considered a pilot study by its authors does not, in and of itself, stand as a bar to its use in support of an NDA. However, there are questions about the conduct and outcome of the trial that raise concerns about the results as reported.

While the sponsor reports the trial as clearly positive, we are concerned about several points. First, I believe that the protocol states reasonably clearly that the primary outcome was to be the proportion of patients who were exacerbation free. Given this, it is somewhat disturbing that an analysis that includes all patients randomized yields a p-value of 0.18, clearly not significant, and considerably different from the p-value of .039 obtained when only 2 patients are removed. The instability of the p-value in the face of such a small difference in numbers of patients included in the analyses is perhaps not surprising in such a small "pilot"study, but it does raise questions about the reliability of the estimate of treatment effects obtained in such a trial. This is of particular importance when comparing the results of a small study to a considerably larger study of essentially similar design.

The other question raised by this study arises as a result of the fact that a detailed protocol was not available to the sponsor. Specifically, we have evidence that the original study was to enroll 40 patients. An apparently unplanned interim analysis was performed, after which, in a later document, the sample size appears to have been increased to 50 patients. This latter document contains sample size calculations justifying the choice of 50 patients. The interim analysis presumably yielded a nominally significant p-value for the primary outcome measure. While the document containing the results of the interim analysis includes an acknowledgment by Dr. Bornstein that these results should not be disseminated, and we have the sponsor's assurance that the principle investigator was unaware of such results, we have no documentation that the sample size was not increased on the basis of the results of the interim analysis, a maneuver widely regarded as inappropriate and one that, had it occurred, would seriously compromise the interpretation of the trial. We have no written documents that explicitly describe possible actions related to the interim analysis (e.g., rules for stopping the study

for futility if the p-value was unacceptable, or for success if the p-value was very low), and, therefore, we cannot know how, if at all, the final reported p-value should have been corrected for this interim look, even if we had assurance that the sample size had not been altered. In this regard, it is important to note that in the 10/1/82 document submitted as the protocol, there is an explicit statement that the Committee can stop the study for an "overwhelming beneficial effect".

The larger, Teva sponsored trial was an adequate and well controlled trial that was very similar in design to the Bornstein study. Even in this trial, however, the results are not unequivocal, especially in comparison to the Bornstein study. For example, a simple analysis of the primary outcome that does not include retrospectively chosen covariates yields a borderline p-value of 0.055, and p-values derived from other analyses of this primary measure vary from .02 to .09. although, as Dr. Hoberman points out, simple analyses do tend to produce p-values in the range of 0.02-0.04.

In addition, an examination of some of the estimates of the treatment effects in this trial reveals considerable differences between the 2 studies. For example, estimates of the difference between the treatments in relapse rate in this study vary from 0.2-0.5 relapses/2 years; in the Bornstein study, the estimate for this variable is a difference of 1.8 relapses/2 years. Another example of this phenomenon is the decrease in relapses compared to the previous 2 years. In the Bornstein study, the between treatment difference in this variable is 1.6 (decrease of 3.2 on Cop 1 and 1.6 on Pbo). In the larger study, the between treatment difference is 0.3 (decrease of 1.6 on Cop 1 and 1.3 on Pbo). Analyses of these and other important outcomes consistently give considerably lower estimates of the effect of the treatment in the larger study compared to the Bornstein study, again raising the question of the reliability of the estimates obtained in a small trial.

In addition, it should be noted that the only outcome measure found to be statistically significant in both studies was Relapse Frequency, the primary outcome in Study 9001, but a secondary measure in Dr. Bornstein's trial.

Two issues are raised in regard to safety.

First, as noted earlier, results of routine carcinogenicity studies have not been submitted. Ordinarily, for a drug to be given chronically for a non-immediately life threatening illness, such studies would be required. The sponsor has chosen not to submit such studies with the application for several reasons, including the fact that the first treatment approved for patients with MS was not required to have performed such studies prior to approval, and that as a "natural" product, particularly one that is not intended to enter the circulation intact, carcinogenicity studies are inappropriate. The division has never found these arguments persuasive (we know of cases, for example, in which so-called "natural" substances can induce serious toxicities), and the absence of such studies needs to be evaluated in light of the clinical results. Further, Agency reviewers have concluded that the drug was clastogenic in 2 *in vitro* human lymphocyte assays (the firm disagrees with this interpretation).

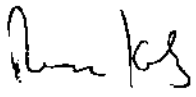
The other general safety concern arises out of the panoply of adverse events seen (chest pain, syncope, unexplained death, etc.), the relative lack of detailed information about them, and theoretical concerns raised by the fact that Cop1 is immunologically active (raised, in particular, by results of animal studies which document immune complex deposition-albeit asymptomatic-in several animal species).

With this as background, we seek your answers to the following questions:

1) Has the sponsor provided substantial evidence of effectiveness for Cop 1 as a treatment for patients with Exacerbating Remitting Multiple Sclerosis?

2) Has the sponsor submitted adequate information to support a finding that Cop 1 is safe for marketing, given appropriate labelling?

I look forward to seeing you all in September.



Russ Katz

TAB D

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	20-622
SPONSOR:	Teva Pharmaceuticals, USA
DRUG:	Copaxone® (Copolymer-1 Injection)
PHARMACOLOGIC CATEGORY:	Acetate salts of synthetic polypeptides containing L-glutamic acid, L-Alamine, L-Fyrosine and L-Lysine
INDICATION:	Slowing progression of disability and reducing frequency of relapses in patients with relapsing-remitting multiple sclerosis.
DOSAGE FORM:	Sterile Lyophilized Powder for Reconstitution, 20mg Subcutaneous Injection
DESIGNATION:	Orphan (November 12, 1987)
DATE OF SUBMISSION:	June 15, 1995
DATE OF REVIEW:	December 5, 1995

1.0 Background

The present submission requests approval of an NDA for the orphan-designated drug Copolymer-1 (Copaxone) for Injection (20mg/vial) for reducing the frequency of relapses and slowing the progression of disability in patients with repasing-remitting multiple sclerosis. The recommended dose of Copaxone for the treatment of relapsing-remitting MS is 20 mg/day injected subcutaneously.

Copolymer-1 is the subject of the following INDs, which are cross-referenced for the supportive evidence of safety/efficacy for this new indication:

IND
IND)
IND

In addition, TEVA initiated a Treatment IND program (Protocol. 01-9002) in June 1993.

The total clinical program with copolymer-1 (excluding the Clinical Pharmacology trials) consists of 11 clinical trials in which a total of 857 with MS have been exposed to the drug (see Table 59, attached). Of these 857 patients, 670 were in the relapsing-remitting phase of the disease and received copolymer-1 by subcutaneous injection at a dose of 20 mg/day for at least 6 months; and 490 received the drug for at least 12 months.

The sponsor has presented the results of two placebo-controlled studies with one's extension to establish the efficacy and safety of Copaxone® (Copolymer-1) for the treatment of relapsing-remitting MS:

PROTOCOL TITLE

BR-1 A pilot trial of copolymer in relapsing-remitting multiple sclerosis. Murray Bornstein, M.D., Albert Einstein College of Medicine, Bronx, NY..(N=51) Publication: Bornstein MW, Miller AJ, Slagel S, et al., 1987. A pilot trial of COP-1 in exacerbating-remitting multiple sclerodis. N ENG J MED 317: 408-14.

01-9001 Long-term, Double-Blind, Placebo-Controlled, Multicenter Phase III Study to Evaluate the Efficacy and Safety of Copolymer-1 Given Subcutaneously in Patients with Relapsing-Remitting Multiple Sclerosis. Principal Investigator: Kennet' P. Johnson, M.D., University of Maryland. (N=251).

01-9001E Extension of Long-term, Double-Blind, Placebo-Controlled, Multicenter Phase III Study to evaluate the Efficacy and Safety of Copolymer-1 given subcutaneously in Patients with Relapsing-Remitting Multiple Sclerosis (N=125)

An original pr study report, case report tabulations were submitted for each pivotal trial.

The focus of this review will be the controlled portion of each pivotal study, as this is the source of the efficacy claim; the open-label chronic experience will be integrated and examined for efficacy and safety in the Safety Review.

2.0 PIVOTAL CONTROLLED TRIALS

3.0 Protocol BR-1: A Pilot Trial of Copolymer-1 in Relapsing-Remitting Multiple Sclerosis. Dr. Murray Bornstein

This study was initiated February 13, 1980 and the last observation was February 22, 1985. The study was conducted under a physician sponsored IND (IND . The results of the trial were published in 1987 (A Pilot Trial of Cop 1 in exacerbating-Remitting Multiple Sclerosis. Bornstein et al, NEJM 317:408-414 [August 13], 1987).

Background

The sponsor's report elaborates on the published account by including the detail expected in an integrated clinical and statistical report included in an NDA, an account of the sponsor's procedures for assuring data validity and accuracy, and a report of the applicant's reanalysis using the cohort presented in the publication ("Bornstein" cohort) as well as a cohort including all randomized patients ("All Patient" cohort).

An external advisory committee was established to monitor the ongoing progress of the trial. This group also served as a safety committee. Any decision for early termination of the trial or for breaking the treatment assignment codes would have been made by this committee. This group was also consulted in regard to changes in trial procedures.

Design

This was a two-year, placebo-controlled, randomized, parallel group, double-blind study involving 50 patients with relapsing-remitting MS in one US center. Patients were enrolled as matched pairs and were treated by daily subcutaneous self-injections of either copolymer-1 20mg (N=25) or placebo (N=25).

Study patients were matched according to sex, number of exacerbations per year within $\pm$ 1 exacerbation, and degree of disability as measured by the Kurtzke Scale in three strata: 0 to 2, 3 to 4, and 5 to 6. The random assignment of the first person of a pair determined the assignment of both.

Data from a personal and disease history and a neurological examination and status evaluation using Kurtzke's Disability Status Scale and eight Functional Groups were recorded at the time of screening and on the patient's entry into the study . Patients visited the clinic one month later and every three months thereafter for two years. At each visit, a neurologist unaware of the patient's treatment group completed a neurologic examination and status evaluation. The patient's self-evaluation of local or generalized side effects and changes in neurologic status were reported to the clinical assisstant, who was not blinded to treatment.

Patients were also seen at the times of suspected exacerbations, when reporting the rapid onset of new symptoms or a worsening of preexisting symptoms that persisted for 48 hours or more. The neurologist verified exacerbations on the basis of study criteria. An event was counted as an exacerbation only when the patient's symptoms were accompanied by observed ojective changes on the neurologic examination involving an increase of at least one grade in the score for one of the eight functional groups or the Kurtzke Scale. Sensory symptoms unaccompanied by objective findings or transient neurologic worsening were not considered to represent an exacerbation. Patients experiencing an acute exacerbation were evaluated at frequent intervals, usually every two weeks until a new, stable neurologic baseline had been established.

Patient Population

To be eligible for the study, patients had to be 20-35 years of age who met Poser's criteria

for clinically definite MS with an initial Kurtzke Disability Status Scale (DSS) score of 0-6.0 (ambulatory with assistance) and a history of at least two relapses in the 2 years prior to study entry, and who were determined to be emotionally stable by psychosocial evaluation. Initially the inclusion criterion required two or more relapses in each of the two years before randomization (i.e., at least four relapses overall). Recruitment difficulties forced relaxation of this criterion to two or more relapses in the two years before randomization (i.e., at least two relapses overall)

Questionnaires completed by 932 volunteers were reviewed; 140 of these candidates were evaluated in neurologic and psychosocial examinations. Ninety of the 140 were excluded-23 because of age; 21, low frequency of exacerbations; 19, lack of documentation; 15, psychosocial inadequacy; 8, transition to a chronic, progressive course; 3, distance from the clinic; and 1 pregnancy. Fifty patients were accepted into the trial.

Concomitant Medications

When clinically indicated, relapses were treated with all appropriate physical, therapeutic (including steroids), and supportive measures for the duration of the relapse. Seventy-four percent of 62 exacerbations in the placebo group and 75 percent of 16 exacerbations in the Cop 1 group were treated with steroids. Symptomatic medications such as cholinergic and spasmolytic drugs, were permitted.

Outcome Measures

The primary outcome measure was the proportion of relapse-free patients over the 24 month follow-up. Initially, a relapse was defined as the rapid onset of new symptoms or a worsening of preexisting symptoms that persisted for at least 24 hours. Relapses were objectively confirmed by the study investigator if the event produced an increase of at least one point in at least one Functional System score or an increase of at least one point in the DSS score. Sensory symptoms unaccompanied by objective findings or brief neurological worsening were not considered to represent a relapse.

In the course of the trial, the principal investigator and the external advisory committee lengthened the duration of the period of worsening to 48 hours in order to avoid a high rate of brief symptomatic episodes that did not represent true relapses. Data that had been previously collected were systematically subjected to the revised criteria and corrected retrospectively before the treatment assignment was broken.

Secondary outcome measures included frequency of relapses, change in DSS score from baseline, proportion of progression-free patients and time to progression. Progression was defined as an increase of at least one unit in the DSS score that persisted for at least 3 months.

Statistical Methods

The sample size was determined to have approximately 80% power to detect a difference of 40% in the proportion of patients who remained relapse-free over two years.

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The study design included planned subgroup analyses according to the disability status of the patients when they were randomized (Kurtzke units 0 to 2, 3 to 4, and 5 to 6). However, only one patient entered with a score of 4, and three with a score of 5. Therefore, two of the three strata were combined (3 to 4 and 5 to 6), creating two strata (0 to 2 and 3 to 6) with approximately equal numbers of patients for subgroup analyses.

For the matched-pair analysis, the difference between treatment arms was tested with use of a McNemar's statistic for the 22 matched pairs. A two-tailed Fisher's exact test was used for other two-by-two contingency tables. The chi-square test was used to test two-by-three contingency tables for frequency of exacerbations.

Survival curves were calculated with life-table methods for the length of time before progression, with "progression" defined as an increase of at least one unit in the Kurtzke score. Progression was noted at the time of the visit during which it was observed; however, it had to be maintained for at least three months to be counted.

All statistical tests were conducted at the alpha=0.05 two sided level of significance. In addition to the cohort of patients analyzed in the publication (the "Bornstein" cohort), the sponsor conducted the same analyses using the "all patient" intent to treat cohort.

Results

Patient Disposition

Fifty patients were enrolled: 48 in matched-pairs and two unmatched. One unmatched patient was randomly assigned to each treatment group (Patient 726, copolymer 1; Patient 898, placebo). The disposition of the cohorts used in the efficacy and safety analyses is presented in Sponsor's Table 9 following

TABLE 9. DISPOSITION OF ALL PATIENTS WHO ENTERED THE TRIAL (MATCHED AND UNMATCHED)

PATIENTS	COP-1(N=25)	PBO (N=25)
Randomized	25	25
Matched	24	24
Unmatched	1	1
Efficacy and Safety Analysis(All Patient cohort)	25	25
Matched	24	24
Unmatched	1	1
Efficacy and Safety Analysis (Bornstein cohort)*	25	23
Matched	22	22
Unmatched	3	1

*Placebo patients #16 and #640 were excluded, as described in the publication.

For the Bornstein cohort, two placebo patients (#16 and #640) who did not complete the two-year follow-up and who were considered by the investigator to be unevaluable due to psychogenic reasons were excluded from the analysis. The exclusion of these two patients resulted in a sample including 22 matched pairs (44 patients) plus four unmatched patients, the additional two unmatched cases (#606 and #639, both on copolymer-1) being a consequence of the exclusions. Unmatched-pair analysis was used for the remaining 48 patients. In total, seven patients (3 copolymer-1 and 4 placebo) failed to complete 2 full years on their assigned treatments.

Summary statistics for demographic and baseline characteristics are presented for all 50 randomized patients in Table 10 (attached). For both the All Patient and Bornstein cohorts, there was no statistically significant difference at baseline between the treatment groups. Patients had an average duration of disease of approximately 5.6 years (range 1-13 years) with a two-year prior relapse rate of about 3.8. Baseline Kurtzke DSS scores were between 0 and 6 and almost half the patients had scores between 0 and 2. The extent of exposure was comparable for both groups. The total patient-months exposure in patients treated with copolymer-1 was 586 months compared to 559 months in the placebo group.

Premature Terminations

Seven patients failed to complete the two year trial. Of these, two patients, Patient 16 and Patient 640 (both placebo), were excluded from the Bornstein cohort efficacy analysis. Both patients, in the opinion of the investigator, had symptomatology considered psychogenic in nature that might interfere with evaluation of treatment effect on the disease, However, they were retained in the All Patient analyses of efficacy and in all safety summaries. Sponsor's Table 13 following summarizes the number of patients who prematurely withdrew prior to completing the trial and the reasons for premature termination. The rate of premature termination and time to withdrawal were similar for both groups.

TABLE 13. PREMATURE TERMINATION

	Copolymer-1 (N=25)		Placebo (N=25)	
	N	%	N	%
Number of Patients Who Withdrew	3	12.0	4	16.0
Principal Reason for Withdrawal				
Hospitalization for Relapse	0	0.0	1	4.0
Reaction to Injection	2	8.0	0	0.0
Termination by Investigator	0	0.0	2	8.0
Patient's Own Volition	0	0.0	1	4.0
Unspecified	1	4.0	0	0.0

Concomitant Medications

According to the publication, approximately 75% of relapses in both the placebo and

copolymer-1 groups were treated with steroids. Nearly half the placebo patients and one quarter of the copolymer-1 patients received anti-inflammatory agents, steroids and/or combination anti-inflammatory therapy

RESULTS: EFFICACY

Table 89 (attached) presents the results of all efficacy variables evaluated.

The primary outcome measure of the proportion of relapse-free patients significantly favored copolymer-1 (56% vs. 26.1% for placebo, p=0.039; Bornstein cohort).

The two-year relapse rate was 16/25 or 0.6 per patient for copolymer-1 and 59/23 or 2.6 per patient for placebo (p=0.002). The corresponding annualized rates were 0.3 for Copolymer-1 and 1.3 for placebo. The effect on relapse rate with copolymer-1 therapy was even greater in patients with baseline DSS scores of 0-2 (4/13 or 0.3 per patient vs. 24/10 or 2.4 per patient for placebo).

For patients with baseline DSS scores of 3-6 the relapses rates were 12/12 or 1.0 per patient for COPAXONE® and 35/13 or 2.7 per patient for placebo.

The proportion of patients with DSS scores which remained stable or improved when compared to baseline approached statistical significance in favor of COPAXONE®. (Fisher's exact probability test, p=0.066). Using a logistic regression, placebo patients were 3.67 times more likely to have a worsening in DSS score as compared with those patients on COPAXONE® (p=0.046).

The proportion of progression-free patients over the 24 month trial was 80% in the COPAXONE® group and 48% in the placebo group (p=0.034).

Patients receiving placebo were four times more likely to have progression than patients receiving COPAXONE®.

The adverse experience profile was similar to that observed in the other pivotal trial. No significant effects on laboratory evaluations were found in either COPAXONE® or placebo-treated patients.

COMMENT

The applicant's reanalysis of data using both the the cohort defined in the publication (Bornstein cohort) and a cohort consisting of all randomized patients (All Patient, ITT cohort) confirmed the conclusion of the publication.

For the primary end-point, the proportion of relapse-free patients, 56% of copolymer-1-treated patients compared with 26.1% of those on placebo were relapse-free (p=0.039, Bornstein cohort). An additional primary outcome measure for this trial was the number of relapses during the 24 month trial. Analysis revealed that for both the Bornstein and All Patient

cohorts, significantly more copolymer-1 treated patients had either none or fewer than 3 relapses compared to those on placebo, demonstrating that copolymer-1 is effective in reducing the frequency of relapses. For both DSS baseline categories (DSS of 0-2 and 3-6) there were fewer relapses in the copolymer treated patients. The most pronounced effect was observed in the low DSS category.

This study was reviewed statistically by FDA statistician Jay Levine when the publication first appeared. He concluded that Cop-1 appeared to reduce the frequency of exacerbations in patients with relapsing-remitting MS during the study, and the effect during the first year of the study is greater than the effect during the second year. Reviewer statistician Dr. Hoberman summarizes the results of the primary endpoints. The Fisher's Exact p-value was .004 for the sponsor's categorization of relapse frequencies. The p-value for proportion of relapse-free patients is .15 using Fisher's Exact test and .18 using McNemar's test. The p-value for time to progression was .023 using the log rank test. The p-value for the comparison of proportion of patients who worsened in Kurztke Scores from baseline was .13.

To summarize, the Bornstein study provides highly significant results of the efficacy of Copolymer-1 in the frequency of relapses and the proportion of relapse-free patients with relapsing-remitting multiple sclerosis.

4.0 Protocol 01-9001 Long-Term, Double-Blind, Placebo-Controlled, Multicenter Phase III Study to Evaluate the Efficacy and Safety of Copolymer-1 Given Subcutaneously in Patients with Relapsing-Remitting Multiple Sclerosis.
First patient enrolled October 23, 1991 and last observation May 25, 1994

This was a two-year, placebo-controlled, randomized, parallel group, double-blind study involving 251 patients with relapsing-remitting MS in 11 US centers ranging from 6 to 16 per cell, using daily subcutaneous self-injections of either Copaxone® 20mg (N=125) or placebo (N=126).

Patients, 18-45 years of age, who met Poser's criteria for clinically or laboratory-supported definite MS, with an initial Kurtzke Expanded Disability Status Scale (EDSS) score of 0-5.0 and a history of at least two relapses in the 2 years prior to study entry were eligible for the trial. In addition, patients were required to have objective evidence of neurologic disease reflecting predominantly white matter damage and a stable neurologic state for at least 30 days before entry. Patients who had received prior immunosuppressant therapy were excluded from the study. During the trial patients could receive corticosteroids for up to 28 days during relapses. Chemotherapeutic agents, chronic steroid therapy, or immunosuppressive drugs were not allowed during the study.

Randomization was centralized. The protocol was amended to include a double-blind extension phase that increased follow-up to a maximum of 35 months. (The extension phase is summarized separately as Trial 01-9001E).

The primary outcome measure was the mean number of relapses over the 24-month double-blind trial period. A relapse was defined as the appearance or reappearance of one or more neurologic abnormalities that lasted for at least 48 hours. Relapses were objectively confirmed by the study investigators if the event produced an increase of at least 0.5 point in the EDSS score or an increase of at least 2 points in one Functional System score or an increase of at least 1 point in at least two Functional System scores during the relapse. Patients were required to have a stable or improving neurologic state for $\geq$ 30 days before a new relapse was confirmed.

A number of secondary outcome measures were also employed, including the proportion of relapse-free patients, median time to first relapse, change in disability (i.e., EDSS score) from baseline, Ambulation Index, proportion of progression-free patients, and time to progression. Progression was defined as an increase of at least one unit in the EDSS score that persisted for at least 3 months.

Efficacy Variables are summarized as follows:

Primary

Number of relapses during treatment

Secondary

Proportion of relapse-free patients
Time to first relapse
Proportion of progression-free patients
Time to Progression (increase of at least one point in the EDSS score from baseline maintained for at least 3 months
Change in Kurtzke EDSS score from baseline
Change in Ambulation Index from baseline
Change in Functional Systems score sum from baseline

Statistical Methodology

Before breaking the blind, a more detailed analytical plan was written as a companion to that originally specified in the protocol. It refers to various model fittings using ANOVA and ANCOVA with sex, duration of disease, prior 2-year relapse rate, and baseline Kurtzke score as potential covariates to predict relapse rate, i.e., the number of relapses per patients over 24 months. Using stepwise progression procedures, the sponsor identified prior 2-year relapse rate and baseline Kurtzke scale as the only statistically significant covariates. The final model upon which the reported p-values are based was a regression model with drug and center as factors and baseline Kurtzke score and prior 2-year response rate as covariates. Time to event analyses used the logrank test, Cox modeling and fitting the data to Wiebull and exponential distributions.

The all patients (intent to treat) cohort was considered the primary cohort for inferences. The "evaluable" cohort was included as a secondary cohort. Also, more of the data was analyzed, including LOCF, patients treated at least 24 months ("completed patients"),

retrieved dropouts, and patients treated for at least 6 months.

All statistical testing was conducted at the two-sided alpha = 0.05 level of significance.

Patient Disposition
Outcome was evaluated using the intent-to-treat population. Following screening (N=284), 251 patients were randomized. Thirty-six patients (19 [15%]COPAXONE® and 17 [13%] placebo) failed to complete 2 full years on their assigned treatments.

PATIENT DISPOSITION	NUMBER OF PATIENTS SCREENED=284			
	Copolymer-1		Placebo	
	n	%	n	%
Randomized	125	100.0	126	100.0
Completed[a]	106	84.8	109	86.5
Included in Safety Analysis	125	100.0	126	100.0
Included in Efficacy Analysis				
Intent to Treat Cohort	125	100.0	126	100.0
Evaluable Cohort[b]	105	84.0	115	92.0
Treated at Least 6 Months Cohort	119	95.2	119	95.2
Completed (≥730 days) Cohort				
All	99	79.2	109	87.2
Evaluable	90	72.0	106	84.8
[b] See Section 6.3.1 for definition				

Of the 284 patients screened, 251 eligible patients were identified. Of these, 125 were randomized to copolymer-1 and 126 to placebo. All 251 randomized patients were included in the intent-to-treat cohort for evaluation of efficacy. All patients received at least one dose of double-blind treatment and thus were included in the safety assessment. A total number of 220 patients (105 on copolymer-1 and 115 on placebo) were considered evaluable "per protocol", having not violated the exclusion criteria.

Patient Demographics

The two treatment groups were well balanced with respect to demographic characteristics and MS history. Mean age across groups was 34.4 years, 73 percent of the patients were female. The duration of MS was 7.3 years for copolymer-1 patients vs. 6.6 for placebo patients. The two year relapse rate before randomization was 2.9 for cop-1 patients and 2.4 for placebo patients. Baseline Kurtzke EDSS score was 2.8 for cop-1 patients and 2.4 for placebo patients.

DEMOGRAPHIC CHARACTERISTICS: ALL PATIENTS (N=126)		
Parameter	**Copolymer-1 (N=125)**	**Placebo (N=126)**
Age		
Mean±SD	34.6±6.0	34.3±6.5
Minimum-Maximum	19.0-46.0	19.0-46.0
Sex[n(%)]		
Male	37 (29.6)	30 (23.8)
Female	88 (70.4)	96 (76.2)
Race [n(%)]		
Caucasian	118 (94.4)	118 (93.6)
Black	7 (5.6)	8 (6.3)
Duration of Disease (yrs)		
Mean±SD	7.3±4.9	6.6±5.1
Minimum-Maximum	0.6-21.2	1.0-23.0
Prior 2-Year Relapse Rate		
Mean±SD	2.9±1.3	2.9±1.1
Minimum-Maximum	2.0-11.0	0.0-6.0
Baseline Kurtzke EDSS Score		
Mean±SD	2.8±1.2	2.4±1.3
Minimum-Maximum	0.05-5.0	0.05-5.0

Efficacy Results

Efficacy results are listed in the attached table (page 8). The primary outcome measure of covariate-adjusted two-year relapse rate was significantly reduced by 29% in favor of COPAXONE®; 1.19 vs. 1.68 relapses per patient for placebo (p=0.007). The corresponding annualized rates were 0.60 for COPAXONE® and 0.84 for placebo.

Few patients in either treatment group had confirmed disease progression (21.6% v. 24.6%);

no significant differences between treatments were observed for the proportion of patients that progressed nor in the time to progression. Also, no significant differences were seen for the Ambulation Index.

Overall, 161 relapses were reported for COPAXONE® and 210 for placebo patients (Table 23, attached). The effect on relapses was apparent early over time but the overall rate of relapses declined during the second year of the study. Table 24 displays the distribution of patients by number of relapses. Two-thirds of the copolymer patients were equally divided between 0 and 1 relapse.

Sponsor's Table 21 tabulates the mean number of relapses by patient cohort. The results are significant for copolymer-1 across all the cohorts.

The positive effect of COPAXONE® was maintained across all levels of degrees of disability but was most pronounced in patients with baseline EDSS scores of 0-2, where the relapse rate was reduced by 33%.

The proportion of relapse-free patients was 33.6% in the COPAXONE® group, compared with 27% in the placebo group (p=0.098).

Compared with patients receiving placebo, the distribution of the number of relapses per patient was significantly different in favor of those patients treated with COPAXONE® (p=0.023). The relative risk of experiencing a relapse was 1.7 times greater for placebo patients.

The median time to first relapse was 287 days for the COPAXONE® patients and 198 days for placebo patients. The difference approached statistical significance (p=0.097). Approximately three-fourths of the patients in both groups were progression-free during the 24-month treatment period.

The change in EDSS score for each patient from baseline to each clinic visit was characterized as: improved (EDSS change $\leq$-1 point), no change (EDSS change $\pm$ 0.5) or worsened (EDSS change $\geq$ 1). Significantly greater number of COPAXONE® patients had improved EDSS scores and fewer COPAXONE® patients had worsening EDSS scores compared with patients who received placebo (p=0.037). At 24 months the change in EDSS score category from baseline also favored COPAXONE® over placebo (p=0.024).

Repeated measures analysis demonstrated a significant effect in favor of COPAXONE® for mean change in EDSS score (p=0.023). This difference was primarily due to consistent increases in mean EDSS score at each visit for placebo patients. This change was -0.05 at month 24 for COPAXONE® and +0.21 for placebo.

There were no statistical differences with respect to progression-free patients, time to progression, ambulation score, and functional systems score.

There were 14 patients (11%) with MS-related hospitalizations in the COPAXONE® treated group compared with 20 (16%) in the placebo group.

Serum samples were monitored every 3 months for the development of antibodies to COPAXONE®. COPAXONE® reactive antibodies developed in almost all COPAXONE® therapy and subsequently declined to a stable level over time. There was no correlation between a patient's antibody development and clinical outcome.

No clinically significant effects on vital signs, ECG or laboratory evaluations of hematology, blood chemistries and urinalysis were found in either COPAXONE® or placebo patients.

At the end of two years on their assigned treatment, trial patients had the option of continuing on their assigned treatment under blinded conditions (Protocol 01-9001E Extension). Ninety-four percent (94%) of the patients (99 COPAXONE® and 104 placebo patients) who completed the 24-month trial elected to continue into the extension.

Patients were treated for up to 35 months. Results of the core trial and the core trial plus extension are presented in Table 1 (page 7, attached) for the intent-to-treat cohort.

Through the end of the extension, the overall covariate-adjusted mean relapse rate was 32% lower for COPAXONE® patients (1.34) compared with placebo patients (1.98, p=0.002).

The proportion of relapse-free patients was significantly higher for COPAXONE® patients (33.6%) compared with placebo patients 24.6%, (p=0.035).

The time to first relapse approached statistical significance in favor of COPAXONE®. 287 vs. 198 days, (p=0.057).

While not statistically significant, the treatment difference in favor of COPAXONE® for the proportion of progression-free patients was greater at the end of the extension than at the end of the two-year core trial (76.8% vs. 70.6%).

The change in disability significantly favored COPAXONE® over time through the extension period (p=0.020). Including the extension period, the change in EDSS for COPAXONE® treated patients was -0.11 vs. 0.34 for placebo patients.

COMMENT

The reviewer statistician Dr. Hoberman examined the impact of imputation on the 36 premature dropouts, 19 in the drug group and 17 in the placebo group who failed to complete the two full years. The sponsor used a hybrid imputation rule: If a patient withdrew before 6 months, the patient was assigned the greater of the observed number of relapses or the overall average number of observed relapses per 24 months computed across treatment groups. If the patient completed 6 or more months of treatment, the observed number of relapses was multiplied by the inflation factor 730/actual number of days of treatment. The

relapse data was reanalyzed by applying each of the above methods separately to the "all patient" (ITT) cohort. The following three models were used:

1. Analysis of variance [drug (D), investigator (I), D x I interaction
2. Analysis of covariance (baseline Kurtzke EDSS, prior 2-year number of relapse, D, I, D x I interaction)
3. Analysis of covariance (baseline Kurtzke DSS, prior 2-year number of relapses, D and I main effects only)

Sponsor's following table highlights the p-values associated with the test of treatment effect using each imputation rule separately on all patients. In all cases, the mean (unadjusted and adjusted) number of observed relapses for the copolymer-1 group was less than that seen for the placebo group.

Algorithm	Model	P-value
>6 months of treatment (730/no.days on trt)	Drug(D),Investigator(I) D xI Interaction	0.037
	Baseline EDSS, prior 2-yr Relapses, D, I, DxI	0.006
	Baseline EDSS, prior 2-yr Relapses, D, I	0.005
<6 months of treatment (greater of either the observed number or the average across all patients)	Drug (D),Investigator (I), DxI Interaction	0.084
	Baseline EDSS, prior 2-yr relapses, D,I,DxI	0.040
	Baseline EDSS, prior 2-yr Relapses, D,I	0.013

If one does impute and put in a covariate, there is some data dredging performed to get a p-value of <.05. If one takes the imputed score with base model from the protocol, one does not reach p=.05. For every other group-completers, retrieved dropouts, no imputation-one does attain .05. If one does impute, the data barely makes it on drug center and center action. Imputation is not necessary if everyone drops out at the same rate randomly.

5.0 SUMMARY

Study 9001 has a small treatment effect. There is formal statistical significance, however, the

differences are very slim. The results are marginal but consistent. The Bornstein study demonstrated highly significant results. Could the difference between the studies be attributed to a difference in the patients? In the Bornstein study, even the placebo patients improved. In the multicenter study, th re were larger numbers of patients which are probably more representative of the whole of the MS diagnosis and how the drug would be used under conditions of real life. One remembers that the 50 Bornstein patients were recruited from an initial 932 questionnaires; 140 of these were evaluated in neurologic exams to yield the fifty paients. In the multicenter trial, 284 patients were screened, of which 251 eligible patients were identified. Also, the Bornstein patients were younger (20-35) v. (18-45) for the multicenter trial.

The question is which study is more representative. For the multicenter trial, the data is marginal but consistent. In the Bornstein study, for PBO patients, exacerbations were more prevalent in year 1 than in the second year. There were few exacerbations in the drug group, but many in the the PBO group.

Based on these two studies, Copolymer-1 appears to reduce the frequency of exacerbations in patients with exacerbating-remitting multiple sclerosis.

Janeth Rouzer Kammeyer MD

Janeth-Rouzer-Kammeyer, M.D.

cc:
Orig:NDA#20-622
HFD-120/Dr. Leber
/Dr. Katz
/Ms. Wheelous
12-8-95

E 58. COPAXONE ® CLINICAL PROGRAM

ype/Trial Number	COPOLYMER-1					Placebo				
	RR-MS	CP-MS	MS-Unsp	Other	Total	RR-MS	CP-MS	MS-Unsp	Other	Total
CAL PHARMACOLOGY										
BR-OB	4	12			16					
BR-OA			4	3	7					
BR-OC		5			5					
BR-OD	6	15			21					
Subtotal	10	32	4	3	49					
MS TRIALS										
RR-MS CONTROLLED (US)										
01-9001/9001E	125				125	126				126
BR-1	25				25	25				25
Subtotal	150				150	151				151
RR-MS UNCONTROLLED										
US										
01-9002*	241				241					
01-9004*										
Subtotal	241				241					
NON-US										
1110-1	282				282					
1110-2	63				63					
1140*										
Subtotal	345				345					
-MS CONTROLLED (US)										
BR-2		51			51		55			55
OMPASSIONATE USE & BR-PTP										
BR-3*	43	22	5		70					
1150*										
BR-PTP*										
Subtotal	43	22	5		70					
RAND TOTAL	789	105	9	3	906	151	55			206

ata available at time of this NDA
ven patients also participated in Trial 1110-1 and were subsequently transferred to this trial.
patient also participated in Trial BR-1 and 3 patients also participated in Trial BR-OB and were then enrolled in this trial

BLE 59. IND SOURCE

Type/Trial	Country	IND			Data Source			Data Lock Date (dy-mo-yr)
		Bornstein		Teva				
		14,115	28,583	27,998	CRFs	Publication	Other	
CAL PHARMACOLOGY								
BR-OB	US	x		x[a]	x	x	x[b]	N/A[d]
BR-OA	Israel			x[a]		x		N/A
BR-OC	UK			x[a]		x		N/A
BR-OD	Germany			x[a]			x[c]	N/A
TRIALS								
RR-MS CONTROLLED (US)								
01-9001	US			x	x			7/22/94
01-9001E	US			x	x			1/31/95
BR-1	US	x		x[a]	x	x	x[b]	4/27/94
RR-MS UNCONTROLLED								
US								
01-9002	US			x	x			2/28/95
01-9004	US			x				N/A
NON-US								
1110-1	Israel			x	x			12/31/94
1110-2	Israel			x	x			12/31/94
1140	Europe							N/A
S CONTROLLED (US)								
BR-2	US	x		x[a]	x	x	x[b]	2/6/95
PASSIONATE USE & TP (US)								
BR-3	US		x	x[a]	x		x[b,c]	N/A
1150	Italy							N/A
BR-PTP	US	x						N/A

orts prepared by TEVA were filed to IND 27,998 and are included in this NDA.
er from the investigator
gress notes and other source documents provided by Dr. Bornstein
us reports filed by Dr. Bornstein to IND
- Not available

TABLE 10. SUMMARY STATISTICS OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS: ALL PATIENT COHORT

	Copolymer-1 (N=25)	Placebo (N=25)	P-Value
Sex			
Male	11	10	>0.99
Female	14	15	
Race			
White	23	25	0.49
Black/Other	2	0	
Age (years)			
Mean ± S.D.	30.0 ± 3.2	31.0 ± 3.5	0.34
Minimum	20.0	25.0	
Maximum	33.0	35.0	
Duration of Disease (years)			
Mean ± S.D.	4.9 ± 2.7	6.1 ± 3.9	0.22
Minimum	2.0	1.0	
Maximum	10.0	13.0	
Prior Relapse Rate (number over 2 years)			
Mean ± S.D.	3.8 ± 1.4	4.0 ± 1.2	0.59
Minimum	2.0	2.0	
Maximum	8.0	7.0	
Baseline Kurtzke DSS Score			
Mean ± S.D.	2.8 ± 1.9	3.2 ± 2.0	0.56
Minimum	1.0	0.0	
Maximum	6.0	6.0	
Baseline Kurtzke DSS Score			
0-2	13	11	
3-4	5	7	
5-6	7	7	

Cross Reference: Appendix I, Table 3, Appendix J, Outputs 10, 11 & 12, Appendix K Listings 2A & 2B

TABLE 23. OVERALL DISTRIBUTION OF RELAPSES BY TIME ON TREATMENT: ALL PATIENTS

Time Interval to Onset of Relapse (months)	Number of Relapses: Copolymer-1 (N = 125) n	Placebo (N = 126) n
0 ≤3	38	43
>3 - 6	20	29
>6 - 9	23	26
>9 - 12	21	30
>12 - 15	19	18
>15 - 18	13	25
>18 - 21	18	16
>21	9	23
Total	161	210

Source: Appendix I4.2.7.1

TABLE 24. DISTRIBUTION OF PATIENTS BY NUMBER OF RELAPSES: ALL PATIENTS

Number of Relapses	Copolymer-1 (N = 125) n	%	Placebo (N = 126) n	%
0	42	33.6	34	27.0
1	42	33.6	39	31.0
2	18	14.4	16	12.7
3	12	9.6	21	16.7
4	9	7.2	9	7.1
5	1	0.8	4	3.2
6	1	0.8	1	0.8
7	0	0	2	1.6

Source: Appendix I4.1.1.1, J4.1.1.1

TABLE 21. COVARIATE ADJUSTED MEAN NUMBER OF RELAPSES BY PATIENT COHORT

Patients in Analysis	Copolymer-1 (N = 125) n	Copolymer-1 (N = 125) Adjusted Mean±SE	Placebo (N = 126) n	Placebo (N = 126) Adjusted Mean±SE	p-Value[a]
Primary Cohort:					
All Patients (ITT)	125	1.19±0.13	126	1.68±0.13	0.007
Secondary Cohorts:					
Evaluable Patients	105	1.27±0.14	115	1.75±0.13	0.013
Patients Treated at Least 183 Days	119	1.25±0.13	119	1.73±0.13	0.010
Patients Treated at Least 730 Days	99	1.23±0.15	109	1.74±0.14	0.015
Evaluable Patients Treated at Least 730 Days	90	1.21±0.16	106	1.76±0.15	0.011
All Patients with Imputation of Relapses	125	1.32±0.14	126	1.78±0.14	0.021
Evaluable Patients with Imputation of Relapses	105	1.39±0.15	115	1.86±0.15	0.026
Retrieved Dropouts: All Patients	125	1.22±0.13	126	1.68±0.13	0.011
Retrieved Dropouts: Evaluable Patients	105	1.30±0.14	115	1.75±0.14	0.021

[a] p-value for ANCOVA between treatment group analysis.

Source: Appendix K4.2.1.1.1 - K4.2.5.9.2

...ults – Core and Extension	Core Trial (24 Months)				Core Trial including Extension (up to 35 Months)				Reference (Vol/Pg)	
	COPAXONE (N=125)	Placebo (n=128)	Reduction vs. Placebo	P	COPAXONE (N=125)	Placebo (n=128)	Reduction vs. Placebo	P	Technical Section	Report
...l ...ed	1.19	1.88	-38%	0.007	1.34	1.88	-32%	0.002	157 001	042 107 084 074
...an	0.80	0.84			0.49	0.72				
...ge	33.6%	27.0%		0.086	33.6%	24.6%		0.035	157 001	042 109 084 076
...t	287	198		0.097	287	198		0.057	157 001	042 111 084 079
...s 	42 60 23	34 55 37		0.023	42 53 30	31 51 44		0.008	157 001	042 111 084 078
	78.4%	75.4%		0.476	78.6%	70.6%		0.189	157 001	042 112 084 080
...ge	-0.05	0.21		0.023	-0.11	0.34		0.020	157 001	042 113 084 081
...	0.28	0.26			0.28	0.36			157 001	042 115 084 084
...	24.8%	15.2%		0.024	27.2%	12.0%		0.001	157 001	042 114 084 083
...	54.4%	58.0%			54.4%	58.8%				
...	20.8%	26.8%			18.4%	31.2%				

...the extension phase.

Clinical Results – Core and Extension	Core Trial (24 Months)				Core Trial including Extension (up to 35 Months)				Reference (Vol/Pg)	
	COPAXONE (N=125)	Placebo (n=128)	Reduction vs. Placebo	P	COPAXONE (N=125)	Placebo (n=128)	Reduction vs. Placebo	P	Technical Section	Report
[illegible] Relapse	1.19	1.88	-39%	0.007	1.34	1.88	-32%	0.002	157 001	042 107 084 074
[illegible] Relapse	0.80	0.84			0.49	0.72				
[illegible] of relapse [illegible]	33.6%	27.0%		0.086	33.6%	24.6%		0.035	157 001	042 109 084 078
[illegible] time to first [illegible] (days)	287	198		0.097	287	198		0.057	157 001	042 111 084 079
[illegible] of relapses [illegible] patient 0 1-3 ≥3	42 60 23	34 56 37		0.023	42 53 30	31 51 44		0.008	157 001	042 111 084 079
[illegible] End-[illegible] Evaluation Day:										
[illegible] of [illegible]-free [illegible]	78.4%	75.4%		0.478	78.8%	70.8%		0.189	157 001	042 112 084 080
[illegible] EDSS change [illegible] baseline [illegible]	-0.05	0.21		0.023	-0.11	0.34		0.020	157 001	042 113 084 081
[illegible] Ambulation [illegible] Change from [illegible] [illegible]	0.28	0.28			0.28	0.36			157 001	042 115 084 084
[illegible] of [illegible] with:										
Improved disability (EDSS change ≤-1)	24.8%	15.2%		0.024	27.2%	12.0%		0.001	157 001	042 114 084 083
No change (EDSS change ≤0.5)	54.4%	58.0%			54.4%	58.8%				
Worsened Disability (EDSS change ≥ 1)	20.8%	28.8%			18.4%	31.2%				

Up to 35 months in the extension phase.

TAB E

REVIEW AND EVALUATION OF CLINICAL DATA: SAFETY

Application Information

NDA # 20-622

Sponsor: Teva Pharmaceuticals

Clock Date January 30, 1996

Drug Name

Generic Name: Copolymer 1

Proposed Trade Name: Copaxone

Drug Characterization

Pharmacological Category: Immunomodulator

Proposed Indication: Treatment of Multiple Sclerosis

NDA Classification:

Dosage Forms, Strengths, and Routes of Administration:
Subcutaneous injection, 20 milligram strengths.

Reviewer Information

Safety Reviewer: John Dikran Balian, M.D.

Review Completion Date: 3/14/96 Revised: 7/8/96

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1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system (CNS). Myelin basic protein (MBP), the protective sheath that surrounds the axons of the CNS is the target for demyelination in MS. The animal model for MS, experimental allergic encephalomyelitis (EAE) is an autoimmune neurological disease induced by injections of MBP. The immunological processes in EAE are similar to those seen in human MS patients.

Copolymer-1 (Cop-1) is a synthetic copolymer of 4 amino acids (L-alanine, L-lysine, L-glutamic acid and L-tyrosine) in specific ratios but random order. These same 4 amino acids form the basic composition of the MBP. Cop-1 has been shown to be effective against EAE, possibly via interference with the immunological processes presumed to induce MS.

It is hypothesized that the basis of the efficacy of Cop-1 lies in its cross reactivity with MBP. The pre-clinical study results indicated binding of Cop-1 to the MHC class II molecules on antigen presenting cells. This in turn produces two specific effects that ameliorate the pathogenesis of MS: 1) Cop-1 induces specific suppressor T-cells and 2) inhibits specific effector T-cells.

Cop-1 is thought to initiate its immunomodulatory action at the site of the injection. Therapeutic effects are then mediated by systemic distribution of locally activated T-cells. In vitro and in vivo animal studies provided evidence that the drug is rapidly degraded at the site of injection and components reaching the circulation most likely are inactive. Exposure of non-immune systems (heart, lung, liver, kidneys, etc.) to the parent compound appears unlikely. The relevant effects of any systemic distribution of the drug itself or its degraded components are unknown.

Extrapolating from animal studies, serum concentrations of the drug in humans should be low or not detectable following subcutaneous administration of 20 mg once-daily. Therefore, even if detectable, blood levels of Cop-1 or its metabolites would not be expected to predict therapeutic effect.

Following the above findings, the sponsor decided to develop this drug as treatment for MS. In the 70s, studies in humans were begun and after initial encouraging results the sponsor expanded the trials from small open label studies to a small pilot controlled trial. The sponsor reported a trend toward protection from increasing neurologic disability. A trial in chronic progressive (CP) MS patients failed to demonstrate a statistically significant slowing of progression, hence the trials were focused upon the relapsing-remitting (RR) MS patient

group. The RR-MS patient group was studied in a series of open labelled and uncontrolled trials, one small controlled trial (BR-1) and one larger controlled study (01-9001). Study 01-9001 is designated pivotal by the sponsor, because it represents close to 90% of the overall exposure in the placebo-controlled trials of the RR-MS patient group. Except for study BR-2, the placebo-controlled trial in CP-MS, all the trials were performed using a single dose (20 mg once daily).

The main adverse events reported, across all trials consisted of injection site reactions and transient reactions during which patients noted flushing, sweating, palpitations, a feeling of tightness in the chest, dyspnea and associated anxiety (these series of concurrent symptoms were later coined as "systemic reaction").

The local and "systemic reactions" seen in the early clinical trials prompted pre-clinical investigations designed to test the effect of Cop-1 on the various organ systems. No significant abnormalities were reported in the non-immune systems (cardiovascular, respiratory, etc.) of the animals studied. However, immune complex deposition in the glomeruli of kidneys from chronically dosed rats (6 mos) and monkeys (1 year) were noted.

A brief mention of pertinent positive findings in animal studies may be of use here, (for thorough evaluation of this area please refer to the pharmacology review). During the multidose toxicity studies of subcutaneous administration of Cop-1, the main adverse event noted was local lesions at injection sites. These appeared to be dose related. At doses of 50 mg/Kg the injection site reactions were poorly tolerated by rats. The other notable finding was in the area of immunotoxicity. Studies performed in rats, monkeys, guinea pigs and mice confirmed the antigenic properties of the study drug. All studies confirmed the formation of IgG after repeated administration of Cop-1.

In rats and monkeys, following chronic exposure of 30 mg/Kg for 1 year, evidence of immune complex deposition in the glomeruli of kidneys could be found as both drug and complement were found in the glomeruli of the kidneys. No pathological effects of immune complex deposition were reported. However, in support of immune complex disease, there were reports of fibroid arterial lesions with immunohistochemical evidence of Cop-1 and complement deposits in the glomeruli in monkeys and anti-DNA and anti-histone antibodies in both rats and monkeys. Other animal toxicity data revealed some transient effects such as arrythmic changes and hemodynamic changes in 2 dogs.

In the latest version of the annotated labeling (submitted 3/26/96), Copolymer-1 is described as an "immunomodulator that blocks myelin-specific autoimmune responses" with a mechanism of

action of ameliorating the pathogenesis of MS by binding to the MHC class II molecules on antigen presenting cells with two specific effects: 1) induction of specific suppressor T-cells, and 2) inhibition of specific effector T-cells. It is indicated for "slowing the progression of disability and reducing the frequency of relapses in patients with RR-MS". In the adverse events section of the labeling, there is special mention of injection site reactions and a "transient, self-limited reaction immediately following subcutaneous injection". A brief explanation of this "transient, self-limited reaction," without mention of the symptoms is also included in the labeling.

2 Sc for the Review

The NDA integrated safety summary (ISS), individual study summaries and reports, the data listings, Case Report Forms (CRFs), Patient Narratives (PNs), reports of deaths, premature terminations, common and serious adverse effects, overdose reports, and reports of treatment emergent changes in vital signs, clinical laboratory values, and ECGs were the sources used to review the safety aspects of this drug.

3. Methods of Review

For the safety review the entire database was evaluated for all adverse events, dropouts, uncommon and serious adverse events, suicides and deaths. Where appropriate, the overall data is mentioned in the review, but most tables presented in the review reflect data obtained from the placebo-controlled trials. Data from uncontrolled trials would not be useful to draw any comparisons with placebo. Also, a specific review of the most commonly reported adverse events (occurrence of >5% and 2 times placebo) noted in the placebo-controlled trials were reviewed specifically. The above results are discussed section by section below.

a. Quality of Submission

A critical review of the NDA and the data collection methods for the safety review was performed and the following can be reported:

a.1 Completeness of Submission

Overall, the submission meets the criteria noted in the 45 day refuse to file report of the DNDP for filing and review of the NDA. The Integrated Safety Summary (ISS) submitted is complete, but it is not a document that can be relied upon, because of its inadequate information contents and at least at one point contradictory data (inconsistent figures are given for patient exposure data). Because the ISS is not a reliable source for the review, I concentrated on the individual study reports, which are complete and adequate. The sposnsor was frequently contacted for clarification, confirmation, or reanalysis of specific areas and the sponsor was tremendously helpful.

The tables generally requested by the agency, such as 1% adverse events table and premature terminations table were properly presented by the sponsor. Line Listings of patients of special interest are listed, but not indexed properly for cross referencing. Patient Narrative Summaries of only premature terminations, deaths and hospitalizations are provided. All PNs provided were reviewed and the narratives were found to be sketchy and not comprehensive. PNs are not indexed properly for

cross referencing to locate the same individual in the data listings. The case report forms (CRFs) of deaths and dropouts are also provided. All CRFs of deaths and 20 dropouts (randomly selected) were reviewed. Most useful aspect of CRFs is the listing of reported adverse events, but to formulate a history or a "patient discharge summary" is not possible. The reported adverse events in the CRFs are not indexed to locate and verify the transferred information in the data listings.

There is a lack of information and follow-up regarding deaths. In three of the cases, it is not possible to draw clear conclusions regarding cause of death due to the lack of information in the CRFs and the FNs. Repeated requests made to the sponsor did not materialize in uncovering new information to clarify the histories of these deaths.

b. Quality of Coding

Investigator and patient descriptions for adverse events were categorized by the sponsor using the COSTART II dictionary. Data collection and tabulations of adverse events for the uncontrolled trials and the pivotal controlled trial 01-9001, were recorded directly from the CRFs (reported event, date of onset, duration, severity and outcome). For the other two controlled trials Br-1 and BR-2, information was gathered from CRFs designed to record adverse experiences through a set of symptom checklists. Adverse experiences data for BR-3 and the clinical pharmacology trials, were derived from clinical evaluation of source documents, publications or a letter from the investigator. All of these data were assigned preferred terms using COSTART terminology. Overall, it appears that the sponsor's coding approach was neither too conservative nor too inclusive.

c. Review of Study Design Adherence

The investigators and sponsor seem to have adhered to the protocol designs of all trials, and there is no evidence to the contrary.

There is a well devised plan in place to capture adverse events and to follow patients post termination (two follow-up visits, one 6 months and the second 12 months after termination are in the design of the studies) in the phase II-III trials. Patients who withdrew prematurely from any trial due to adverse experiences were characterized as those who either gave adverse experiences as their principal reason for withdrawal or who had data from the CRF indicating an adverse experience at the time of the withdrawal. Other categories for premature termination were (i)investigator decision based upon investigator's judgement that continued treatment was not in the best interest of the patient, (ii)pregnancy, (iii)poor compliance, (iv)progressive disease, (v)loss to follow-up, and (vi)patient decision (under this fall

patient's decision to discontinue for any reason other than adverse events).

Early phase II-III studies revealed no significant laboratory abnormalities, hence the investigators decided to perform laboratory testing at three to six month month intervals. However, due to the reported adverse events of local skin reactions and "systemic reaction"s in phase I studies and early phase II-III studies, the investigators made special note of capturing these adverse events in subsequent studies.

d. Review of Specific Definitions

Treatment emergent adverse events were interpreted properly by the sponsor: all adverse events, whether considered drug related or not were reported.

The term "systemic reaction" is an underlying theme throughout the ISS. This is a term or rather a case definition that the sponsor uses in an attempt to classify a confusing event, which has defied clinical description. This "systemic reaction" groups a series of adverse events that are "transient, self-limited reactions immediately following subcutaneous injection" of the drug. The issue of this "reaction" came to light in 1987, when Dr. Bornstein coined it as a "vasomotor response." Later, upon the suggestion of this division, clinical consultants devised a case definition for these concurrently occurring adverse events and the term "systemic reaction" was utilized as an umbrella for these events. The adverse events that characterize the case definition of "systemic reaction" are "vasodilatation or chest pain with palpitations, anxiety, and/or dyspnea". Hence any patient with a reported adverse event of vasodilatation or chest pain and an additional concomitant report of palpitations, anxiety, and/or dyspnea would be classified as a patient that experienced "systemic reaction". In this reviewer's opinion, the sponsor's arbitrary case definition for "systemic reaction" is restrictive. for example, the symptoms of "vasodilatation", chest pain, palpitations, anxiety, angioedema, flushing, urticaria, constriction of the throat and dyspnea might be all relevant. There appears to be a clear event that triggers the simultaneous appearance of some of these adverse events. A discussion with the sponsor to reach an appropriate case definition with a broader grouping of adverse events under this umbrella may be needed. This may facilitate future surveillance and reporting of the "systemic reaction".

Vasodilatation is a COSTART term that the sponsor has used as a blanket term to describe a multitude of reported events, such as "blood rushing to head, diffuse flush, face redness, flushed and warm skin" and many other symptoms that impart the idea of flushing, redness and warmth.

Angioedema was not listed as a COSTART term by the sponsor in the dictionary of adverse events of this submission. Additionally, "angioedema" was not among the patient or investigator reported adverse events, however there were symptoms listed under "vasodilatation" and "facial edema" that may be consistent with angioedema.

e. Findings From the Audit

An audit of CRFs and Patient Narratives (PNs) was performed, as mentioned above. A random sample was reviewed and there were no contradictions or misreporting.

Due to the lack of indexing and cross referencing, it is not possible to perform an audit to validate the proper transfer of the adverse events from the CRFs to the data listings.

4. Quality of Adverse Events Surveillance in the Development Program

A review of the CRFs revealed a rather thorough surveillance of the spontaneous reporting of the adverse events at every visit. But, it was not possible to certify the transfer of these reports to the data listings or verify their coding due to absence of cross-referencing and indexing. Aside from the spontaneous reporting system, surveillance or searches for specific adverse events were lacking. Another major weakness of the submission (this is common to almost all NDAs) is the total absence of clinical descriptions of the adverse events in the CRFs. Issues of co-morbidity, previous history, workup, follow-up, clinical characterization of a symptom, special testing, special treatment and start and stop dates of a symptom are usually not addressed in the CRFs. Occasionally, PNs may shed some light on these issues, but most PNs are very scanty and when not reflective of the contents of the CRF a reviewer can not determine their reliability. When the above were requested, the sponsor made a genuine attempt to be as comprehensive as possible and submitted a data listing of the adverse events that attempted to characterize them. But these were tables of the reported events, which revealed when and how often they occurred and whether the investigator considered them drug related or not. Although helpful, by no means these tables are explanatory when it comes to specific adverse events that need further investigation.

5. Study Population and Demographics

There are three adequate and well-controlled trials (01-9001 with its extension 9001E, BR-1 and BR-2) in this submission. The safety data presentations of this review will concentrate on these controlled studies, without disregarding the other studies and the entire safety database.

Study 01-9001, the largest of the controlled studies is a two-year, placebo-controlled, randomized, parallel-group, double-blind study involving 251 patients (Cop-1 125 and placebo 126). Patients 18-45 years of age, who met the protocol criteria of RR-MS were enrolled. Aside from the various efficacy outcome measures, the sponsor's safety analysis included looking at relapse episodes, hospitalizations, antibody levels, and clinically significant effects on vital signs, ECG or laboratory abnormalities. At the end of the two years of assigned treatment, the patients had the option of continuing on the same treatment under blinded conditions. 80% of Cop-1 patients and 83% of placebo patients from the original enrollment groups decided to extend their treatment for 35 months.

a. Extent of Exposure

The number of unique normal subjects and patients receiving Cop-1 worldwide is as follows:

Phase I (Clinical Pharmacology)

Drug	Number of Patients
Cop-1	49

Phase II-III (Clinical Trials)

Drug	Number of Patients
Cop-1	852
Placebo	206

The total clinical program (excluding the clinical pharmacology trials) consists of 11 clinical trials in which a total of 852 patients with MS have been exposed. Of 779 patients with RR-MS exposed to Cop-1, 670 were exposed for at least 6 months; 490 received the drug for at least 12 months, 290 for at least 2 years, 87 for at least 3 years, 15 for at least 5 years,and 4 for at least 10 years. With the exception of 63 patients in one trial in which the drug was administered at a dose of 20 mg every other day, all the rest were administered a single daily dose of 20 mg.

A total of 73 patients (BR-2 and BR-3) with CP-MS were exposed to Cop-1. In trial BR-2 the dose was 15 mg twice daily and in trial

BR-3, 20 mg once daily.

Due to missing data, precise information on patient years of exposure for the entire database is difficult to assess. Table 5.a.1 displays the exposure for the studies with reliable data:

Table 5.a.1
Duration of Patient Exposure in Patient Years

Type of Trial		COP-1	Placebo
Controlled Trials (9001/9001E, BR-1)	N Patient Years	150 338.7	151 356.2
Uncontrolled Trials (9002,1110-1,1110-2)	N Patient Years	586 753.7	0
Total	N Patient Years	736 1092.4	151 356.2

b. Extent of Exposure by Dose

Appendices 5.b.1 and 5.b.2 show the number of patients with RR-MS and CP-MS exposed to Cop-1. For all practical purposes, this NDA is a single dose exposure development (20 mg subcutaneous injections once daily).

c. Extent of Exposure by Disease Type

Relatively few patients with CP-MS were enrolled into the studies.

d. Demographics

Appendix 5.d.1 shows the demographics of all RR-MS studies, 5.d.2 the RR-MS controlled trials and 5.d.3 the CP-MS controlled trial. The RR-MS patients receiving the drug in these trials are representative in terms of demographic and disease characteristic of those likely to receive the drug after it is marketed. Each of the trials had more females than males, consistent with the overall MS population. The ages ranged from 18-68, with an average age of 30 years.

6. Review of Deaths

In the Cop-1 NDA, a total of 7 patient deaths were reported across all the clinical studies. These 7 deaths are summarized in Appendix 6.1. Two of the deaths were in RR-MS patients and the remaining five were from the CP-MS cohort.

There is no duration of exposure data from studies BR-3 and BR-2 (CP-MS trials), where 5 deaths occurred, hence it was not feasible to assess a crude rate of mortality and the mortality adjusted for time of exposure to drug. The 2 other deaths occurred in study 1110-1, an uncontrolled open label study. There were no deaths reported in the placebo group.

The patient narratives (PNs) and the CRFs on these patients are not very revealing. For all practical purposes, there is no information provided on one patient (#2039, study BR-3). For the rest, I relied upon sketchy PNs. Most had no post mortems performed. Patient #8501 from study 1110-1 may have had a post mortem (there are conflicting reports about whether there was a post mortem or not), in any case there is no appended report and the PN simply states that nothing significant was noted. The sponsor could not provide any further information on these deaths.

Two deaths are noteworthy for their possible association with a group of adverse events falling under the case definition of "systemic reaction" (discussed above and in greater detail below in section 10). Patient 01-2038 from study BR-3, a 46 year old male expired after approximately 3 years of treatment with Cop-1. 2 years into treatment, the patient started experiencing symptoms consistent with the description of "systemic reaction". The patient started reporting these symptoms two weeks prior to lapsing into an unexplained "coma". While hospitalized he continued receiving injections of Cop-1 and the family reported recurrences of the same symptoms (chest tightness, dyspnea with constriction of the throat and anxiety). The patient expired in the process of changing of his tracheostomy tube.

Patient 01-2039 from study BR-3, a 48 year old female expired after approximately 1.5 years of treatment with Cop-1. The case report form covers the treatment period up to two weeks prior to termination of study and a month prior to death. During this time, the patient reported symptoms consistent with the description of "systemic reaction" including constriction of the throat. There are no further details.

It is difficult to draw any conclusion regarding the causal relationship of the deaths to "systemic reaction", and hence to study medication.

7. Review of Serious Events

The Code of Federal Regulations (CFR) defines serious adverse events as "...any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose" (21 CFR § 312.32). Of note, there was an apriori arrangement between the sponsor and agency, where the sponsor was allowed to separate hospitalizations from serious adverse events. For example, if a patient suffered an MI and was subsequently hospitalized, the patient would be reported under the serious AEs for the MI. However, a patient hospitalized due to an accident would not be reported under the serious AEs but would be listed under hospitalizations. There is separate reporting for all hospitalized patients.

The overall incidence rates of serious adverse events were reported to be 6.5% (55/844) in the Cop-1 group and 6.8% (16/206) in the placebo group. There were no serious adverse events reported in study BR-1, while in the other two controlled trials the incidence was reported to be 28.6% (36/176) in the Cop-1 group and 12.7% (23/181) in the placebo group. The overall (including phase I) incidence rates of hospitalizations are reported to be 6.5% (58/893, of which 19 were secondary to aggravation of MS) in the Cop-1 group and 13.6% (28/206, of which 23 were secondary to MS) in the placebo group. In the controlled trials the incidence was reported to be 10.9% (22/201, of which 14 were secondary to MS) in the Cop-1 group and 13.6% (28/206, of which 23 were secondary to MS) in the placebo group.

Additionally, incidence rates of serious events (as defined by the CFR) are reported under specific headings (review of systems, etc.). It should be noted once again that most information (CRFs and PNs) is very sketchy, when available, and to draw conclusions as to whether an event is drug related or not is very difficult. Nonetheless, an attempt was made to classify the events as drug related or not and lists prepared (if a case falls under the related category, it simply means that in this reviewer's clinical jugdement from reading the sketchy PNs, there is no strong evidence to rule out disassociation from the drug). Appendices 13.1 and 13.2 display a listing of drug unrelated serious adverse events and hospitalizations and appendix 13.3 displays a listing of serious adverse events that may possibly be drug related. These appendices closely resemble the information and tables provided by the sponsor. In the text, some cases of interest that are thought to be possibly causally related to treatment are discussed (e.g. the two death cases). The incidence rates are low and not sufficient to relate causality on a statistical basis.

8. Review of Dropouts

a Overall Pattern of Dropouts

When all studies are taken into consideration, both controlled and uncontrolled, approximately 23.7% (200/844) of Cop-1 assigned patients dropped out (this probably reflects longer duration of treatment in the uncontrolled studies) and 16.0% (33/206) for placebo. The highest dropout rate in the placebo group is due to patient decision (8.74%), while the highest rate of dropout in the Cop-1 group is for adverse reactions (7.5%). Over the entire database, with 49 patients treated in clinical pharmacology studies and 844 in phase II-III studies, a total of 72 (72/893=8.1%) patients terminated prematurely due to an adverse event.

Table 8.a summarizes the reasons for patients's premature terminations in the database for the RR-MS controlled trials of the phase 2-3 studies:

Table 8.a
Distribution of Patients (RR-MS) who Prematurely Terminated Treatment

Reason	9001/9001E		BR-1		Total	
	COP-1 N=125	Placebo N=126	COP-1 N=25	Placebo N=25	COP-1 N=150	Placebo N=151
Adverse Experience	17	4	2	0	19	4
Investigator Decision	0	0	0	2	0	2
Patient Decision	7	17	0	1	7	18
Protocol Violation	0	6			0	6
Disease Progression	1	0			1	0
Treatment Failure	1	0			1	0
Lost to Follow-up	2	2			2	2
Unspecified			1	1	1	1
Total	28(22%)	29(23%)	3(12%)	4(16%)	31(21%)	33(22%)

In the RR-MS controlled trials the treatment groups of Cop-1 and placebo are similar in the total number of dropouts. The main reason for dropouts in the Cop-1 arm is adverse experience, while in the placebo, patient decision and protocol violation. The sponsor's explanation of "patient decision" is discontinuation by patient for any reason other than adverse events.

Table 8.b summarizes the reasons for patients's premature terminations in the database for the CP-MS controlled trials of the phase 2-3 studies:

Table 8.b
Distribution of Patients (CP-MS) who Prematurely Terminated Treatment

Reason Discontinued	BR-2	
	COP-1 (N=51)	Placebo (N=55)
Adverse Experience	6	1
Investigator's Decision	0	0
Patient Decision	4	5
Protocol Violation	0	1
Disease Progression	7	13
Treatment Failure	0	0
Lost to Follow-up	0	1
Unspecified	0	0
Total	17(33%)	21(38%)

In the Cop-1 arm of trial BR-2, the main reason for dropout is disease progression and adverse experience, while in the placebo, disease progression and patient decision.

b. Dropout Secondary to Adverse Events

Appendices 7.b.1 and 7.b.2 display all patients who dropped out secondary to an adverse event occurrence in the placebo-controlled studies. The most common adverse event associated with dropout was injection site reaction (all injection site reactions combined: 13/201=6.5% for Cop-1 and 2/206=1% for placebo, in trials 01-9001, BR-1 and BR-2). "systemic reaction" is not listed as a separate adverse event, but based on the definition of

"systemic reaction" not more than four patients could have dropped out secondary to "systemic reaction" from all three studies, since only one patient dropped out secondary to chest pain and 3 secondary to vasodilatation.

9. Other Safety Findings

a. ADR Incidence Table And AE Lists

Appendices 9.a.1, 9.a.2 and 9.a.3 display the incidence of adverse events in the placebo-controlled studies 01-9001, BR-1 and BR-2, respectively. Because of the small sample size and to avoid inclusion of every reported adverse event, for study BR-1 and BR-2 the usual ≥ 1% table was replaced with a ≥ 2% table. Pertinent adverse events are discussed in section 10.a under the review of systems.

b. Dose Response For Common Adverse Events

It is not possible to draw any conclusion about dose response relationships in this NDA, since all but one (BR-2) trials were fixed dose (20 mg/day).

c. Common and Drug Related Adverse Events

Adverse events with an incidence of ≥ 5% and reported at least twice as frequently in the Copolymer-1 group as in the placebo group are displayed in tables 9.c.1, 9.c.2 and 9.c.3.

Table 9.c.1
Controlled Study 01-9001/01-9001E

Body System	Adverse Experience	Number of Patients (%)	
		COP-1 (N=125)	Placebo (N=126)
Body as a Whole	chest pain	33 (26.4)	13 (10.3)
	face edema	11 (8.8)	2 (1.6)
	injection site erythema	73 (58.4)	17 (13.5)
	injection site hemorrhage	9 (7.2)	4 (3.2)
	injection site induration	25 (20.0)	1 (0.8)
	injection site inflammation	35 (28.0)	9 (7.1)
	injection site mass	33 (26.4)	10 (7.9)
	injection site pruritus	48 (38.4)	5 (4.0)
	injection site urticaria	9 (7.2)	0 (0)
	injection site welt	19 (15.2)	5 (4.0)
Cardiovascular	palpitation	14 (11.2)	6 (4.8)
	syncope	8 (6.4)	4 (3.2)
	vasodilatation	34 (27.2)	14 (11.1)
Metabolic and Nutritional	peripheral edema	14 (11.2)	7 (5.6)
	weight gain	7 (5.6)	0 (0)
Nervous	tremor	14 (11.2)	7 (5.6)
Respiratory	dyspnea	23 (18.4)	8 (6.3)
Skin and Appendages	erythema	8 (6.4)	4 (3.2)
Special Senses	eye disorder	8 (6.4)	1 (0.8)

Table 9.c.2
Controlled Study BR-1

Adverse Experience	Number of Patients (%)	
	COP-1 (N=25)	Placebo (N=25)
fever	2 (8.0)	0
injection site inflammation	22 (88.0)	4 (16)
injection site pain	23 (92)	9 (36,
injection site pruritus	3 (12)	0
injection site reaction	2 (8)	0 (0)
vasodilatation	3 (12)	0
vomiting	2 (8)	1 (4)
hypesthesia	2 (8)	1 (4)
insomnia	2 (8)	0
dyspnea	3(12)	0
pruritus	18 (72)	7 (28)

Table 9.c.3
Controlled Study BR-2

Adverse Experience	Number of Patients (%)	
	COP-1 (N=51)	Placebo (N=55)
Chills	3(6)	1(2)
infection	4 (8.0)	1(2)
injection site inflammation	41 (80.0)	9 (16)
injection site hemorrhage	3 (6)	1(2)
injection site pruritus	29 (57)	7(13)
injection site welt	3 (6)	0
injection site mass	19 (37)	9 (16)
vasodilatation	18(35)	7(13)
palpitation	14 (27)	6 (11)
pain	3 (6)	0

It is apparent that most of the adverse events reported, reflect the commonly experienced problems with injection site reactions and symptoms associated with "systemic reactions". The most commonly experienced adverse events such as injection site reactions, chest pain, eye disorder, etc. are discussed in section 10.a under the review of systems.

d. Adverse Event Incidence Over Phase 2-3 Integrated Primary Database

Appendix 9.d.1 includes all other adverse events reported from the clinical trials that are not reported in the incidence ≥ 1% table (Appendices 9.a.1, 9.a.2 and 9.a.3).

10. Review of Systems

In this section I will concentrate, system by system, on the commonly reported adverse events. However, aside from reporting incidence rates and occasional commentary, it is not possible to analyze specific AEs or cases. As mentioned in section 4, issues of co-morbidity, previous history, workup, follow-up, clinical characterization of a symptom, special testing, special treatment and start and stop dates of a symptom are not available. Aside from symptoms of injection site reactions and the "systemic reaction", 11 adverse events (eye disorder, weight gain, edema, facial edema, tremor, confusion, agitation, nystagmus, chest pain, syncope, and lymphadenopathy) were selected for specific analysis, because they were the most commonly reported adverse events in study 01-9001.

For an unknown reason, study 01-9001 had a higher reporting rate for all the commonly reported AEs, when compared to the other controlled trials or to the rest of the database. There was no specific analysis done by the sponsor to clarify the discrepancy in the reporting frequencies.

a.1 Neurology--Obviously, a thorough neurologic evaluation and reporting was performed at every visit to evaluate the effect of Cop-1 on the progression of MS. There were no seizures reported.

In study 01-9001, tremor (a COSTART term used by the sponsor that encompassed a series of reported events that included tremor, tremble, shaky feeling) was reported in 11.2% (14/125) of cop-1 patients and 5.6% (7/126) of placebo patients. In all controlled trials combined, tremor was reported in 7.5% (15/201) of cop-1 patients and 3.4% (7/206) of placebo patients. The incidence of tremor overall was reported to be 2.6% (22/844) of cop-1 patients and 3.4% (7/206) of placebo patients.

In study 01-9001, confusion (a COSTART term used by the sponsor that encompassed a series of reported events that included confusion, dazed, disorientation) was reported in 4% (5/125) of cop-1 patients and 0.8% (1/126) of placebo patients. In all controlled trials combined, confusion was reported in 3% (6/201) of cop-1 patients and 0.5% (1/206) of placebo patients. The incidence of confusion overall was reported to be 1.2% (10/844) of cop-1 patients and 0.5% (1/206) of placebo patients.

In study 01-9001, agitation (a COSTART term used by the sponsor that encompassed a series of reported events that included agitation, irritation, possible panic attacks, wired feeling) was reported in 5.6% (7/125) of cop-1 patients and 3.2% (4/126) of placebo patients. In all controlled trials combined, agitation was reported in 4.5% (9/201) of cop-1 patients and 1.9% (4/206) of placebo patients. The incidence of agitation overall was reported to be 1.4% (12/844) of cop-1 patients and 1.9% (4/206)

of placebo patients.

All three adverse events were COSTART terms for a series of symptoms reported. There were no specific tests done by the sponsor to study the three frequently reported neurological symptoms. In the overall database the incidence rate for serious AEs related to the nervous system was 1.7%(14/844) in the drug group and 2.9%(6/206) in the placebo group.

a.2 Opthalmology--Eye disorder was a COSTART term used by the sponsor that encompassed a series of reported events that included stye, eye irritation, eye contusion, "eye problems", etc.. In study 01-9001, eye disorder was reported in 6.4% (8/125) of cop-1 patients and 0.8% (1/126) of placebo patients. In all controlled trials combined, eye disorder was reported in 4.5% (9/201) of cop-1 patients and 0.5% (1/206) of placebo patients. The incidence of eye disorder overall was reported to be 1.1% (9/844) of cop-1 patients and 0.5% (1/206) of placebo patients.

Similarly with nystagmus. It was a COSTART term used by the sponsor that encompassed a series of reported events that included oscillocopsia, "eye problems", eye jerkiness, etc.. In study 01-9001, nystagmus was reported in 5% (4/125) of cop-1 patients and 1.6% (2/126) of placebo patients. In all controlled trials combined, nystagmus was reported in 2.5% (5/201) of cop-1 patients and 1.0% (21/206) of placebo patients. The incidence of nystagmus overall was reported to be 0.4% (3/844) of cop-1 patients and 1.0% (2/206) of placebo patients.

Both these AEs, almost exclusively, seem to be reported in study 01-9001. There were no specific tests done by the sponsor to study opthalmologic symptoms reported such as doing visual field studies. No serious AEs were reported for this system.

a.3 Psychiatry--There were no reported completed suicides in this NDA submission. One Cop-1 patient attempted suicide (overdose; patient #08-813 study 01-9001). The patient recovered without sequelae.

In a review of the patient narrative summaries, 3 more treatment emergent suicide attempts (overdoses using other drugs--patients 04-403 and 03-302 study 01-9001 and patient 01-106 study BR-2), and a patient (07-712, study 01-9001) with suicidal ideation were discovered. In the overall database the incidence rate for serious AEs related to psychiatry was 1.1%(9/844) in the drug group and 1.0%(2/206) in the placebo group.

a.4 Pulmonary--No specific tests done. Despite the frequently reported adverse event of dyspnea and/or "constriction of the throat" in association with "systemic reaction", there were no specific attempts made to do peak flows, spirometry or other studies to measure the presence and severity of bronchospasm. In

the overall database the incidence rate for serious AEs related to pulmonary was 0.4%(3/844) in the drug group and 0% in the placebo group.

a.4 Cardiovascular--As in pulmonary, symptoms associated with "systemic reaction" included chest tightness, palpitation and "vasodilation", but there was no cardiovascular testing beyond the ECG at the termination of the study.

Chest pain was a COSTART term used by the sponsor that encompassed chest pain and chest tightness. In study 01-9001, chest pain was reported in 26.4% (33/125) of cop-1 patients and 10.3% (13/126) of placebo patients. In all controlled trials combined, chest pain was reported in 22% (44/201) of cop-1 patients and 10.7% (22/206) of placebo patients. The incidence of chest pain overall was reported to be 10.3% (87/844) of cop-1 patients and 10.7% (22/206) of placebo patients.

This time, studies 01-9001 (33/125=26.4%) and BR-2 (11/51=21.5%) had a higher reporting rate of chest pain when compared to the rest of the database (none were reported in BR-1). There was no explanation regarding the discrepancy in the reporting frequencies in the different studies.

In trial 9001/9001E, there were 33 cases of chest pain (or tightness) in the cop-1 group. Included in these numbers are 6 cases that met the sponsor set criteria of "systemic reaction." In other words, of the 19 cases from trial 9001/9001E that the sponsor classified as experiencing ""systemic reaction"" 6 gave chest pain as their primary symptom. In all cases the chest pain was reported as a short episode (usually few minutes) not requiring therapeutic intervention.

As mentioned in section 4, there is total absence of clinical descriptions of the adverse events in the CRFs. When specific information regarding the chest pains were requested, the sponsor made a genuine attempt to be as comprehensive as possible and submitted a data listing of the adverse event that attempted to characterize them, but these were tables of the reported events, that revealed when and how often they occurred and whether the investigator considered them drug related or not. Although helpful, by no means these tables answer burning issues of interest.

In most instances the AE chest pain occurred while as an outpatient and the patient did not report the event until the next visit. There are no ECGs done while the episode was in progress and follow-up ECGs (when done at all, mostly done at study termination) were not significant. From all cases and reports reviewed, the indication is that the chest pain or tightness reported does not lead to any lasting cardiac injury. From the information provided, it is difficult to assess the

relationship of time of onset of chest pain to injection of the drug or placebo, although in some instances it is reported to occur immediately following injection, but for the vast majority this information is not provided. Most episodes appear to be brief, 2/3 of the cases are recurrent (on the average 3 episodes), very few cases discontinued secondary to this AE and few more had temporary interruption of treatment. Whenever available, the vast majority of follow-up ECGs are unchanged from baseline. There is also no evidence to support the hypotheses whether the drug may or may not cause transient ischemia from decreased perfusion of the cardiac muscles. Any thoughts regarding possible transient coronary vessel constriction (as may occur with cocaine or other drugs) can not be substantiated with the data provided. Further investigation of this issue is warranted.

In study 01-9001, syncope was reported in 6.4% (8/125) of cop-1 patients and 3.2% (4/126) of placebo patients. In all controlled trials combined, syncope was reported in 5% (10/201) of cop-1 patients and 2.4% (5/206) of placebo patients. The incidence of syncope overall was reported to be 1.3% (11/844) of cop-1 patients and 2.4% (5/206) of placebo patients. As is the case with chest pain, the causal relationship of syncopal events to cop-1 is difficult to assess.

In the overall database the incidence rate for serious AEs related to the cardiovascular system was 0.6%(5/844) in the drug group and 2.4%(5/206) in the placebo group. Chest pain itself was reported as a serious event in only 2 patients in study 01-9001/9001E.

a.5 Renal--There was no specific testing done, such as looking for immune complex disease on autopsy specimens.

a.6 Gastrointestinal--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to this system was 1.4%(12/844) in the drug group and 1.0%(2/206) in the placebo group.

a.7 Musculoskeletal--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to this system was 1.4%(12/844) in the drug group and 0% in the placebo group.

a.8 Hematologic--No specific focus in AE surveillance or conduct of specific testing (such as biopsy) despite the appearance of lymphadenopathy as a frequent AE.

Lymphadenopathy was a COSTART term used by the sponsor that encompassed a series of reported events that included swollen neck lymph glands, groin lymphadenopathy, lump in the groin, lump

in the left lower quadrant, submandibular swelling, etc.. In study 01-9001 lymphadenopathy was reported in 18.4% (23/125) of cop-1 patients and 9.5% (12/126) of placebo patients. All controlled trials combined, lymphadenopathy was reported in 12.4% (25/201) of cop-1 patients and 5.8% (12/206) of placebo patients. The incidence of lymphadenopathy overall was reported to be 4.3% (36/844) of cop-1 patients and 5.8% (12/206) of placebo patients. Again, the causal relationship of lymphadenopathy events to cop-1 is difficult to assess.

In the overall database the incidence rate for serious AEs related to the hematologic/lymphatic system was 0.2%(2/844) in the drug group and 0% in the placebo group. One of these cases is of interest: Patient 707, study 01-9001, was a 26 year old female that after 39 days of cop-1 treatment experienced enlarged lymph nodes that increased in size with continued treatment. Upon a temporary stoppage of treatmment due to an unrelated event, the lymph nodes decreased in size. Upon rechallenge, the lymph nodes once again were enlarged. An excision biopsy revealed "reactive nodes in the left groin and the remaining nodes were benign". Although, the PN mentions a pathology report, it was not attached and the sponsor states that there is no more information at hand.

a.9 **Body as a Whole**--No specific focus in AE surveillance or conduct of specific testing.

In study 01-9001, weight gain was reported in 5.6% (7/125) of cop-1 patients and 0% (0/126) of placebo patients. In all controlled trials combined, weight gain was reported in 3.5% (7/201) of cop-1 patients and 0 (0/206) of placebo patients. The incidence of weight gain overall was reported to be 1.4% (22/844) of cop-1 patients and 0% (0/206) of placebo patients.

In study 01-9001, edema was reported in 4% (5/125) of cop-1 patients and 0.8% (1/126) of placebo patients. In all controlled trials combined, edema was reported in 2.5% (5/201) of cop-1 patients and 0.5% (1/206) of placebo patients. The incidence of edema overall was reported to be 1.4% (12/844) of cop-1 patients and 0.5% (1/206) of placebo patients.

In study 01-9001, facial edema was reported in 8.8% (11/125) of cop-1 patients and 1.6% (2/126) of placebo patients. In all controlled trials combined, facial edema was reported in 6% (12/201) of cop-1 patients and 1.0% (2/206) of placebo patients. The incidence of facial edema overall was reported to be 1.8% (15/844) of cop-1 patients and 1.0% (2/206) of placebo patients. There were no cases of angioedema reported and angioedema was not listed under the AEs in the sponsor's dictionary.

All three adverse events were COSTART terms for a series of symptoms reported. Once again, study 01-9001 had a higher reporting rate when compared to the other controlled trials and

to the rest of the database. There were no specific tests done by the sponsor to either clarify the discrepancy in the reporting frequencies or to study the reported events.

In the overall database the incidence rate for serious AEs related to the body as a whole was 4.5%(38/844) in the drug group and 3.4%(7/206) in the placebo group.

a.10 Endocrine/Metabolic--No specific focus in AE surveillance or conduct of specific testing. In the overall database the incidence rate for serious AEs related to this system was 0.2%(2/844) in the drug group and 0% in the placebo group.

a.11 Immunology

Human allergic reactions are caused by immediate release of mediators from mast cells and basophils after interaction with an antigen. These mediators, such as histamine, induce the characteristic clinical signs and symptoms of the allergic response. Activation of the mediators can be both immunologic (IgE) and non-immunologic (direct activation by the agent without antibody involvement). For the immunologic process, prior exposure to the antigen is necessary (Anderson, JAMA 1992; Champion et al. Br J Dermatol 1969).

Considering the mechanism of action of Cop-1 (activation of T-cells), and the two most common adverse events ("systemic reaction" and injection site reaction), the critical issue becomes whether an immunologic process is responsible for these effects. A series of studies were performed by the sponsor in an attempt to discover an etiology for these reactions and thus an explanation whether the drug is immunogenic or not.

In one such study (placebo-controlled trial 01-9001), serum samples were monitored every 3 months for the development of Cop-1 reactive antibodies. Results revealed that, antibody levels reached maximum values within 3-6 months of exposure. 80% of the patients experienced increases of >150% over baseline levels. These levels declined subsequently to around 50% above baseline values in majority of the patients. Placebo treated patients did not experience a significant or consistent response. The peak antibody levels in the placebo group (in 80% of the patients were below 50% over baseline values) were not as high as in the Cop-1 group. Also the peaks in the placebo group were random and occurring at random timepoints. There is evidence (from animal and human data) that the Cop-1 reactive antibody is IgG and not IgE.

Another small study revealed that Cop-1 induced histamine release from basophils only at very high concentrations: concentrations much higher than would be expected from regular dosing of 20 mg/day.

Skin testing of intradermal injections of Cop-1 caused a positive reaction (a wheal of >5mm) in naive as well as in previously exposed patients; prior administration of an antihistaminic agent (terfenadine) greatly reduced the size of the skin wheal.

Based upon the in vitro, preclinical and above mentioned data, the sponsor claims that the clinical picture is not consistent with an allergic sensitization, as there is no memory response and no associated symptoms. The sponsor goes on to conclude that, the formation of antibodies is a "simple manifestation of its bioavailabity and antigenicity and is not related to allergic sensitization", and the decline in antibody levels upon continued treatment reflects the tolerance of the antibody producing system. The sponsor deduces that the antibody is neutral: it does not interfere with the activity of the drug. The evidence supporting this claim comes from observation that (i)no matter how high the antibody levels, they do not interfere with the mechanism of action of the drug (activation of T-cells); and (ii)efficacy data reveal continued effectiveness with continued exposure to the drug even at highest levels of antibody levels.

The sponsor claims that no correlation was evident between antibody levels and episodes of "systemic reaction"s. Also there was no correlation between relapses and reactive antibody levels. However, in a somewhat inconsistent finding with the above statement, one small study revealed higher IgG levels among patients with systemic symptoms than those without adverse events. The sponsor has no explanation for this finding.

In this reviewer's opinion, the symptoms associated with "systemic reaction" are consistent with a generalized drug reaction. It is also apparent that there is activation of basophils and mast cells by Cop-1. The studies conducted and the many reported adverse events confirm these statements. To determine whether an immunologic process (such as systemic anaphylaxis) or a non-immunologic process (such as generalized anaphylactoid reaction) is responsible for the effects of the drug, more data is needed. There are studies and laboratory tests confirming the absence of IgE in the process. Hence, to refute the sponsor's claim (that the drug is not immunogenic) is difficult.

Another concern with this drug are the reports from animal studies (rats and monkeys) that, following chronic exposure, both drug and complement were found in the glomeruli of the kidney. No pathological effects of immune complex deposition were reported. However, in support of immune complex disease, there were reports of fibroid arterial lesions in a number of monkeys and anti-DNA and anti-histone antibodies in both rats and monkeys. There are no human studies that investigated autoimmune disorders or immune complex disease. There is no evidence that Cop-1 causes general immunosuppression, as there are no reports of increased

infections in the treated group.

There were no reported serious AEs under this system by the sponsor, however there were two cases that were reported as serious AEs and may be classified under this section: Patient 02-1, study BR-1 "experienced sweating, anxiety, vasodilatation and sensitivity at the injection site and syncope." Patient improved with treatment for anaphylaxis and was not discontinued. This AE could very well have been a "systemic reaction", but it did not qualify as defined by the sponsor; and Patient 8428, study 1110-1, was a 31 year old female that after 25 day of cop-1 treatment experienced sysmptoms of injection site erythema and hypersensitivity lasting 2 days. 8 days later experienced the same symptoms and was given a diagnosis of "serum sickness (arthus phenomenon)". Patient improved with discontinuation.

a.11.1 "systemic reaction"

"Systemic reaction" is the "adverse event" of greatest notoriety in this submission. This is a term or rather a case definition that the sponsor uses in an attempt to classify a confusing event, which has defied clinical description. As mentioned before, this "systemic reaction" was an arbitrary definition used by the sponsor that attempts to group a series of adverse events that are "transient, self-limited reactions immediately following subcutaneous injection" of the drug. The term "systemic reaction" was utilized as an umbrella for the concurrent AEs of "vasodilatation or chest pain with palpitations, anxiety, and/or dyspnea". Hence any patient with a reported adverse event of vasodilatation or chest pain and a simultaneous report of palpitations, anxiety, and/or dyspnea was classified as a patient that experienced "systemic reaction."

Vasodilatation is a COSTART term that the sponsor has used as a blanket term to describe a multitude of reported events, such as "blood rushing to head, diffuse flush, face redness, flushed and warm skin" and many other symptoms that impart the idea of flushing, redness and warmth. Angioedema is not listed as a COSTART term by the sponsor in the dictionary of adverse events of this submission. Additionally, "angioedema" is not among the patient or investigator reported adverse events, however there are symptoms listed under "vasodilatation" and "facial edema" that may be consistent with angioedema.

As presented in the ISS (using the sponsor's case definition), no episodes of "systemic reaction" were reported in the clinical pharmacology studies and of 844 patients in the clinical trials, 87 (10.31%) reported at least one such episode. Of these 87 patients, 52 reported only one episode, 17 had two episodes, 11 had three, 4 had four, 2 had five, no patient reported 6 episodes and one patient reported a total of 7 episodes.

Table 10.b.1 documents the incidence of "systemic reaction"s in study # 01-9001.

Table 10.b.1

"systemic reaction"	Cop-1 (N=125)	Placebo (N=126)
Number of Patients	19 (15.2%)	4 (3.2%)
Number of Episodes		
1	10	4
2	4	0
3	3	0
4	1	0
7	1	0

The 4 placebo patients in this table also met the sponsor set criteria of "systemic reaction".

In this reviewer's opinion, the sponsor's arbitrary case definition for "systemic reaction" is restrictive in the number of symptoms used under its umbrella. The symptoms of "vasodilatation", chest pain, palpitations, anxiety, angioedema, flushing, urticaria, constriction of the throat and dyspnea may be all reflective of "systemic reaction" and relevant to this "adverse event". For example, if any three of these symptoms qualified as a "systemic reaction" the incidence then will be higher. Appendix 10.b.1 displays such a list of patients that could be designated as having experienced "systemic reaction." This list was compiled from patient narratives of only two groups: premature terminations and hospitalizations. This list reveals a high frequency of recurrent episodes of this adverse event. Obviously, the list is not comprehensive.

It is apparent that these reactions may occur at any time interval during exposure and may occur only once or may have an irregular episodic pattern. Of special note, the time to first occurrence of most cases of the "systemic reaction" averages several months after initiation of cop-1, and as mentioned earlier, some experience only one episode while it is recurrent with others.

Aside from the case definition and the true etiology of this "systemic reaction," the question arises, as to whether the grouping of the individual adverse events that designate this "syndrome or systemic reaction" is misleading. The individual adverse events may completely be separate entities occurring together only coincidentally. This scenario is highly unlikely. But, in view of the seriousness of adverse events such as chest pain, it is only wise to consider this possibility. Also, the two death cases discussed in section 6, though can not be directly

linked to "systemic reaction", are worisome and a relationship can not be ruled out, in view of lack of details.

Although there is no evidence to support it, the sponsor puts forth a hypothesis that a possible trigger of the events may be secondary to injecting the drug into the wrong location (blood vessels instead of subcutaneously). Ascribing a causal relationship of the "systemic reaction" to the study drug is not in dispute. The difficulty lies in describing an etiology for it. The majority of cases may fall into the category as defined by the sponsor: "simple manifestation of its bioavailabity and antigenicity and is not related to allergic sensitization"--most likely mediated by non-immunologic mechanisms, i.e. direct activation of mediators.

There are few cases where an explanation of a true allergic manifestation (urticaria, angioedema, bronchospasm, etc.) of Cop-1 is plausible. In others, the possibility of immune-complex disease should also merit consideration. In some animal studies, there was evidence of immune complex formation and complement deposition. From the available human data, it is difficult to confirm this hypothesis, since there are no skin biopsies, renal tests, and autopsies provided on these patients. For immune-complex formation a high antigen load is necessary. There is evidence of rise in IgG antibody, but with continued treatment there is a decline in the levels. There are also conflicting reports of the association of IgG levels with the adverse event. Also, the almost always prevalent symptom of fever in immune-complex disease was missing in these patients.

The sponsor concludes that the "systemic reaction" is non-immunologic. I would venture that different patients may react differently: in some, drug allergy is a possibility, in the majority, it very well may be a non-immunologic process, and in others, immune-complex disease can not be ruled out. Currently, there is no convincing human data to support any of these hypotheses.

a.12 Skin--In the overall database the incidence rate for serious AEs related to this system was 0.4%(3/844) in the drug group and 0% in the placebo group. Most noteworthy issue here is the injection site reactions:

a.12.1 Injection Site Reaction

The most commonly occurring adverse events attributable to cop-1 were reactions at the site of injection (the incidence in study 01-9001/9001E was 90% of patients treated with cop-1 and 60% of patients treated with placebo). These are also the most common AEs associated with premature discontinuations. Injection site pain, erythema, pruritus and ecchymosis were the major complaints.

The joint occurrence of injection site reactions to "systemic reaction" was examined to analyze a possible relationship. In study 01-9001/9001E, of the 19 patients that reported "systemic reaction" only 5 reported any moderate or severe local injection site reaction, and only one of the five reported the two events at the same time. It does not appear that experiencing a moderate or severe local injection site reaction is predictive of "systemic reaction".

The presentation of timing of symptoms and severity varied from immediate reactions post injection to reactions appearing with chronic exposure. As in the case of "systemic reaction" there is no evidence to support or refute the sponsor's claim that a possible trigger for this adverse event may be the injection of the drug into the wrong location (blood vessels instead of subcutaneously). It is the sponsor's claim that the immediate local reaction is most likely mediated by non-immunologic mechanisms, i.e. direct activation of mediators and release of histamine by Cop-1 without IgE release. Unfortunately, no skin biopsies were done on these cases to shed more light on this issue.

11. Laboratory Findings, ECG and Vital Signs

a. Laboratory Findings

The sponsor has submitted an analysis of the laboratory data and tabulated the results. The sponsor has not used the analysis approach recommended by this division: incidence tables, tabulations of the statistical summary of mean changes from baseline or other shift tables. Nonetheless, since there are no significant abnormalities noted in my review, it was decided not to make a request to reanalyze the data, but simply to document the findings. In the controlled trials, laboratory testing was performed at every visit (every three months), while in the other studies laboratory testing was done at 3-6 month intervals. Under th e laboratory section only one placebo patient was reported with a serious chemistry AE. The data of the controlled trials (as presented below) reflects the overall database and no particular issues of concern were noted.

a.1 Serum Chemistry

Appendix 11.a.1.1 lists the criteria (used by DNDP) and incidence of clinically significant chemistry laboratory abnormalities in the controlled trials. As this table indicates, there are no areas of concern regarding chemistry abnormalities in the available data and none of the changes can be causally ascribed to Cop-1.

a.2 Hematology

Appendix 11.a.2.1 lists the sponsor's criteria and incidence of clinically significant hematology laboratory abnormalities in the controlled trials. As this table indicates, there are no areas of concern regarding hematology abnormalities in the available data and the changes can not be causally ascribed to Cop-1.

a.3 Urine Analysis

There were no reports of serious adverse experiences or premature terminations due to abnormalities in urinalysis parameters. For this section, no individual cases were reviewed. From the available data it is apparent that no particular urine analysis abnormality can be attributed to Cop-1.

b. ECG Findings

ECGs, at baseline and termination were performed in the large controlled trial 01-9001/9001E. A review of each ECG abnormality reported, revealed no particular tendencies and no overall increase of adverse events were noted when compared to placebo.

Cop-1 does not appear to induce heart rate, PR, QRS, or QTc

interval abnormalities.

c. Vital Signs

Appendix 11.c.1 lists the criteria and incidence of clinically significant Vital Signs abnormalities in the controlled trials. Evaluation of postbaseline shifts for vital signs disclosed no differences between the Cop-1 and the placebo groups.

In animal studies, hypotensive effects were reported. Also, from human cell culture studies, Cop-1 was shown to induce release of interleukin-2, a cytokine that can initiate the release of other cytokines that may destabilize the cardiovascular system. Despite these findings, there is no clinical data to raise concern.

12. Effect of Age and Gender on Adverse Event Incidence

Age based analysis is not possible to perform. There was only one patient above the age of 65 enrolled in the clinical trials. No reliable analyses of adverse event incidences on the basis of gender were performed. Tabulations provided by the sponsor revealed that in the large placebo-controlled trial few more females receiving cop-1 reported "vasodilatation and lymphadenopathy".

13. Important Events Considered Not Drug Related

The definition of a serious adverse event is given above in section 9. All CRFs and patient narratives provided on serious adverse events and hospitalizations were reviewed and appendix 13.1 displays a listing of such adverse events for Cop-1 that in this reviewer's opinion are not attributed to treatment. Also, appendix 13.2 displays a listing of hospitalizations that in this reviewer's opinion are not attributed to treatment. Please note that fatalities have already been included in Appendix 6.1 and are not repeated in Appendices 13.1 and 13.2.

14. Human Reproductive Data

Pregnancy was an exclusion criterion for enrollment. Seven patients became pregnant while being treated with Cop-1 in the phase II-III studies.

Three of the patients elective terminated the pregnancies. Three other patients withdrew form the study after 424, 714 and 905 days of treatment and their pregnancies were uneventful resulting in births of normal healthy babies. No information is available regarding the seventh patient.

15. Overdose Experience

During the worldwide development of Cop-1 there was one attempted overdose using Cop-1 as the agent. Patient 08-813 from study 01-9001 injected four doses (80 mg total) of Cop-1 with no reported adverse events.

16. Withdrawal Phenomenon/Abuse Potential

No specific studies to evaluate the effects of withdrawal from Cop-1 were performed.

In addition, the sponsor does not report any studies to evaluate instances of Cop-1 abuse or dependence. There was lack of voluntary and persistent dose escalation by patients. Overall, there seems to be no evidence of withdrawal phenomenon or abuse potential for this drug.

17. Summary of Drug Interactions

a. Drug-Demographic Interactions

The sponsor has not performed any studies to assess the effects of age on the pharmacokinetics of Cop-1.

b. Drug-Disease Interactions

The sponsor has not performed any studies to explore drug-disease interactions.

c. Drug-Drug Interactions

The sponsor has not performed any studies to explore interactions of Cop-1 with other drugs.

18. Labeling Review

The latest version of the annotated labeling (submitted 3/26/96), falls short on a clear discription and definition for the "systemic reaction", calling it a "transient, self-limited reaction". Also, there are no highlights of the commonly occurring AEs, except for the presentation of the >2% incidence AE table of AEs from study 01-9001/9001E.

19. Conclusions

Cop-1 is a synthetic basic copolymer of random amino acids that has been shown to be effective in suppression of EAE and is presented in this NDA as a candidate drug for the treatment of RR-MS.

Cop-1 is thought to initiate an immunomodulatory action at the site of injection. Therapeutic effects are then mediated by systemic distribution of locally activated T-cells. Based on animal studies, the drug is rapidly degraded at the site of injection and serum concentrations of the drug in humans are presumed to be low or undetectable following subcutaneous administration of 20 mg once-daily.

Ascribing a causal relationship to the treatment emergent adverse events grouped under the sponsor's definition of "systemic reaction" and injection site reaction seen with cop-1 is not in dispute, but describing an etiology is elusive. There are few cases where an explanation of a true allergic manifestation of Cop-1 is plausible. The majority of cases may fall into the category as defined by the sponsor "simple manifestation of its bioavailabity and antigenicity and not related to allergic sensitization": most likely mediated by non-immunologic mechanisms, i.e. direct activation of mediators. The sponsor concludes that the treatment emergent adverse events are non-immunologic.

Ascribing a causal relationship to the other commonly reported treatment emergent adverse events such as chest pain is not possible with the data and explanations available. In summary, the main safety concerns for this NDA are the AEs grouped by the sponsor as "systemic reaction" and injection site reactions. More data is needed to determine whether an immunologic process (such as systemic anaphylaxis) or a non-immunologic process (such as generalized anaphylactoid reaction) is responsible for the effects of the drug. Hence, to refute the sponsor's claim that the drug is not immunogenic is difficult.

20. Recommendations

In my opinion, the New Drug Application for Cop-1 is approvable from a safety standpoint if the efficacy review finds the drug to

be efficacious. However, to further support the safe and effective use of Cop-1, it is recommended that the following issues be explored by the sponsor:

(i) A cla. ification of the pharmacokinetics of the drug in humans. There is evidence from rat studies that with chronic exposure the systemic distribution of larger components of the drug increases;

(ii) Dose-response and dose-ranging studies should be performed. Is 20 mg the optimum dose? Are daily injections necessary?

(iii) A study to rule out autoimmune disease in humans. There were reports of fibroid arterial lesions in a number of monkeys and anti-DNA and anti-histone antibodies in both rats and monkeys;

(iv) A study to rule out immune complex disease in humans. In animal studies (rats and monkeys), following chronic exposure, both drug and complement could be found in the glomeruli of the kidney;

(v) A study to clarify the etiology of injection site reactions. This may be in the form of skin biopsies;

(vi) A study to characterize and understand the adverse event "chest pain/tightness" to rule out transient ischemic changes;

(vii) A study to better characterize and understand the ""systemic reaction"s" after an agreed upon case definition is formulated;

(viii) Postmarketing surveillance for evidence of vasculitis, immune complex disease, autoimmune disease, serum sickness glomerulonephritis, or other systemic effects of immune mediated diseases;

(ix) A discussion with the sponsor to reach an appropriate case definition for ""systemic reaction"". A broader grouping of adverse events under this umbrella may be necessary. This may facilitate future surveillance and reporting of the ""systemic reaction""; and

(x) Revise the labeling.

John D. Balian, MD 7/8/96

John Dikran Balian, M.D. Date
Clinical Reviewer Safety Group,
Div. of Neuropharmacologic Drug Products

Orig. NDA 20-622;
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APPENDICES

APPENDIX 5.b.1

Number of Patients with RR-MS Exposed to 20 mg Cop-1 Daily - Duration of Exposure (Trials 01-9001/9001E, BR-1, 01-9002, 1110-1, 1110-2, BR-3)

Months	Patients in Study at each Interval
<6	779
≥6-<12	670
≥12-<18	490
≥18-<24	334
≥24-<30	290
≥30-<36	175
≥36-<42	87
≥42-<48	50
≥48-<54	33
≥54-<60	15
≥60-<72	15
≥72-<84	4
≥84-<96	4
≥96-108	4
≥108-<120	4
≥120	4
Total Patient Years	1092

APPENDIX 5.b.2
Duration of Exposure: 30 mg Cop-1 Daily
CP-MS[a], Controlled Study BR-2

Months	Number of Patients in Study at each Interval	
	COP-1	Placebo
<6	51	55
≥6-<12	45	52
≥12-<18	41	43
≥18-<24	38	37
≥24-<30	21	18

[a]Total patient months were not calculated because precise start/stop dates are not available for any patient.

APPENDIX 5.d.1
Demographics
All Studies in RR-MS Patients
(9001/9001E, BR-1, 9002, 1110-1, 1110-2 and BR-3)

Characteristic	COP-1	Placebo
Age (years) Mean ± SD Range	N = 779 36.8 ± 9.0 18 - 68	N = 151 33.6 ± 6.1 19 - 46
Weight (kg)[a] Mean ± SD Range	N=696 69.2 ± 14.9[a] 39.0 - 131.8[a]	N=151 67.4 ± 16.1 40.9 - 136.8
Sex Male N (%) Female N (%)	N=729 255 (33) 517 (67)	N=151 40 (27) 111 (73)
Race [b] Caucasian N (%) Non Caucasian N (%) Unknown [c] N (%)	N=426 366 (86) 20 (5) 40 (9)	N=151 143 (95) 8 (5)

[a] Data are not available in study BR-1 and BR-3
[b] Data are not available in studies 1110-1 and 1110-2.
[c] Study BR-3

APPENDIX 5.d.2

Demographics
Controlled Studies in RR-MS Patients
(9001/9001E and BR-1)

Characteristic	COP-1 (N=150)	Placebo (N=151)
Age (years) Mean ± SD Range	 33.8 ± 5.6 19 - 46	 8±6.1 19 - 46
Weight (kg)[a] Mean ± SD Range	 70.5 ± 17.0 41.7 - 126.8	 67.4 ± 16.1 40.9 - 136.8
Male N (%) Female N (%)	48 (32) 102 (68)	40 (26) 111 (74)
Caucasian (%) Non Caucasian (%)	141 (94) 9 (6)	143 (95) 8 (5)

[a] Data are not available in studies BR-1 and BR-3

APPENDIX 5.d.3

Demographics
Controlled Study in CP-MS Patients
(BR-2)

Characteristic	COP-1	Placebo
Age (years) Mean ± SD	N=51 41.6 ± 9.0	N=55 42.3 ± 8.2
Sex Male N (%) Female N (%)	N=51 23 (45.1) 28 (54.9)	N=55 25 (45.5) 30 (54.5)
Race Caucasian N (%) Non Caucasian N (%)	N=51 48 (94.1) 3 (5.9)	N=55 54 (98.2) 1 (1.8)

APPENDIX 6.1
SUMMARY OF PATIENT DEATHS

Study Number	Patient Number	Treatment Group	Age	Sex	Months in Study	Highest Dose (mg/day)	Cause of Death
BR-2	01-578	Cop 1	33	Male	11	30	Complications of neuroglioblastoma (6 months following premature termination)
BR-3	2038	Cop 1	46	Male	22	20	Complications of tracheostomy change
	2049	Cop 1	41	Female	36	20	Pneumonia
	2051	Cop 1	59	Female	36	20	Colon Malignancy
	2039	Cop 1	48	Female	19	20	Unknown
1110-1	8417	Cop 1	40	Female	796 Days	20	Unspecified
	8501	Cop 1	43	Female	-	20	Unspecified (Pneumonia and sepsis)

Appendix 7.b.1
Adverse Experiences for which any Patient Discontinued Therapy

Body System	Adverse Experience	9001/9001E		BR-1	
		COP-1 N=125	Placebo N=126	COP-1 N=25	Placebo N=25
Body as a Whole	Bacterial Infection	1	0	0	0
	Chest Pain	1	0	0	0
	Face Edema	1	0	0	0
	Infection	1	0	0	0
	Injection Site Atrophy	2	0	0	0
	Injection Site Erythema	1	0	0	0
	Injection Site Induration	2	0	0	0
	Injection Site Inflammation	1	0	0	0
	Injection Site Pain	2	2	0	0
	Injection Site Urticaria	1	0	0	0
	Unspecified	2	0	1	0
Cardiovascular	Syncope	1	0	0	0
	Vasodilatation	2	1	0	0
Digestive	Nausea	1	0	0	0
	Vomiting	1	0	0	0
Hemic and Lymphatic	Lymphadenopathy	1	0	0	0
	Splenomegaly	1	0	0	0
Nervous	Depression	1	0	0	0
	Psychotic Depression	1	0	0	0
Respiratory	Dyspnea	2	1	0	0
Skin and Appendages	Rash	1	0	0	0
	Urticaria	2	0	0	0
Urogenital	Unintended Pregnancy	3	0	0	0

Appendix 7.b.2
Adverse Experiences For Which Any Patient Discontinued Therapy, Study BR-2*

Body System	Adverse Experience	COP-1 (N=51)	Placebo (N=55)
Body as a Whole	asthenia	1	0
	injection site inflammation	2	0
	injection site pain	1	0
	injection site welt	1	0
	injection site mass	1	0
	neoplasm	1	0
	suicide attempt	1	0
Cardiovascular	hypotension	1	0
	palpitations	1	0
	tachycardia	2	0
	vasodilatation	1	0
Nervous	anxiety	1	1
	depression	1	0
	dizziness	2	0
	hypertonia	1	0
	tremor	2	0
Skin and Appendages	pruritus	1	0

*Chronic Progressive MS study

Appendix 9.a.1
Incidence of Adverse Clinical Experiences (≥ 1%)
Controlled Study 9001/9001E

Body System Adverse Clinical Experience	Copolymer-1 (N=125)		Placebo (N=126)	
	N	%	N	%
Body as a Whole				
Abdominal Pain	16	12.8	14	11.1
Abscess	3	2.4	0	0
Allergic Reaction	2	1.6	2	1.6
Allergic Rhinitis	9	7.2	7	5.6
Asthenia	81	64.8	78	61.9
Back Pain	33	26.4	28	22.2
Bacterial Infection	11	8.8	9	7.1
Chest Pain	33	26.4	13	10.3
Chills	5	4.0	1	0.8
Cyst	5	4.0	1	0.8
Drug Reaction	2	1.6	1	0.8
Face Edema	11	8.8	2	1.6
Fever	15	12.0	13	10.3
Flank Pain	2	1.6	1	0.8
Flu Syndrome	38	30.4	34	27.0
Headache	76	60.8	75	59.5
Injection Site Atrophy	3	2.4	0	0
Injection Site Erythema	73	58.4	17	13.5
Injection Site Hemorrhage	9	7.2	4	3.2
Injection Site Induration	25	20.0	1	0.8
Injection Site Inflammation	35	28.0	9	7.1

Body System Adverse Clinical Experience	Copolymer-1 (N=125)		Placebo (N=126)	
	N	%	N	%
Injection Site Mass	33	26.4	10	7.9
Injection Site Pain	83	66.4	46	36.5
Injection Site Pruritus	48	38.4	5	4.0
Injection Site Reaction	4	3.2	1	0.8
Injection Site Urticaria	9	7.2	0	0
Injection Site Welt	19	15.2	5	4.0
Neck Pain	16	12.8	9	7.1
Pain	53	42.4	52	41.3
Cardiovascular				
Hypertension	3	2.4	1	0.8
Migraine	9	7.2	5	4.0
Palpitation	14	11.2	6	4.8
Syncope	8	6.4	4	3.2
Tachycardia	7	5.6	7	5.6
Vasodilatation	34	27.2	14	11.1
Digestive				
Anorexia	6	4.8	3	2.4
Bowel Urgency	3	2.4	1	0.8
Diarrhea	24	19.2	22	17.5
Dyspepsia	25	20.0	23	18.3
Dysphagia	7	5.6	6	4.8
Gastroenteritis	6	4.8	2	1.6
Gastrointestinal Disorder	10	8.0	8	6.3
Nausea	29	23.2	22	17.5

Body System Adverse Clinical Experience	Copolymer-1 (N=125)		Placebo (N=126)	
	N	%	N	%
Oral Moniliasis	3	2.4	0	0
Rectal Disorder	4	3.2	3	2.4
Salivary Gland Enlargement	2	1.6	0	0
Tooth Caries	3	2.4	0	0
Tooth Disorder	4	3.2	3	2.4
Ulcerative Stomatitis	2	1.6	0	0
Vomiting	13	10.4	7	5.6
Hemic and Lymphatic				
Ecchymosis	15	12.0	12	9.5
Lymphadenopathy	23	18.4	12	9.5
Metabolic and Nutritional				
Edema	5	4.0	1	0.8
Peripheral Edema	14	11.2	7	5.6
Weight Gain	7	5.6	0	0
Musculoskeletal				
Arthralgia	31	24.8	22	17.5
Nervous				
Abnormal Dreams	3	2.4	2	1.6
Agitation	7	5.6	4	3.2
Amnesia	7	5.6	7	5.6
Anxiety	30	24.0	29	23.0
Confusion	5	4.0	1	0.8
Emotional Liability	2	1.6	1	0.8
Euphoria	2	1.6	1	0.8

Body System Adverse Clinical Experience	Copolymer-1 (N=125)		Placebo (N=126)	
	N	%	N	%
Foot Drop	6	4.8	4	3.2
Hypertonia	44	35.2	37	29.4
L'hermittes Sign	3	2.4	3	2.4
Nervousness	4	3.2	2	1.6
Nystagmus	5	4.0	2	1.6
Sleep Disorder	2	1.6	2	1.6
Speech Disorder	5	4.0	3	2.4
Stupor	2	1.6	0	0
Tremor	14	11.2	7	5.6
Vertigo	12	9.6	11	8.7
Vestibular Disorder	2	1.6	1	0.8
Respiratory				
Bronchitis	18	14.4	12	9.5
Cough Increased	13	10.4	12	9.5
Dyspnea	23	18.4	8	6.3
Laryngitis	2	1.6	2	1.6
Rhinitis	29	23.2	26	20.6
Skin and Appendages				
Eczema	3	2.4	2	1.6
Erythema	8	6.4	4	3.2
Herpes Simplex	8	6.4	6	4.8
Herpes Zoster	2	1.6	1	0.8
Pustular Rash	2	1.6	1	0.8
Rash	21	16.8	19	15.1

Body System Adverse Clinical Experience	Copolymer-1 (N=125)		Placebo (N=126)	
	N	%	N	%
Skin Atrophy	2	1.6	1	0.8
Skin Disorder	5	4.0	2	1.6
Skin Nodule	4	3.2	1	0.8
Sweating	15	12.0	10	7.9
Urticaria	7	5.6	5	4.0
Wart	3	2.4	0	0
Special Senses				
Deaf	2	1.6	2	1.6
Diplopia	9	7.2	8	6.3
Ear Disorder	6	4.8	4	3.2
Ear Pain	15	12.0	12	9.5
Eye Disorder	8	6.4	1	0.8
Otitis Media	7	5.6	7	5.6
Taste Perversion	3	2.4	3	2.4
Urogenital				
Amenorrhea	2	1.6	1	0.8
Breast Pain	2	1.6	2	1.6
Dysmenorrhea	12	9.6	9	7.1
Hematuria	2	1.6	1	0.8
Impotence	3	2.4	0	0
Menorrhagia	3	2.4	2	1.6
Pap Smear Suspicious	3	2.4	1	0.8
Unintended Pregnancy	4	3.2	0	0

Body System Adverse Clinical Experience	Copolymer-1 (N=125)		Placebo (N=126)	
	N	%	N	%
Urinary Urgency	20	16.0	17	13.5
Vaginal Hemorrhage	2	1.6	0	0
Vaginal Moniliasis	16	12.8	9	7.1

Appendix 9.a.2
Incidence of Adverse Clinical Experiences (≥2%)
Controlled Study BR-1

Body System Adverse Clinical Experience	Copolymer-1 (N=25)		Placebo (N=25)	
	N	%	N	%
Body as a Whole				
Fever	2	8.0	0	0
Headache	10	40.0	9	36.0
Injection Site Erythema	19	76.0	11	44.0
Injection Site Inflammation	22	88.0	4	16.0
Injection Site Pain	23	92.0	9	36.0
Injection Site Pruritus	3	12.0	0	0
Injection Site Reaction	2	8.0	0	0
Cardiovascular				
Palpitation	7	28.0	4	16.0
Vasodilatation	3	12.0	0	0
Digestive				
Anorexia	5	20.0	3	12.0
Constipation	10	40.0	6	24.0
Nausea	7	28.0	4	16.0
Vomiting	2	8.0	1	4.0
Nervous				
Dizziness	12	48.0	8	32.0
Hypesthesia	2	8.0	1	4.0

Body System Adverse Clinical Experience	Copolymer-1 (N=25)		Placebo (N=25)	
	N	%	N	%
Insomnia	2	8.0	0	0
Respiratory				
Dyspnea	3	12.0	0	0
Skin and Appendages				
Pruritus	18	72.0	7	28.0
Kash	6	24.0	5	20.0
Sweati.ıg	8	32.0	6	24.0

Appendix 9.a.3
Incidence of Adverse Clinical Experiences (≥2%)
Controlled Study BR-2

Body System Adverse Clinical Experience	Copolymer-1 (N=51)		Placebo (N=55)	
	N	%	N	%
Body as a Whole				
Accidental Injury	2	4.0	0	0.0
Arthralgia	16	31.0	11	20.0
Asthenia	2	4.0	0	0.0
Chills	3	6.0	1	2.0
Infection	4	8.0	1	2.0
Laryngysmus	10	20.0	7	13.0
Pain	3	6.0	0	0.0
Injection Site Hemorrhage	3	6.0	1	2.0
Injection Site Hypersensitivity	2	4.0	1	2.0
Injection Site Erythema	40	78.0	12	22.0
Injection Site Inflammation	41	80.0	9	16.0
Injection Site Pain	41	80.0	23	42.0
Injection Site Pruritus	29	57.0	7	13.0
Injection Site Welt	3	6.0	0	0.0
Injection Site Mass	19	37.0	9.0	16.0
Injection Site Reaction	2	4.0	0	0
Cardiovascular				
Palpitation	14	28.0	6	11.0

Body System Adverse Clinical Experience	Copolymer-1 (N=51)		Placebo (N=55)	
	N	%	N	%
Decreased BP	2	4.0	0	0.0
Chest Pain	10	20.0	9	16.0
Hematologic				
Lymphadenopathy	2	4.0	0	0.0
Nervous				
Anxiety	16	31.0	11	20.0
Respiratory				
Hyperventilation	2	4.0	0	0.0
Dyspnea	12	24.0	7	13.0
Skin and Appendages				
Rash	10	27.0	6	11.0

Appendix 9.d.1
Other Adverse Events Observed
During the Premarketing Evaluation of Copolymer-1

Other adverse experiences observed during clinical trials not already accounted for in the table of adverse events which occurred at an incidence of at least 1% in the Copolymer-1 group were as follows:

Body as a whole: abdomen enlarged, abdominal pain, accidental injury, allergic reaction, allergic rhinitis, bacterial infection, benign neoplasm, cellulitis, death, disease progression, drug reaction, fever, fever and chills, flank pain, fungal infection, generalized edema, headache, hernia, infection, injection site abscess, injection site edema, injection site ecchymosis, injection site fibrosis, injection site hematoma, injection site hypersensitivity, injection site hypertrophy, injection site melanosis, lack of drug effect, laparotomy, leg pain, Lyme Disease, malaise, moniliasis, moon face, mucous membrane disorder, neck rigidity, neoplasm, pain, photosensitivity reaction, polypectomy, reaction unevaluable, serum sickness, suicide attempt, surgery.

Cardiovascular: arrhythmia, atrial fibrillation, blood pressure unstable, bradycardia, cardiovascular disorder, decreased blood pressure, extrasystoles, fourth heart sound, hypertension, hypotension, midsystolic click, pallor, peripheral vascular disorder, postural hypotension, systolic murmurs, tachycardia, varicose vein, vascular disorders.

Gastrointestinal: appendectomy, bowel urgency, cholecystitis, colitis, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, esophageal ulcer, esophagitis, fecal incontinence, flatulence, gastritis, gastrointestinal carcinoma, gastrointestinal discomfort, gastrointestinal disorder, gingivitis, glossitis, gum hemorrhage, hemorrhoidectomy, hepatomegaly, increased appetite, melena, mouth ulceration, nausea and vomiting, pancreas disorders, pancreatitis, periodontal abscess, rectal disorder, rectal hemorrhage, salivary gland enlargement, stomatitis, tenesmus, tongue discoloration, tooth disorder, ulcer duodenal, ulcerative stomatitis, viral hepatitis A.

Endocrine: Cushing's Syndrome, goiter, hyperthyroidism, hypothyroidism.

Hemic and Lymphatic: anemia, cyanosis, eosinophilia, leukopenia, lymphedema,

pancytopenia, splenomegaly.

Metabolic and Nutritional: alcohol intolerance, gout, healing abnormal, increased alcohol tolerance, weight decreased, xanthoma.

Musculoskeletal: arthritis, bone pain, bursitis, joint disorder, kyphoscoliosis, muscle atrophy, muscle disorder, myalgia, myasthenia, myopathy, osteomyelitis, tendon disorder, tenosynovitis.

Nervous: abnormal dreams, abnormal gait, amnesia, anxiety, ataxia, circumoral paresthesia, coma, depersonalization, depression, dizziness, dysesthesia, emotional lability, euphoria, facial paralysis, foot drop, hallucinations, hostility, hypesthesia, hypokinesia, incoordination, insomnia, L'hermittes Sign, libido decreased, manic reaction, memory impairment, meningitis, movement disorders, myoclonus, nervousness, neurosis, paranoid reaction, paraplegia, paresthesia, psychiatric disorder, psychotic depression, seizure, sleep disorder, somnolence, speech disorder, stupor, thinking abnormal, twitch, vertigo, vestibular disorder,.

Respiratory: asthma, cough increased, epistaxis, hyperventilation, hypoventilation, laryngismus, laryngitis, lung disorder, pharyngitis, pneumonia, respiratory disorders, sinusitis, voice alteration.

Skin and Appendages: acne, alopecia, angioedema, contact dermatitis, dry skin, dermatomycosis, eczema, erythema nodosum, fungal dermatitis, furunculosis, hair disorder, herpes simplex, herpes zoster, hirsutism, maculopapular rash, nail disorder, pruritus, psoriasis, pustular rash, rash, skin atrophy, skin benign neoplasm, skin carcinoma, skin disorder NOS, skin discoloration, skin hypertrophy, skin reaction, skin striae, urticaria, vesiculobullous rash.

Special Senses: abnormal vision, amblyopia, cataract, conjunctivitis, corneal lesion, corneal ulcer, deaf, diplopia, dry eyes, ear disorder, eye pain, lacrimation disorder, mydriasis, optic neuritis, otitis media, otitis externa, photophobia, ptosis, taste loss, taste perversion, tinnitus.

Urogenital: abortion, amenorrhea, breast engorgement, breast enlarge, breast pain, carcinoma cervix in situ, cervix disorder, cystitis, dysuria, endometrial disorder, fibrocystic breast, hematuria, hysterectomy, kidney calculus, kidney pain, menorrhagia, menstrual disorder, nocturia, ovarian cyst, Pap smear suspicious,

pregnancy, priapism, prostatectomy, prostatic disorder, pyelonephritis, sexual function abnormal, testicular disorder, urethritis, urinary frequency, urinary incontinence, urinary retention, urinary tract infection, urine abnormality, vaginal disorder, vaginal hemorrhage, vaginitis.

APPENDIX 10.b.1
CASES OF "systemic reaction"S

Study	Patient	Age	Sex	Dose mg/d	~Days	Comments
9001E	02-206	33	M	20	35	After 6 days of treatment, rashes on lower extremities and injection site lasting 1 month. On day 35 there was temporary (2 day) interruption of treatment due to tightness in the chest and syncope. With rechallenge-recurrence of the symptoms (chest tightness, flushing). With continued treatment no more adverse events were reported until two months later, when he reported hives. The medication was stopped again and rechallenged 6 days later with recurrence of the hives, this time he was removed from the study. Concomitant med-amoxicillin.
	02-214	32	F	20	48	PT** due to Syncope, chest tightness, flushing, N/V and SOB immediately following injection.Hx of PCN and sulfa allergy.
	07-707	26	F	20	120	PT due to enlarged lymph nodes. @ 4 months-vomiting, palpitations, chest tightness and SOB. A biopsy of the nodes revealed hyperplasia. Hx of PCN, shellfish and sulfa allergy.
	07-713	43	F	20	330	PT due to rash of 2 and1/2 month duration, also complained of angioedema and chest tightness.
	07-720	38	F	20	60	PT due to flushing, chest tightness and SOB. Hx of PCN allergy.
	07-727	33	F	20	90	One month into the study Pt** developed cervical and inguinal lymph node enlargement. At third month-hepatomegaly and later splenomegaly.
9002	020-002	30	F	20	90	PT due to rash and dyspnea. At one mo. she experienced a rash with interruption of therapy.
	01-007	40	F	20	60	PT due to allergic reaction (facial edema and SOB).
	012-003	47	F	20	90	PT due to chest tightness and SOB.
	005-007	35	F	20	210	PT due to itchy rash, flushing, chest tightness and SOB.

PT** = premature termination.

Study	Patient	Age	Sex	Dose mg/day	Days	Comments
BR-1	694	31	M	20	720	PT due to "systemic reaction". At 15 mo- SR***. A similar episode at 21 mo. Hx of a similar reaction post IVP.
	910	31	F	20	120	PT due to SR. Several months later rechallenged with recurrence, and reoccurring hives post discontinuation for several weeks.
BR-2	02-40	56	F	20	42	PT due to SR, two episodes 3 days apart.
	02-100	41	F	20	195	PT due to allergic like syndrome. @ 6 weeks- SR. @5.5mos SR. A brief interruption but reported welts at injection site after restarting and was discontinued.
	01-506	38	M	20	17	@ 14 days- SR- used two anaphylactic kits and symptoms lasted 45 min. 3 days later following injection a second episode . Was PT.
	01-2058	31	F	20	330	PT due to a series of "reactions" @ 1, 3, 10 and 11 months, characterized by allergic like symptoms.
1110-1	8005	44	M	20	160	PT due to a series of ""systemic reaction"s"
	8010	26	M*	20	216	PT due to a series of (3) ""systemic reaction"s," approximately a month apart.
	8038	23	F	20	105	PT due to a series of (6) ""systemic reaction"s," at first a month apart, then a week or 2 weeks apart.
	8048	31	F	20	427	PT due to a series of (4) ""systemic reaction"s," starting two weeks after study initiation, a month later, three months and a year later.

Study	Patient	Age	Sex	Dose mg/day	Days	Comments
1110-1	8059	39	F	20	174	PT due to a series of (5) ""systemic reaction"s" following the injection of the drug.The episodes started 5 mos into the study and each reaction lasted 7-10 min. Allergy skin tests were positive.
	8065	46	M	20	111	PT due to respiratory difficulty lasting 20 min on day 109, followed by a rash and peripheral edema the next day lasting a day.
	8080	39	F	20	126	PT due to welts at injection site lasting 3 mos and one episode of facial flushing lasting 10 min. Concomitant meds included antihistamine.
	8102	34	F	20	624	Injection site reactions (ISR****) a mo. into the study lasting 30 days. 3 mo into study more ISR and SR-chest tightness and dyspnes-lasting 15 min. A week and 2 yrs later more episodes of SR (the last episode lasting 2 hrs) .
	8103	20	F	20	300	PT due to a series of (4) SRs-1st episode starting a mo after study initiation and then at different intervals usually symptoms lasting 10-20 min. but last episode lasted 4 hrs.
	8304	59	M	20	48	PT due to 2 episodes of weakness, shivering, fever and inability to walk.
	8401	24	F	20	282	PT due to a series of (5) SRs-1st episode starting 3 mos after study initiation .
	8402	25	M	20	173	2 episodes of SR at 2 mos and 3 mos of study.
	8419	42	F	20	183	ISR and 2 episodes of SR.
	8448	27	F	20	418	An episode of SR 2 mo into study. Treatment was stopped for 4 mos and then rechallenged. Upon rechallenge the pt experienced five more episodes and then PT.
	8451	31	F	20	108	PT for an episode of SR.
	9108	23	M	20	114	PT for an episode of SR.

Study	Patient	Age	Sex	Dose mg/d	Days	Comments
11101-1	9418	21	F	20	168	PT for an episode of SR.
BR-2	02-40	56	F	20	42	PT for 2 episodes of SR within 2 days.

PT* premature termination.
Pt** Patient
SR*** "systemic reaction" (includes at the minimum three of the following symptoms: chest tightness, palpitations, vasodilatation, angioedema, flushing, anxiety, constriction of the throat and SOB)
ISR **** Injection Site Reaction

APPENDIX 11.a.1.1
INCIDENCE OF CLINICALLY SIGNIFICANT BLOOD CHEMISTRY ABNORMALITIES
(9001/9001E BR-1 and BR-2)

Laboratory Test (Units)	Criteria for Clinically Significant Abnormal Values	Cop 1 (N=201)	Placebo (N=177)
BUN (mg/dL)	≥30 mg/dL	0	0
Calcium (mg/dL)	≤7 mg/dL	0	0
	≥12 mg/dL	0	0
Serum Chloride (mEq/L)	≤95 mEq/L	5(2.5%)	9(3.1)
	≥115 mEq/L	0	0
Creatinine (mg/dL)	≥2 mg/dL	3(1.5%)	2(0.6%)
Serum Glucose (mg/dL)	≤50 mg/dL	4(2.0%)	3(1.7%)
	≥300 mg/dL	1(0.5%)	0
Phosphorus (mg/dL)	≤7 mg/dL	8(4.0%)	2(1 .1%)
	≥12 mg/dL	0	0
Serum Potassium (mEq/L)	≤3 mEq/L	0	0
	≥5.9 mEq/L	0	1(0.6)
AST (SGOT)(U/L)	≥150	0	3(1.7%)
ALT (SGPT) U/L)	≥165	3(1.5%)	6(3.4%)
LDH (U/L)*	≥750	0	0
Total Bilirubin (mg/dL)	≥2mg/dL	2(1%)	4(2.3%)

*LDH not done in 01-9001E

APPENDIX 11.a.2.1
INCIDENCE OF CLINICALLY SIGNIFICANT HEMATOLOGY ABNORMALITIES
(9001/9001E BR-1 and BR-2)

Laboratory Test (Units)	Criteria for Clinically Significant Abnormal Values	Cop 1 (N=201)	Placebo (N=177)
Hemoglobin (g/dL)	≤11.5 g/dL (male)	0	0
	≤ 9.5 g/dL (female)	0	1
Hematocrit (%)	≤37% (male)	0	0
	≤32% (female)	1(0.5%)	3(1.7%)
WBC ($x10^3/\mu L$)	≤2.8 x $10^3/\mu L$	5(2.5%)	1(0.4%)
	≥16 x $10^3/\mu L$	7(3.5%)	5(2.8%)
Platelets* ($x10^3/\mu L$) N=292	≤75 x $10^3/\mu L$	0	2(1.13%)
	≥700 x $10^3/\mu L$	0	0

*Platelets not done in BR-1 and BR-2

APPENDIX 11.c.1
INCIDENCE OF CLINICALLY SIGNIFICANT VITAL SIGN ABNORMALITIES:
FOR 01/9001 and 9001E*

Vital Sign	Criterion Value	Change from Baseline	Cop 1 (N=125)	Placebo (N=126)
Systolic BP	≤ 90 mmHg	Decrease of ≥20	11(8.8%)	6(4.8%)
	≥180 mmHg	Increase of ≥20	0	1(0.8%)
Diastolic BP	≤ 50 mmHg	Decrease of ≥15	11(8.8%)	8(6.3%)
	≥105 mmHg	Increase of ≥15	0	0
Heart Rate	≤ 50 bpm	Decrease of ≥15	0	0
	≥120 bpm	Increase of ≥15	3(2.4%)	0

*Data not available for BR-1 and BR-2

Appendix 13.1*
Serious Adverse Experiences Considered Unlikely to be Related to Study Drug

Body System	Study Number	Patient Number	Age	Dose mg/day	Duration of Treatment (days)	Adverse Event
Body as a Whole	01-9001/9001E	403	34	20	914	Abdominal Pain
	01-9001/9001E	528	32	20	125	Back Pain
	01-9001/9001E	807	39	20	117	Benign Neoplasm
	01-9001/9001E	302	22	20	276	Suicide Attempt
	01-9001/9001E	813	27	20	109	Suicide Ideation
	01-9002	2/2	62	20	80	Accidental Injury
	01-9002	9/1	39	20	97	Asthenia
	01-9002	9/1	39	20	97	Fever
	01-9002	8/8	37	20	191	Infection
	1110-1	8053	36	20	225	Accidental Injury
	1110-1	8114	53	20	718	Accidental Injury
	1110-1	8320	43	20	780	Accidental Injury
	1110-1	8331	44	20	288	Accidental Injury
	1110-1	8441	44	20	212	Accidental Injury
	1110-1	8309	21	20	157	Laparotomy
	1110-1	8440	52	20	N/A	Subcutaneous swelling, left shoulder, possible Lipoma
Body as a whole (Continued)	1110-2	9401	42	20, every other day	684	Accidental Injury
	BR-2	01-578	35	30	454	Neoplasm
Cardiovascular	01-9001/9001E	212	31	20	613	Atrial Fibrillation
	01-9001/9001E	403	34	20	N/A	Hypertension
Digestive	01-9001/9001E	403	34	20	N/A	Gastritis
	1110-1	8106	58	20	1148	Appendectomy
	1110-1	8426	35	20	595	Hemorrhoidectomy
	1110-1	8427	35	20	364	Ulcer Duodenal

Body System	Study Number	Patient Number	Age	Dose mg/day	Duration of Treatment (days)	Adverse Event
	1110-1	8311	31	20	381	Viral Hepatitis A
Hemic and Lymphatic	1110-1	8114	53	20	81	Leucopenia
Musculoskeletal	01-9001/9001E	216	36	20	316	Arthralgia
	1110-1	8008	21	20	47	Osteomyelitis
Nervous	01-9001/9001E	403	34	20	312	Anxiety
	01-9001/9001E	403	34	20	163	Depression
	01-9001/9001E	1002	30	20	898	Significant Exacerbation of MS
	01-9001/9001E	1024	46	20	1022	Significant Exacerbation of MS
	01-9001/9001E	403	34	20	N/A	Terrible Sadness
	01-9001/9001E	126	25	20	806	Vertigo/Recurrent Vomiting
	01-9001/9001E	403	34	20	77	Faintness
	01-9001/9001E	403	34	20	496	Difficulty Walking and Fatigue
	01-9002	9/1	39	20	97	Ataxia
	01-9002	23/2	44	20	180	Depression
	01-9002	5/2	27	20	71	Dizziness, Nausea, Vertigo, Asthenia
	01-9002	1/6	39	20	93	Hallucinations
	01-9002	38/ 1		20	N/A	Loss of Consciousness
	01-9002	25/ 25	40	20	N/A	Optic Atrophy
Respiratory	01-9001/9001E	403	34	20	139	Bronchitis
	01-9002	9/1	40	20	97	Rhinitis
Skin and Appendages	01-9001/9001E	221	46	20	337	Skin Carcinoma
Urogenital	01-9001/9001E	424	29	20	388	Unintended Pregnancy

Body System	Study Number	Patient Number	Age	Dose mg/day	Duration of Treatment (days)	Adverse Event
	01-9001/9001E	905	30	20	732	Unintended Pregnancy
	01-9001/9001E	423	29	20	18	Unintended Pregnancy
	1110-1	8053	36	20	599	Hysterectomy
	1110-1	8122	38	20	355	Pregnancy
	1110-1	8106	58	20	1020	Prostatectomy
	1110-2	9413	35	20, every other day	268	Hysterectomy

*The same patient may appear more than once in appendices 13.1 and 13.2 and may appear in both appendices. However, every line represents a different event.

Appendix 13.2[a]
Hospitalizations Considered Unlikely to be Related to Study Drug

Body System	Study Number	Patient Number	Age	Dose mg/day	Duration of Treatment (months)	Adverse Event
Body as a Whole	9001/9001E	403	38	20	31	Abdominal Pain
	9001/9001E	528	32	20	4	Back Pain
	9001/9001E	403	34	20	12	Drug Intoxication
	9001/9001E	403	34	20	26	Headache, Asthenia
	9001/9001E	302	27	20	10	Suicide Attempt
	9001/9001E	813	27	20	4	Suicide Ideation
	9001/9001E	216	36	20	26	Surgery
	9002	02/002	62	20	3	Accidental Injury
	9002	05/002	26	20	2.5	Asthenia
	9002	36/010	54	20	3	Gallstone surgery
	9002	12/005	32	20	3	Urticaria
	1110-1	8053	36	20	356 days	Accidental Injury
	1110-1	8304	59	20	31 days	Fever, Chills, Asthenia
	1110-1	8537	41	20	72 days	Hiatal Hernia
	1110-1	8315	25	20	204 days	Laparotomy
	1110-2	9408	55	20	24	Carcinoma Breast
Body as a Whole (Continued)	BR-3	01-1000	Unk	20	Unknown	Obesity
	BR-3	01-2030	20	20	7 yrs	Pain
	BR-3	01-2015	20	20	21	Surgery
	BR-2	01-578	35	30	25	Asthenia, Headache
	BR-2	01-184	32	30	2	Back Pain
Cardiovascular	9001/9001E	212	31	20	20	Atrial Fibrillation
	9001/9001E	0322	36	20	30	Atrial Fibrillation

Body System	Study Number	Patient Number	Age	Dose mg/day	Duration of Treatment (months)	Adverse Event
	9001/9001E	811	27	20	7 mos	Heart Murmur
	9001/9001E	609	46	20	20	Deep Vein Thrombosis
	9001/9001E	807	39	20	6	Thrombophlebitis
Digestive	9001/9001E	514	43	20	16	Gastroenteritis
	9002	08/008	37	20	6	Intestinal Infection
	9002	05/002	26	20	2.5	Nausea
	9002	05/002	26	20	2.5	Vomiting
	1110-1	8537	41	20	72 days	Esophagitis
Hemic and Lymphatic	1110-2	9401	42	20 every other day	unknown	Lymphadenopathy
Metabolic and Nutritional	9001/9001E	403	34	20	6	Dehydration
Musculoskeletal	BR-3	01-2030	20	20	5 yrs 9 mos	Muscle Disorder
	BR-2	01-578	35	30	25	Myasthenia
Nervous	9001/9001E	403	34	20	27	Depression
	9001/9001E	126	28	20	31	Depression
	9001/9001E	712	38	20	15	Depression
	9002	01/006	39	20	3	Agitation, Hallucination, Hostility
	BR-3	01-2018	36	20	17	Anxiety
	BR-3	01-2018	36	20	26	Psychiatric Disorder
	BR-3	01-2051	59	20	42	Somnolence, Stupor
Respiratory	9001/9001E	403	34	20	6	Bronchospasm
	9001/9001E	807	39	20	5	Lung Biopsy
	1110-1	8044	42	20	707 days	Lung Infection
	BR-3	01-2049	41	20	35	Pneumonia
	BR-3	01-2054	35	20	29	Pneumonia
Urogenital	1110-1	8053	36	20	615 days	Myoma

Body System	Study Number	Patient Number	Age	Dose mg/day	Duration of Treatment (months)	Adverse Event
	1110-2	9110	33	20 every other day	20	Abortion
	BR-2	02-136	45	30	2.5	Cystitis

*The same patient may appear more than once in appendices 13.1 and 13.2 and may appear in both appendices. However, every line represents a different event.

Appendix 13.3
Serious Adverse Experiences Considered Possibly Related to Study Drug

Body System	Study Number	Patient Number	Age	Dose mg/day	Duration of Treatment (days)	Adverse Event
Body as a Whole	01-9001/9001E	403	34	20	259	Chest Pain (musculoskeletal)
	01-9001/9001E	807	39	20	117	Injection site Staph infection
	01-9002	4/4	56	20	19	Rash
	01-9002	5/2	26	20	75	Asthenia
	01-9002	36/1	44	20	266	Syncope
	1110-1	8304	59	20	31	Fever/Chills, Asthenia
	1110-1	8428	31	20	-	Serum Sickness
	BR-2	1-184	32	30	60	Back Pain
	BR-2	02-1	33	30	91	Syncope
	BR-3	2058	31	20	609	"Severe Reaction"
Cardiovascular	01-9002	36/1	44	20	-	Loss of consciousness
Digestive	01-9002	4/4	56	20	19	Abscess
	01-9002	36/10	54	20	57	Cholecystectomy
	01-9002	5/2	26	20	74	Nausea/vomiting
	1110-1	3537	41	20	72	Esophagitis
Hemic and Lymphatic	01-9001/9001E	707	26	20	-	Lymphadenopathy
Nervous	01-9002	5/2	26	20	75	Dizziness/vertigo

TAB F

Statistical Review and Evaluation

NDA#: 20-622

Applicant: TEVA Pharmaceuticals, USA

Name of Drug: Copolymer-1 for Injection

Documents Reviewed: Vols 1.47, 1.57, 1.58, 1.161, 1.236, amendment dated 11/30/1995

Medical Input: Janeth Rouzer-Kammeyer, M.D., HFD-120

Background

The sponsor has submitted two randomized, placebo-controlled, double-blind studies evaluating the effect of Copolymer-1 (cop-1) in patients with relapsing-remitting multiple sclerosis. Study 9001 is multicenter and Study BR-1 was conducted at a single center.

Study 9001

This study used randomization within center to assign 125 patients to cop-1 and 126 patients to placebo. Eleven (11) centers participated. The range of the number of patients in any treatment by investigator cell was from 6 to 16 with treatments groups well-balanced within center. **Table 1** displays the patient disposition over the trial, while **Table 2** displays baseline characteristics. All patients were ambulatory having baseline Kurtzke EDSS scores from 0-5. All patients were to have had at least 2 relapses in the previous 2 years. There was, however, 1 patient who had had none. The only statistically significant baseline differences were on Kurtzke EDSS score and Functional Systems score. Nineteen (19) patients on cop-1 and 17 on placebo prematurely terminated the 24 month treatment. There was no clear pattern in the reasons for dropping out except possibly for adverse experiences. See **Table 3**.

The primary endpoint was number of relapses over the 2 years of follow up. The definition of a relapse was the appearance of neurological abnormalities lasting at least 48 hours together with objective changes consistent with an increase of .5 on the EDSS score or one point in the score for two or more of the Functional Systems (FS) or two points in the score for one of the FS as compared with the previous evaluation. Other endpoints were 1) time to first relapse, 2) time to progression defined as one unit or greater increase in the Kurtzke EDSS from baseline sustained for at least 90 days, 3) proportion of relapse-free patients at 2 years, 4)change in Kurtzke EDSS, 5)Ambulation Index, and 6)Functional Score Sum.

The planned sample size of 120/group was based upon a relapse rate of 65% in the placebo group and 44% in the cop-1 group to achieve 85% power.

The statistical analysis plan was developed after the original protocol and before unblinding. It refers to various model fittings using ANOVA and ANCOVA with sex, duration of disease, prior 2-year relapse rate and baseline Kurtzke score as potential covariates to predict relapse rate, i.e., the number of relapses per patients over 24 months. Using stepwise regression procedures, the sponsor isolated prior 2-year relapse rate and baseline Kurtzke as the only statistically significant covariates. The final model upon which the reported p-values are based was a regression model with drug and center as factors and baseline Kurtzke score and prior 2-year response rate as covariates. Note that **treatment by center interaction was not in the model.** Time to event analyses used the logrank test, Cox modeling, and fitting the data to Weibull and exponential distributions.

Four (4) different cohorts were used:
a) observed cases
b) patients with at least 6 months treatment
c) completers
d) retrieved dropouts

There was also a distinction between an Intent to Treat (ITT) cohort and an 'evaluable' cohort defined as the ITT sample minus protocol violators. This review focuses on analyses which include protocol violators regardless of cohort. In addition, the sponsor used an imputation scheme for imputing values for non-completers: If a patient withdrew before 6 months, "the patient was assigned the greater of the observed number of relapses or the overall average number of observed relapses per 24 months computed across treatment groups. If the patient withdrew between 6 months and 730 days, the observed number of relapses was adjusted to account for 730 days of treatment using the multiplication factor 730/actual number of days of treatment."

The following table displays various p-values for treatment effect on relapse rate. The sponsor's report of least square means of **1.68 (placebo)** is stable over the analyses whereas **the 1.19 reported for cop-1** rises to about 1.28 in some analyses. The p-values are cross-classified by the terms in the linear model and the data base used (D=Drug, C=Center).

	No Imputation (LOCF)	Completers	Imputed	Retrieved Drop Outs
D, C, DxC	.055	.03	.09	.07
D, C, DxC, bl EDSS, prior relapse	.02	.03	.03	.02
D, C, bl EDSS, prior relapse (sponsor's **reported** analysis)	.007	.015	.02	.01

Instead of depending solely on the sponsor's hybrid imputation rule (different ones for patients leaving before and after 6 months), the division requested the sponsor to submit supplementary analyses using each imputation rule separately on all patients. The first column of the table below displays the p-values using the **inflation factor of 730/#days on treatment**. The second column uses the **greater of either the observed number or the average across all patients.**

D, C, DxC	.037	.084
D, C, DxC, bl EDSS, prior relapse	.006	.04
D, C, bl EDSS, prior relapse	.005	.013

Table 4 displays the distribution of relapses over time and **Table 5** displays the distribution of patients over the number of relapses. Note that there are considerably fewer relapses overall in the second year of the study. **Table 6** lists results for different cohorts using the sponsor's model.

Time to first relapse was analyzed by logrank (p=.23) and by fitting a Weibull to get p=.097 which is the result that the sponsor reports in the text. The proportions of relapse-free patients (34%: cop-1 vs 27%: placebo) were not statistically significantly different using logistic regression with the same terms as the relapse rate analysis. A simple test of proportions yields p=.25. **The result of the trial differs markedly from the assumption in the design of a 56% relapse-free proportion in the cop-1 group and 35% in the placebo group.**

An ordinal logistic regression taking into account the whole distribution of relapses was significant (odds ratio 1.7).

Although the sponsor's ANCOVA on mean change from baseline in EDSS score was not significant using LOCF, the sponsor's repeated measures analysis (average over 24 months) was significant (p=.023).

There were no statistical differences with respect to progression-free patients, time to progression, ambulation score, functional systems score, and quality of life.

Reviewer's Comments

The main issues concerning the primary endpoint (relapse rate) are the use of covariance models and ways to characterize the putative difference between cop-1 and placebo.

First, the sponsor's use of a linear model may pose problems because 1) the model was found by data searching and 2) the assumption of no treatment by covariate interaction is essentially untestable due to the categorical nature of the EDSS score. Regarding 1), the table above indicates that the treatment effect is not significant without controlling for the 2 baseline covariates found by a data conditioned model. As for 2), when the treatment, baseline EDSS main effect and the interaction term are in the model, neither the treatment nor interaction term is significant. This is due to the fact that the correlation between the indicator variable for treatment and the interaction term is .85. Thus the linear model may be pathological for this kind of data.

As an alternative, this reviewer has found that a simple two-sample t-test is significant (p=.04). So is a CMH analysis using mean scores (P=.04). Controlling for center, the latter analysis yields p=.02. Alternatively, since there appears to be a higher mean EDSS score (which is positively correlated with relapse rate) in the cop-1 group at baseline, it seems reasonable to do a CMH analysis controlling for baseline EDSS. This is significant at p=.02. Thus, it appears that simple tests yield statistical significance without resorting to complicated linear or logistic models. Recall that there was no unique analysis specified in the protocol.

Although the groups were well-balanced for the mean number of prior relapses in the previous 2 years (2.9 in both groups), they were not balanced with respect to the frequencies in the two most populous categories: 2 and 3 relapses in the prior 2 years. Sixty-three (63) cop-1 and 51 placebo patients had had 2 relapses while 29 cop-1 and 40 placebo patients had had 3 relapses. However, it is not clear that this imbalance is important since the mean number of relapses on study in the cop-1 group was 1.24 in the category of 2 prior relapses and .90 in the category of 3 prior relapses (goes down), while in the placebo group, the respective means were 1.4 and 1.8 (goes up). Thus, the relation between number of **previous** relapses and mean number of relapses **on study** is seemingly reversed between the treatment groups.

The table below tabulates the number of patients who experienced a decrease, no change or increase in their frequencies of relapse:

	-7	-5	-4	-3	-2	-1	0	1	2	3	4
COP 1	1	5	7	22	27	42	9	7	4	0	1
PLACEBO	0	4	7	18	32	27	18	11	5	3	1

The mean decreases in the groups are 1.62 in the cop-1 group and 1.26 in the placebo group. This difference was not significant by either a t-test (p=.10) or Wilcoxon Rank Sum test (p=.17). Note that any differentiation between the distributions occurs only for the case of a decrease of 1 relapse/patient over 2 years (42 vs 27).

The Bornstein Study (BR-1)

This self-described two-year pilot study enrolled 50 patients. Patients were to have experienced at least 2 relapses in the previous 2 years and a disability of no greater than 6 on the Kurtzke DSS Scale. Forty-eight (48) belonged to randomized matched pairs. The other 2 patients were randomized separately. Matching was done on Kurtzke DSS scale: 0-2, 3-4, 5-6 and # of attacks in the previous two years (+ or - 2 years). An inspection of the data shows that 2 patients were not truly matched on one or both factors. **The sample size was determined to have approximately 80% power to detect a difference of 40% in the proportion of patients who remained relapse-free over 2 years.** A relapse was defined as a worsening lasting at least 48 hours (24 hours for an earlier period during the study, but all data was later revised in a blinded fashion to reflect the 48 hour definition). Worsening was defined as an objective change of at least 1 grade in the score for one of the eight Functional Systems or the Kurtzke DSS Scale. Note that this definition is somewhat different from that in Study 9001.

In a document written after the original protocol, the **major endpoints are stated to be # of relapses and proportion of relapse-free patients**. However, in the published report, only the latter was stated as a primary endpoint.

Table 7 displays the baseline comparisons for all patients. Seven (7) patients did not complete the two years. Two patients were deemed 'inevaluable' because symptomotology was judged to be psychogenic by the investigator. This review discusses only the 'all patients' analysis.

Table 8 displays the sponsor's categorization of **relapse frequencies**. The Fisher's Exact p-value was .004. **Figure** 1 displays the frequency histogram. Note the long tail for the placebo group, only.

The p-value for **proportion of relapse-free** patients is .15 using Fisher's Exact test and .18 using McNemar's test.

The p-value for **time to progression** was .023 using the logrank test

Figure 2 displays the histogram of **change in Kurtzke Scores from baseline**. The p-value for the comparison of proportions of patients who worsened from baseline was .13.

Conclusions

The **Bornstein** study produces a clear statistical difference between cop-1 and placebo. Study **9001**'s results are borderline with secondary endpoints going in the 'right' direction. The sponsor's covariate analysis was not really prespecified since it used a model to choose significant covariates. In addition, it was not possible to check the assumptions of the model. However, other analyses do produce p-values below .05. Thus, it is possible to argue that two studies produced statistically significant results for number of exacerbations. However, the overall experience in the two studies appears different. In **Study 9001**, 23/125, or **18%** of the Cop-1 patients had 3 or more exacerbations whereas only 1 of the 25 patients on Cop-1 did in the **Bornstein Study**. The respective numbers in the placebo groups were 37/126 (29%) and 11/25 (44%). This accounts for the larger treatment difference in the **Bornstein** study relative to that in **Study 9001**.

This difference is also reflected in the **average decreases in relapses from the previous 2 years**. In the Cop-1 group in the **Bornstein** study, the average decrease was 3.2 relapses and in the placebo group the average decrease was 1.6 relapses. Note that the 1.6 for placebo is similar to that for placebo in **9001** (1.3). However the change in the Cop-1 group is quite different: 3.2 (**Bornstein**) vs 1.6 (**9001**). Thus, the change over the next 2 years was nearly the same in the placebo groups in the two studies, but different between the Cop-1 groups.

One indication that the studies' patients may have been drawn from different populations is that the **Bornstein Study**'s patients had a shorter duration of disease on average (5.5 vs 7 years) and a higher previous 2-year relapse rate (3.9 vs 2.9). Moreover, screening of patients was much more rigorous in the **Bornstein** study.

David Hoberman, Ph.D.
Mathematical Statistician

concur: Dr. Sahlroot JTS 12-21-95

Dr. Chi 12/22/95

cc:
Orig: NDA# 20-622
HFD-701/Dr. Anello
HFD-120/Dr Leber
HFD-120/Dr. Katz
HFD-120/Dr. Rouzer-Kammeyer
HFD-120/Mr. Purvis
HFD-120/Ms Wheelous

HFD-710/Dr Chi
HFD-710/Mr Ortecke
HFD-710/Dr Sahlroot
HFD-344 Dr Lisook
HFD-710/Dr. Hoberman
HFD-710/chron

Randomized	125	100 0	126	100 0
Completed[a]	106	84 8	109	86 5
Included in Safety Analysis	125	100.0	126	100 0
Included in Efficacy Analysis				
Intent to Treat Cohort	125	100 0	126	100 0
Evaluable Cohort[b]	105	84 0	115	92.0
Treated at Least 6 Months Cohort	119	95 2	119	95 2
Completed (≥730 days) Cohort				
All	99	79 2	109	87 2
Evaluable	90	72 0	106	84 8

TABLE 1
(Study 9001)

[a] Patients who did not prematurely terminate
[b] No violation of exclusion criteria

DEMOGRAPHIC CHARACTERISTICS ALL PATIENTS (N=251)

Parameter	Copolymer 1 (N = 125)	Placebo (N = 126)
Age		
Mean±SD	34 6±6 0	34 3±6 5
Minimum-Maximum	19 0-46 0	19 0-46 0
Sex [n (%)]		
Male	37 (29 6)	30 (23 8)
Female	88 (70 4)	96 (76 2)
Race [n (%)]		
Caucasian	118 (94 4)	118 (93 6)
Black	7 (5 6)	8 (6 3)
Duration of Disease (yrs)		
Mean±SD	7 3±4 9	6 6±5 1
Minimum-Maximum	0 6 21 2	1 0-23 0
Prior 2-Year Relapse Rate		
Mean±SD	2 9±1 3	2 9±1 1
Minimum-Maximum	2 0-11 0	0 0-6 0
Baseline Kurtzke EDSS Score		
Mean±SD	2 8±1 2	2 4±1 3
Minimum-Maximum	0 0-5 0	0 0-5 0

TABLE 2
(Study 9001)

PATIENTS WHO WITHDREW PREMATURELY FROM TRIAL DRUG ALL PATIENTS

Reason Treatment Not Completed	Copolymer-1 (N = 125) n	%	Placebo (N = 126) n	%
Total Premature Terminations	19	15 2	17	13 5
Reason for Premature Terminations				
Serious adverse experiences	2	10 5	0	0
Adverse experiences without serious sequelae[b]	5	26 3	1	5 9
Patient decision	5	26 3	8	47 1
Lost to follow-up	2	10 5	2	11 8
Other[a]	5	26 3	6	35 3

TABLE 3
(Study 9001)

[a] Pregnancy (

TABLE 4
(Study 9001)

OVERALL DISTRIBUTION OF RELAPSES BY TIME ON TREATMENT ALL PATIENTS

Time Interval to Onset of Relapse (months)	Number of Relapses Copolymer-1 (N = 125) n	Placebo (N = 126) n
0 ≤3	38	43
>3 - 6	20	29
>6 - 9	23	26
>9 - 12	21	30
>12 - 15	19	18
>15 - 18	13	25
>18 - 21	18	16
>21	9	23
Total	161	210

Source Appendix I4 2 7 1

TABLE 5
(Study 9001)

DISTRIBUTION OF PATIENTS BY NUMBER OF RELAPSES ALL PATIENTS

Number of Relapses	Copolymer 1 (N = 125) n	%	Placebo (N = 126) n	%
0	42	33 6	34	27 0
1	42	33 6	39	31 0
2	18	14 4	16	12 7
3	12	9 6	21	16 7
4	9	7 2	9	7 1
5	1	0 8	4	3 2
6	1	0 8	1	0 8
7	0	0	2	1 6

Source Appendix I4 1 1 1, J4 1 1 1

TABLE 6
(Study 9001)

COVARIATE ADJUSTED MEAN NUMBER OF RELAPSES BY PATIENT COHORT

Patients in Analysis	Copolymer-1 (N = 125) n	Copolymer-1 (N = 125) Adjusted Mean±SE	Placebo (N = 126) n	Placebo (N = 126) Adjusted Mean±SE	p-Value[a]
Primary Cohort					
All Patients (ITT)	125	1 19±0 13	126	1 68±0 13	0 007
Secondary Cohorts					
Evaluable Patients	105	1 27±0 14	115	1 75±0 13	0 013
Patients Treated at Least 183 Days	119	1 25±0 13	119	1 73±0 13	0 010
Patients Treated at Least 730 Days	99	1 23±0 15	109	1 74±0 14	0 015
Evaluable Patients Treated at Least 730 Days	90	1 21±0 16	106	1 76±0 15	0 011
All Patients with Imputation of Relapses	125	1 32±0 14	126	1 78±0 14	0 021
Evaluable Patients with Imputation of Relapses	105	1 39±0 15	115	1 86±0 15	0 026
Retrieved Dropouts All Patients	125	1 22±0 13	126	1 68±0 13	0 011
Retrieved Dropouts Evaluable Patients	105	1 30±0 14	115	1 75±0 14	0 021

[a] p-value for ANCOVA between treatment group analysis

TABLE 7
(Bornstein)

SUMMARY STATISTICS OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS ALL PATIENT COHORT

	Copolymer-1 (N=25)	Placebo (N=25)	P-Value
Sex			
Male	11	10	>0 99
Female	14	15	
Race			
White	23	25	0 49
Black/Other	2	0	
Age (years)			
Mean ± S D	30 0 ± 3 2	31 0 ± 3 5	0 34
Minimum	20 0	25 0	
Maximum	33 0	35 0	
Duration of Disease (years)			
Mean ± S D	4 9 ± 2 7	6 1 ± 3 9	0 22
Minimum	2 0	1 0	
Maximum	10 0	13 0	
Prior Relapse Rate (number over 2 years)			
Mean ± S D	3 8 ± 1 4	4 0 ± 1 2	0 59
Minimum	2 0	2 0	
Maximum	8 0	7 0	
Baseline Kurtzke DSS Score			
Mean ± S D	2 8 ± 1 9	3 2 ± 2 0	0 56
Minimum	1 0	0 0	
Maximum	6 0	6 0	
Baseline Kurtzke DSS Score			
0-2	13	11	
3-4	5	7	
5-6	7	7	

TIENT COHORT

Number of Relapses	Copolymer-1 (N=25) n	%	Placebo (N=25) n	%
0	14	56 0	8	32 0
1-2	10	40.0	6	24 0
3 or more	1	4 0	11	44 0
Mean/Patient ± SD	0.6 ± 0.9		2.4 ± 2.4	
Total Number of Relapses	16		59	

Relapse Grouping p=0 004 - Fisher's Exact Probability

FIGURE 1 (Bornstein)

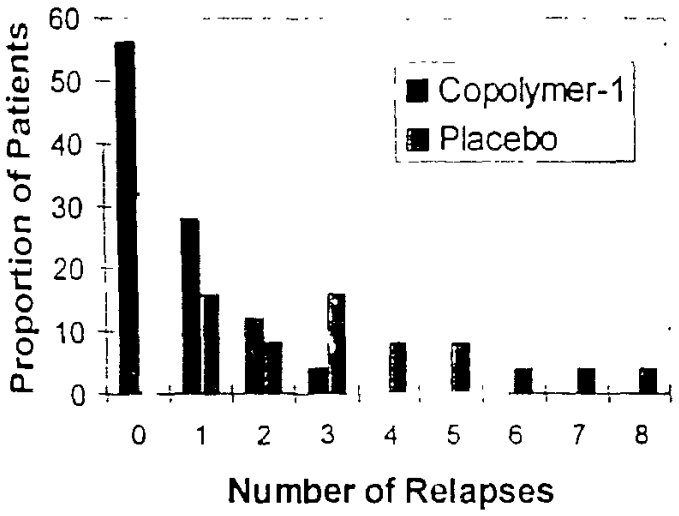
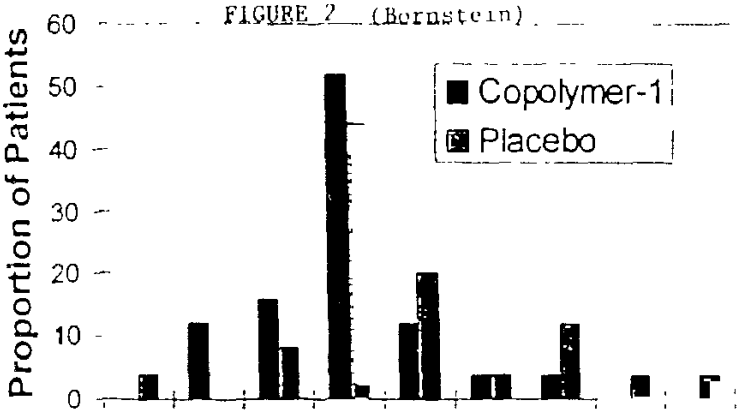


FIGURE 2 (Bornstein)



Memorandum

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

Date July 30, 1996 AUG 1 1996

From David Hoberman, Ph D , HFD-710

Thru George Chi, Ph D Director of Biometrics Division I
Todd Sahlroot, Ph D , Team Leader, Biometrics Team 2

Subject Bornstein Study and Study 9001 submitted in NDA 20-622 (Copolymer 1)

To File (NDA 20-622)

This memo supplements the review dated Dec 22, 1995 in which the sponsor's use of Fisher's Exact test in the **Bornstein** trial was reported as the analysis of the frequency of relapse Since the randomization to drug or placebo was done within each pair, a proper analysis would take this part of the design into account Fisher's Exact test ignores the pairing A better method is the signed rank test on the difference in frequency within each pair Since there were 2 patients not paired, only the 24 matched pairs were used The result is essentially the same as the unpaired (Fisher's) analysis (p= 005) This result does not appear to be the result any bias due to Cop I patients leaving the trial early and thus not being eligible for further follow up In particular, there were 3 patients on drug who discontinued prematurely patient #777 left the study at 1 month with 2 relapses, patient #910 left the study at 19 months with no relapses, and patient #694 left the study at 23 with 1 relapse

In addition, this reviewer employed the signed rank test on the **difference in frequency of relapse from the previous two years**, an endpoint mentioned in one of Dr Bornstein's documents The median of this difference between the treatment groups was 1 relapse (p= 025)

In study **9001**, the sponsor fitted several covariate models and reported p-values in the range of 01- 02 depending upon how many patients were included in the data set These were based upon a model which included only the statistically significant covariates (baseline Kurtzke score and prior two-year relapse total) This reviewer does not believe that these low p-values should be taken at face value for two reasons 1) they are is derived from exploratory analyses, i e the covariates were not specified in advance and 2) the r-square value measuring each covariable's relation to the number of on-study relapses was less than 05 in both cases This weak association is reflected in the fact that the mean square error, the measure of 'noise' in the data, decreased only trivially with inclusion of the covariates (a decrease of about 1 from 2 1) This means that the only way that the covariate adjustment could have 'favored' the COP I arm is the small

average difference at baseline in Kurtzke scores (2 8 COP I, 2 4 placebo). There was no difference in number of prior relapses (2 9 in each group) Consequently, it appears that the a p-value of between 025 and 055 is a better estimate of the p-value These are the p-values which result from two separate ANOVA models using investigator and investigator by treatment interaction, respectively, as the only factors other than treatment These p-values are also consistent with those obtained using the extended Cochran-Mantel-Haenszel test

Concur Dr Sahlroot JTS 8-1-96

Dr Chi Chi 8/1/96

David Hoberman, Ph D

cc
NDA# 20-644
HFD-120/Dr Leber
HFD-120/Dr Katz
HFD-120/Dr Rouzer-Kammeyer
HFD-120/Mr Purvis
✓ HFD-120/Ms Wheelous
HFD-344/Dr Lisook
HFD-710/Dr Chi
HFD-710/Dr Sahlroot
HFD-710/Dr Hoberman
HFD-710/chron

COPAXONE®
(Copolymer-1 for Injection)

FDA Advisory Committee Brief

For further Information Contact

Dr Stanley Scheindlin
Sr Director of Regulatory Projects
TEVA Pharmaceuticals USA
1510 Delp Drive
Kulpsville, PA 19443

ummary

Proposed Intended Use

COPAXONE® (Copolymer-1 for injection) is proposed to be indicated for slowing progression of disability and reducing the frequency of relapses in patients with relapsing MS

The recommended daily dose of COPAXONE® for the treatment of patients with relapsing MS is 20 mg injected subcutaneously.

Description

Copolymer-1 is the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0 141, 0.427, 0 095, and 0 338, respectively The average molecular weight of copolymer-1 is 4,700-13,000 daltons

Efficacy Results

The document attached to this executive summary presents data obtained from two adequate and well-controlled studies which provide substantial evidence of the efficacy of copolymer-1 in patients with relapsing MS. The two trials included 150 patients treated with COPAXONE® (125 in Trial 01-9001/9001E and 25 in Trial BR-1) and 151 treated with placebo (126 in Trial 01-9001/9001E and 25 in Trial BR-1) In both trials, a significant reduction in relapse rate, the primary efficacy endpoint in 01-9001/9001E, was demonstrated The greatest differential effect of copolymer-1 was observed in patients with baseline Kurtzke (E)DSS scores of 0-2

Patients receiving COPAXONE® tended to remain stable as measured by Kurtzke EDSS, while patients receiving placebo tended towards an increase in EDSS

Safety

Tne ten most common adverse experiences reported in Trial 01-90001/9001E (the most recent Phase II. trial) occurring at an incidence of at least 2% among patients who received copolymer-1 and at an incidence that was at least 2% more than that observed in the same trial for placebo patients were: injection site pain (66 4% copolymer-1 vs 36 5% placebo), asthenia (64 8% copolymer-1 vs 61 9% placebo), injection site erythema (58 4% copolymer-1 vs 13 5% placebo), injection site pruritus (38 4% copolymer 1 vs 4.0% placebo), hypertonia (35 2% copolymer-1 vs 29 4% placebo), flu syndrome (30.4% copolymer-1 vs 27.0% placebo), injection site inflammation (28.0% copolymer-1 vs 7.1% placebo), vasodilatation (27 2% copolymer-1 vs 11 1% placebo), chest pain (26 4% copolymer-1 vs 10 3% placebo), and injection site mass (26 4% copolymer-1 vs 7 9% placebo) No laboratory adverse experiences that met these criteria were reported

verse experiences associated with the use of copolymer-1 were local reactions at the site of injection. Some of the most common of these local reactions were erythema, pain, inflammation, pruritus, and mass The majority of these reactions were reported as mild, and although more common in patients treated with copolymer-1, they were also observed in patients treated with placebo

Some patients participating in Trial 01-9001/9001E reported symptoms consistent with a transient self-limited systemic reaction. This reaction is characterized by vasodilatation (flushing) or chest tightness with palpitations, anxiety, and/or dyspnea These symptoms generally appeared within minutes of an injection and lasted up to 15 minutes In the largest pivotal Trial, 01-9001/9001E, the component adverse experiences of these reactions were cited as the cause for discontinuation of 3% of those patients receiving copolymer-1 and 1% of those receiving placebo The reactions were transient, self-limited, and had no immediate or long-term sequelae

Benefit Risk

MS is a serious, chronic disorder with no known prevention or cure Two forms of recombinant interferon-beta are currently approved by FDA for the treatment of MS--interferon beta-1b, and interferon-beta-1a. There is, however, still a need for a safe and effective alternative to the interferon-β products

COPAXONE® (Copolymer-1 for Injection) has been developed for the treatment of patients with relapsing MS Two adequate and well-controlled trials have demonstrated that COPAXONE® 20 mg given subcutaneously once daily is effective and safe for use in this population These two adequate and well-controlled trials demonstrate that treatment with COPAXONE® once daily slows the progression of disability and reduces the frequency of relapses

Importantly, COPAXONE® is not associated with the flu-like symptom complex. Data from Trial 01-9001/9001E demonstrate that the incidence of flu was similar in COPAXONE® and placebo treated patients Similarly, based on data from the same trial the incidence of depression or attempted suicide was similar for COPAXONE® and placebo patients and no product related seizures were reported Administration of COPAXONE® resulted in no known product related laboratory abnormalities in 844 patients (1092 patient years) evaluated for safety

There is no evidence that daily treatment with COPAXONE® induces the formation of neutralizing antibodies Although data from clinical trials showed that copolymer-1 reactive antibodies were formed in almost all patients treated with COPAXONE®, the clinical efficacy of COPAXONE® is maintained throughout the dosing period regardless of the changes in antibody titers

COPAXONE® showed no potential for fetotoxicity or teratogenicity in rats or rabbits at doses up to 37 5 mg/kg Furthermore, in Trial 01-9001/9001E, five women conceived after being treated for prolonged periods (up to two years) with COPAXONE® Three of these

e inue their pregnancies and all of them delivered healthy babies. This finding is particularly important given the fact that most MS patients are women of child-bearing potential

The most commonly observed adverse experiences associated with the use of copolymer-1 were local reactions at the site of injection. Some of the most common of these local reactions were erythema, pain, inflammation, pruritus, and mass. The majority of these local reactions were reported as mild and, although common in patients treated with COPAXONE®, were also observed in patients treated with placebo

Clinical trials with COPAXONE® have included reports of self-limited systemic reactions that occurred following a subcutaneous injection. In Trial 01-9001/9001E, a report of either chest pain or vasodilatation in association with one or more of the following palpitations, anxiety, dyspnea, was required for an event to be categorized as a systemic reaction

The occurrences of these systemic reactions have been unpredictable and the majority of patients who have experienced them had only one. Resolution occurred within 15 minutes in all patients. No therapy was required and no sequelae have been reported in association with these events

Overall, multiple sclerosis is a serious, debilitating disease for which treatment options are limited. We believe COPAXONE® has a favorable benefit to risk ratio, and, if approved, will be a significant advance in the treatment of patients with relapsing disease

Summary Points

- **Substantial Evidence of Efficacy** - substantial evidence based on adequate and well-controlled clinical investigations has been provided to show that COPAXONE® 20 mg injected subcutaneously once daily is effective in slowing the progression of disability and reducing the frequency of relapses in patients with relapsing MS. Please see data included in the text for support

- **Long Term Data** - data supporting its long-term safety are extensive for a drug in this therapeutic category

- **Neutralizing Antibodies** - there is no evidence that daily treatment with COPAXONE® induces the formation of neutralizing antibodies. Although data from clinical trials showed that copolymer-1 -reactive antibodies were formed in almost all patients treated with COPAXONE®, the clinical efficacy of COPAXONE® was maintained throughout the dosing period regardless of the changes in antibody titers

- **Safety** - COPAXONE®, 20 mg injected subcutaneously once daily is safe for use in the treatment of relapsing MS. Local injection site reactions occur in a substantial proportion of patients, but are relatively mild and not dose-limiting. A

sy [illegible] ailation, (flushing) or chest tightness together with palpitations, anxiety, and/or dyspnea occurs less frequently, is self-limited and has not been shown to be associated with any sequelae. There appears to be no association between COPAXONE® and depression or suicide attempts, flu-like symptom complex, spontaneous abortions or seizures No skin necrosis has been reported

- **Exposure** - A total of 857 patients were exposed to copolymer-1 in the clinical program A total of 779 patients with relapsing MS were exposed to copolymer-1 Of the 779 patients with relapsing MS, 670 were exposed for at least 6 months, 490 were exposed for at least 1 year, 290 were exposed for at least two years, 87 were exposed for at least three years, 15 were exposed for at least five years, and 4 were exposed for at least 10 years

- **Laboratory Abnormalities** - administration of COPAXONE® resulted in no known product-related laboratory abnormalities in 844 patients (1092 patient years) evaluated for safety in the clinical program

- **Reproduction** - COPAXONE® had no potential for fetotoxicity or teratogenicity in rats or rabbits at doses up to 37 5 mg/kg/day

- **Carcinogenicity** - based on the results of *in vivo* clinical and pathological findings of 6 month/1 year toxicological studies in animals and patients exposed for more than 5 years, COPAXONE® has shown no potential for carcinogenicity Consistent with ICH guidelines, whole life animal studies in two species to assess the carcinogenic potential of COPAXONE® are ongoing

- **Benefit Risk** - The overall benefit to risk assessment is favorable and adequate directions for use have been written

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1 INTRODUCTION

1.1 Pharmacologic Class

COPAXONE® (copolymer-1 for injection) is an immunomodulator that modifies myelin-specific autoimmune responses

1.2 Scientific Rationale

Copolymer-1 was originally synthesized at the Weizmann Institute of Science in Rehovot, Israel, as part of a systematic study to assess the encephalitogenic properties of peptides The encephalitogenic properties of the peptides were studied in experimental allergic encephalomyelitis (EAE), the animal model of human multiple sclerosis (MS) None of the peptides which were synthesized was encephalitogenic On the other hand, some peptides containing basic amino acids exhibited a protective effect. Out of these peptides, the one with the most pronounced and reproducible protective effect was copolymer-1, which was selected for further studies and a drug development program

1.3 Description

Reduced trade secret information

1.4 Proposed Intended Use

COPAXONE® is proposed to be indicated for slowing progression of disability and reducing the frequency of relapses in patients with relapsing MS

The recommended daily dose of COPAXONE® for the treatment of patients with relapsing MS is 20 mg injected subcutaneously

1.5 Multiple Sclerosis

1.5.1 Demographics

MS is a central nervous system disease affecting approximately 300,000 people in the United States (Becker, Gidal & Fleming, 1995, Anderson et al , 1992) It is characterized by the destruction of myelin surrounding neuronal axons in the white matter of the brain and spinal cord The loss of myelin results in loss of

impulse transmission, dysfunction of the nervous system, and sensory, motor, and cognitive disability The cause of MS has not been determined, but it is possible that genetic susceptibility permits environmental triggers to initiate autoimmune processes that result in pathological changes and clinical symptoms (Sadiq & Miller, 1995)

The onset of MS peaks between the ages of 20 and 30 years Rarely does onset of disease occur before the age of 10 or after the age of 60 Its manifestations affect social, family, and economic well-being MS occurs 1 4 to 3 1 times more frequently among women than among men, the male/female ratio is equal in patients with later onset (Sadiq & Miller, 1995)

1 5 2 Symptoms

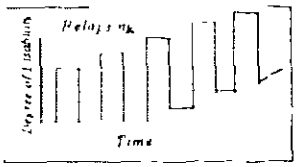
The symptoms of MS may vary greatly Some people may have visual impairment, double vision (diplopia), or involuntary movements of the eyes (nystagmus) People with MS may also experience impairment of speech, numbness or tingling sensation in the limbs and difficulty walking. Dysfunction of the bladder and bowel may also be present. In some cases paralysis of varying severity may make it necessary to use a cane, crutches, and other aids while walking MS is rarely fatal; the average life expectancy approaches that of the general population In a very small number of cases, the disease accelerates and may result in life-threatening complications

1 5 3 Clinical Course

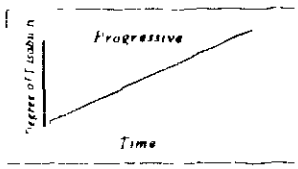
The course of MS varies between patients and in the individual patient In exceptional individuals with silent or subclinical disease, characteristic lesions are found only at autopsy, others with rapidly progressive disease may progress from onset of symptoms to death within a few months. Most patients show a progression from initial symptoms to measurable disability in sensory, motor, or cognitive functions over time

The symptoms and pattern of progression in MS can present in several distinct forms In the past, there has not been unanimous agreement on definitions for the various clinical subtypes of MS Recently, results of an international survey were published in an attempt to standardize definitions for the most common clinical courses of patients with MS, (Lublin, F D , Reingold, S C , 1996) The clinical course usually can be characterized by either acute episodes of worsening (relapses, exacerbations), gradual progressive deterioration of neurologic function, or combinations of both

Figure 1 Clinical Course of Multiple Sclerosis



Relapsing - patients experience acute worsening and may be restored to baseline neurologic function or may fail to return to baseline and progress toward increasing disability
Secondary progressive - patients experience a relapsing disease first, then a progressive course without identifiable relapses



Primary progressive - patients experience a progressive deterioration without history of clinically identifiable relapses. Rarely some of these patients may experience an exacerbation later in the disease but all patients in this group have insidious progression of disability at the time of diagnosis

As demonstrated in Figure 1, patients with relapsing MS worsen acutely and then either return to baseline neurologic function or fail to return to baseline thus experiencing increasing disability. These patients ultimately develop secondary progressive MS with continuing deterioration. Patients with primary progressive MS rarely have relapses. These patients have a continuously deteriorating course with little or no evidence of superimposed acute worsening. Infrequently, a patient with primary progressive MS may experience a relapse, but all patients with this form of MS initially present with an insidious and continuous deterioration in their neurological status.

A number of clinical and demographic factors have been identified which may predict of outcome of relapsing MS

Table 1 demonstrates that patients who experience a greater number of relapses during the first two years after diagnosis appear to deteriorate more quickly than those who have fewer relapses during their first two years after diagnosis.

Table 1 The Relationship Between the Number of Exacerbations in the First Two Years after Diagnosis of Ms and the Number of Years Needed for 50 Percent of Patients to Reach a DSS Score of 6 (Weinshenker et al., 1989; Weinshenker 1995)

Number of Exacerbations in First Two years (n = 730)		Years for 50% of Patients to reach DSS=6
≥5	(n = 34)	7
2 - 4	(n = 244)	13
<2	(n = 452)	18

DSS = Kurtzke Disability Status Scale
EDSS = Kurtzke Expanded Disability Scale

1 5 4 Pathogenesis of Multiple Sclerosis

MS is presumed to be an autoimmune disease of the CNS Abnormalities of the immune system are primarily immunoregulatory defects in T-cell function and are related to T- and B-cell hyperactivity MS results when the immune system is unable to prevent autoreactive T cells directed against myelin-associated antigens from becoming activated These activated T cells then enter the CNS to cause demyelination, loss of neural sheaths that preserve normal nervous system function (Sadiq & Miller, 1995)

Demyelination occurs in both the brain and the spinal cord as focal, scattered lesions Lesions are sharply delineated from surrounding normal tissue and are characterized by variable destruction of the myelin Plaques become inactive over time, with loss of inflammatory leukocytes. Though remyelination may occur, it tends to be aberrant and incomplete Demyelination is followed by reactive gliosis (scar tissue formation) (Sadiq & Miller, 1995). For additional information on pathogenesis see Appendix A

1 5 5 Economic Impact

Although the cause of MS is obscure, the long-term impact of the disease is clear Patients with MS can expect to live 93% of their expected life spans, but they may endure neurological impairment and/or disability for much of that time In fact, the average American with MS may forfeit as much as one third of the expected earnings to unemployment or underemployment Average lifetime losses have

been estimated at $495,845 per person with MS Within 10 to 15 years after diagnosis, only 20% to 30% of people with MS are still employed (NMSS, 1995) In the United States alone, the total cost per patient with MS is $35,000 per year, according to a recent study (Bourdette, 1993)

1 5 6 Current Treatment

MS has no known prevention or cure Two forms of interferon-beta are currently approved by FDA for the treatment of patients with MS-Interferon beta-1b, and interferon-beta-1a

Because not all patients with relapsing MS respond favorably and continuously to and/or can tolerate recombinant human beta-interferons, there continues to be a need for new, safe and effective treatments for patient with multiple sclerosis

1.6 Copolymer-1 - Mechanism of Action

Redacted confidential commercial information

2.1 Early Investigator-Sponsored Clinical Pharmacology Trials

The clinical pharmacology group of studies consists of the early, investigator-sponsored studies BR-OB, BR-OA, BR-OC, and BR-OD (see Table 5) A total of 49 patients were enrolled in these trials. Patients received copolymer-1 at dosages ranging from 2-20 mg/day IM to 15-20 mg/day SC

Table 5 COPAXONE® Clinical Pharmacology Trials (Number of Patients)

	Type of MS				
	RR-MS[a]	CP-MS[b]	MS-Unsp[c]	Other[d]	Total
BR-OB	4	12			16
BR-OA			4	3	7
BR OC		5			5
BR OD	6	15			21
Total	10	32	4	3	49

[a] Relapsing-Remitting Multiple Sclerosis
[b] Chronic Progressive Multiple Sclerosis
[c] Multiple Sclerosis Unspecified
[d] Other = ADE

The first clinical trial of copolymer-1, referred to as Trial BR-OA, was conducted by Dr Abramsky at the Hadassah Medical Center (Jerusalem, Israel). BR-OA was an open label, uncontrolled trial in four advanced MS patients and in three patients with acute disseminated encephalomyelitis (ADE). The results of Trial BR-OA revealed some suggestion of improvement in speech and vision for the MS patients, with no evidence of side effects during the course of treatment (Abramsky, Teitelbaum, and Arnon, 1977)

The second clinical trial of copolymer-1, referred to as Trial BR-OB, was also uncontrolled and open label (Bornstein et al., 1982). It was conducted in the U S by Dr Bornstein under an investigator IND Sixteen (16) patients with MS were treated Twelve (12) of the 16 patients had chronic-progressive (CP) disease and the remaining four patients had relapsing-remitting (RR) MS Of the 12 patients with CP MS, three improved after copolymer-1 treatment Two of the four patients with RR MS improved after copolymer-1 treatment

2 HISTORICAL PERSPECTIVE AND CLINICAL PROGRAM WITH COPAXONE®

For purposes of this document, the clinical program with COPAXONE® consists of the eleven clinical trials included in the NDA and shown in Table 2 which provides the number of patients and type of MS for all patients. Not included in this table are the four clinical pharmacology trials discussed in Section 2.1.

Table 2 COPAXONE® Clinical Program (number of patients)

Trial Type/Trial Number	COPOLYMER-1				Placebo			
	RR-MS	CP-MS	MS-Unsp	Total	RR-MS	CP-MS	MS-Unsp	Total
	125			125	126			126
	25			25	25			25
	150			150	151			151
	241			241				
	241			241				
	282			282				
	63			63				
	345			345				
		51		51		55		55
	43	22	5	70				
	43	22	5	70				
	779	73	5	857				206

[a] Seven patients also participated in Trial 1110-1 and were subsequently transferred to this trial
[b] no data available at time of this NDA
[c] One patient also participated in Trial BR-1 and 3 patients also participated in Trial BR-2 B and were then enrolled in this trial
[d] BE-OTP Post trial period

With the exception of follow-up data for patients who experienced systemic reactions, data contained in this document are limited to those contained in the NDA filed in October of 1995. Seven of the studies shown in Table 2 had data available for this NDA.

It is important to note that the early clinical trials were conducted by independent investigators. TEVA Pharmaceutical Industries Ltd., licensed COPAXONE® in 1985 and sponsored all trials from that point on with the exception of Trial BR-3 (a compassionate use program conducted by Dr. Bornstein under his IND). Table 3 shows the trials conducted in the U.S. by Dr. Bornstein under his investigator IND at the Albert Einstein Medical Center in New York.

Table 3 COPAXONE® Clinical Program (number of patients)

Trial Type/Trial Number	COPOLYMER-1				Placebo			
	RR-MS	CP-MS	MS-Unsp	Total	RR MS	CP-MS	MS Unsp	Total
RELAPSING MS TRIALS								
RELAPSING-MS CONTROLLED (US)								
BR-1	25			25	25			25
CP-MS CONTROLLED (US)								
BR-2		51		51		55		55
COMPASSIONATE USE & BR-PTP								
BR-3[b]	43	22	5	70				
BR-PTP[a]								

[a] No data on this trial available at the of NDA
[b] One patient also participated in Trial BR-1 and 3 patients also participated in Trial BR-OB and were then enrolled in this trial

Data on these trials are included in the NDA. Prior to the submission of the NDA, TEVA ed all available documentation from Dr. Bornstein including source document· eport forms (CRF's), available correspondence and regulatory documentation gh the clinical data were complete and in excellent condition, the original protocol, nd IRB submissions were either unavailable or incomplete. Through the Freedom rmation Act (FOI) TEVA was able to gain access to grant proposals which describe ils for which funding was requested. In an effort to confirm the results of Trial BR-1, ed in Dr. Bornstein's publication in the New England Journal of Medicine in 1987 ndix D), TEVA created a computer database from the original CRF's and source entation from the trial. The data from all 50 patients were audited. Once this process was complete, TEVA compared this database to the data contained in NAPS document no. 04520. The NAPS document was the analysis database used by Dr. Bornstein's statisticians to produce the results in the publication. Database discrepancies were reviewed in a blinded fashion by Aaron Miller, MD, the examining neurologist for this

trial The data were then re-analyzed and the results confirmed In addition, TEVA analyzed an additional cohort of patients, the All Patient cohort (ITT- Intent to Treat) Two patients initially enrolled into the trial (both on placebo), did not meet entry criteria and were discontinued early Both patients, in the opinion of the investigator, had symptomatology considered psychogenic in nature that might interfere with evaluation of treatment effect on the disease Data from both the ITT cohort and the publication cohort are presented throughout this document

From grant proposals it appears that following the enrollment of 26 (12 placebo, 14 copolymer-1) patients into Trial BR-1 (58 patient months for placebo, 56 patient months for copolymer-1) an interim analysis was performed by Dr Bornstein It is clear from the documents and discussions with Dr Miller that the integrity of the blind was never compromised It is unclear whether Dr Bornstein had intended to enroll 40 or 50 patients into the trial prior to the interim analysis Most documents written prior to the analysis, including a brief abstract submitted to the IRB state about 50 patients" A 1980 document submitted to the FDA in 1987 by Dr Bornstein, and described as the Protocol describes 40 patients Following the statement regarding 40 patients, there is a power statement which concludes that 50 patients will be enrolled (25 matched pairs) As Dr Bornstein is now deceased, it is impossible to know exactly what occurred at the time these decisions were being made This seems of little importance in the long run, as no changes were made in the data being collected or the method of collection following the interim analysis

Throughout the years, the usefulness of an ITT analysis has been the topic of much discussion in the scientific community The inclusion of data from patients who clearly should not have been enrolled or who may not have been adequately exposed to study treatment has often been questioned TEVA is of the opinion that the cohort of patients presented in Dr Bornstein's New England Journal of Medicine publication is the most relevant and is the analysis most representative of the effect of copolymer-1 in the proposed population, since these patients participated for a very short period of time and were not followed after discontinuation Recognizing the state of regulatory requirements today, both the ITT and the publication cohorts are presented throughout this document Although Trial BR-1 is clearly a double-blind, placebo controlled trial it is a small and single center trial Following the significant results from this trial a multicenter, industry sponsored Trial (C1-9001/9001E) was conducted to confirm Dr Bornstein's findings

Trial BR 2 was conducted in patients with chronic progressive MS and employed a higher dose (15mg BID) Trial BR-2 was also reviewed with the same vigor as BR-1, but only with regard to safety Trial BR-2 remained under Dr Bornstein's direction until his death and thus only serious adverse events and deaths were reported to TEVA on a regular basis Information on these events was limited

Table 4 shows the trials sponsored by TEVA

Table 4 COPAXONE® Clinical Program (number of patients)

Trial Type/Trial Number	COPOLYMER-1				Placebo			
	RR-MS	CP-MS	MS-Unsp	Total	RR-MS	CP-MS	MS-Unsp	Total
	125			125	126			126
	241			241				
	282			282				
	63			63				

[a] Seven patients also participated in Trial 1110-1 and were subsequently transferred to this trial
[b] no data available at time of this NDA

Only transient local injection site reactions were noted as adverse experiences for any of the trial patients Doses up to 20 mg/day for up to six months were initially employed Following these favorable results, daily treatment with 20 mg copolymer-1 was continued for up to 3 years.

Two additional studies, referred to as BR-OC and BR-OD, and conducted in the U S and Germany, respectively, confirmed the safety profile seen in the two initial trials The results of Trial BR-OC have been published (Baumhefner et al , 1988)

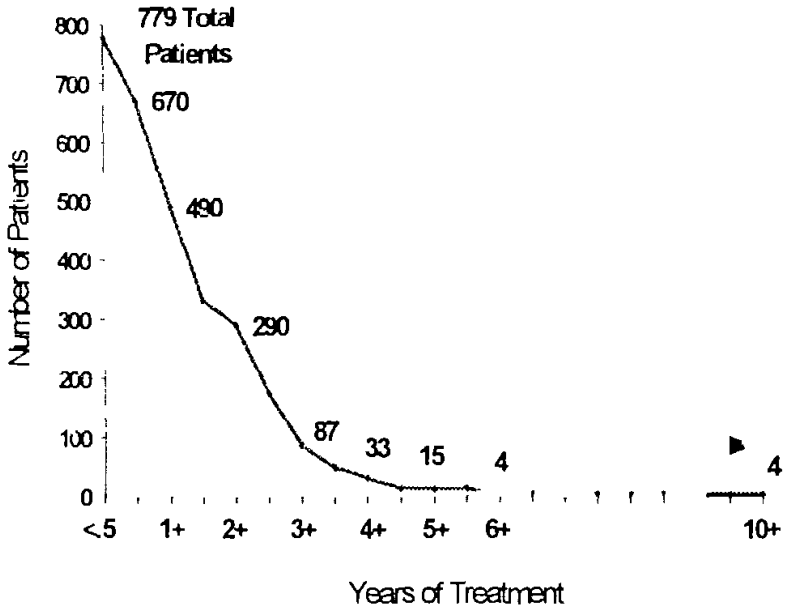
2.2 Scope of COPAXONE® Clinical Program

The suggestion that copolymer-1 may have slowed the progression of disability in two out of four patients in the RR phase of MS in Trial BR-OB provided the rationale for Dr Bornstein to continue his investigations and to initiate a double-blind, placebo-controlled single center trial of copolymer-1 in patients with relapsing MS (Trial BR-1) Trial BR-1 was conducted from February 1980 to February 1985 and was supported by a grant from the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) TEVA filed IND in 1986 and initiated a sponsor-directed multicenter Phase III clinical trial intended to corroborate Dr Bornstein's findings

With assistance from the FDA and leading clinicians and statisticians in the field of MS, TEVA initiated Trial 01-9001/9001E Trial 01-9001/9001E corroborated the results of Trial BR-1 sponsored by Dr Bornstein Kenneth Johnson, M D , at the University of Maryland was the project director for this trial Trial 01-9001/9001E and Trial BR-1 are the two adequate and well-controlled trials each of which provides substantial evidence of the effectiveness of COPAXONE® The remaining clinical studies in this NDA provide supportive evidence of effectiveness and contribute to the evidence demonstrating that COPAXONE® is safe for use as recommended in the proposed labeling

Overall, a total of 779 patients with relapsing MS have been exposed to copolymer-1 (150 in controlled trials, 536 in uncontrolled trials, and 43 in the compassionate use program) Of the 779 patients with relapsing MS, 670 were exposed for at least 6 months, 490 were exposed for at least one year, 290 were exposed for at least two years, 87 were exposed for at least three years, 15 were exposed for at least five years, and 4 were exposed for at least 10 years (Figure 2)

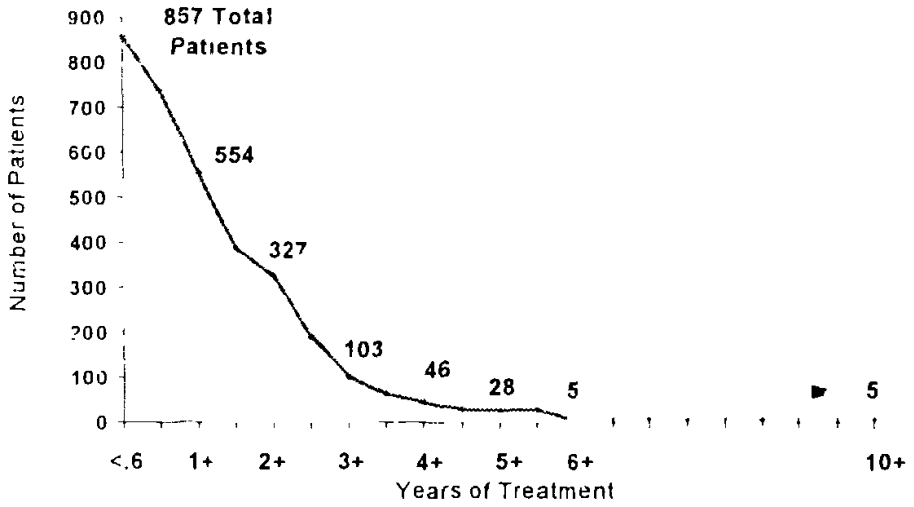
Figure 2 COPAXONE® Duration of Exposure in Relapsing MS



In addition to the relapsing MS patients, 73 patients with chronic progressive MS have been exposed to copolymer-1, 51 in a controlled trial and 22 in the compassionate use program An additional 5 patients with either unspecified forms of MS or other diseases received copolymer-1 in the compassionate use trial

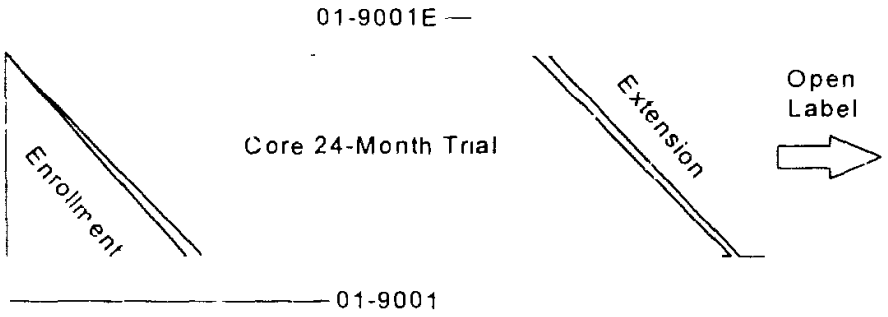
A total of 857 patients were exposed to copolymer-1 in the clinical program, as presented in the NDA (Figure 3) The total number of patient years of exposure was at least 1092 A total of 206 patients (151 with relapsing MS and 55 with CP MS) received placebo All exposure to copolymer-1 was by subcutaneous administration Of the 857 patients exposed to copolymer-1, 743 received 20 mg copolymer-1 self-administered once daily by subcutaneous injection, which is the recommended dosing regimen, 63 received 20 mg copolymer-1 once every other day by subcutaneous injection (Trial 1110-2), and 51 patients (all CP MS) received 15 mg twice daily (i e , 30 mg per day) (Trial BR-2)

Figure 3 COPAXONE® Duration of Exposure in the Clinical Program



The adequate and well-controlled studies providing substantial evidence of efficacy in patients with relapsing MS consist of Trial 01-9001/9001E, sponsored by TEVA, and Trial BR-1, directed by Dr Bornstein These two studies, both conducted in the United States, involved 301 patients, of whom 150 (125 in Trial 01-9001/9001E and 25 in Trial BR-1) were treated with copolymer-1 at a dosage of 20 mg administered by subcutaneous injection once daily Trial BR-1 was a 24 month study. Trial 01-9001/9001E consisted of an initial treatment phase of 24 months which was extended to up to 35 months Patients continued on double-blind therapy without interruption following the completion of 24 months dosing When the last patient completed the core protocol, patients participating in the double-blind extension began to switch to the open-label safety study This trial is still continuing Figure 4 provides a graphical presentation of the trial design

Figure 4 Design of Trial 01-9001/9001E



Although patients had to elect to continue on double-blind therapy at the end of the 24 month trial period, the vast majority did elect to continue Equal numbers continued for comparable lengths of time for both the COPAXONE®-treated patients and placebo treated patients

It is theoretically possible that a subgroup of patients might have opted not to continue the extension phase This could have introduced bias This concern, however, was not borne out Of the 215 patients who completed the core study, 203 (94 4%) continued into the extension phase All centers took part in the extension and patients were equally distributed between the two treatment groups There were no distinguishing baseline characteristics between patients who did or did not complete the core study or who did or did not enter the extension phase. The number of patients who did not enter the extension phase (12) represents a small proportion of the total eligible (215). Further analysis of the eligible patients who did not enter the extension study shows them to be an unremarkable cohort

The group of uncontrolled trials in patients with relapsing MS consists of ongoing trials

Redacted confidential commercial information

One study (Trial BR-2) conducted under Dr. Bornstein's IND, is grouped alone because it employed a total daily dose of COPAXONE® which was 50% greater (e g 15 mg B I D) than that recommended for use in the NDA, and because it was the only controlled study in patients with MS in the chronic progressive phase of the disease Accordingly, the primary end-points were different in Trial BR-2 than those in the two pivotal Trials BR-1 and 01-9001/9001E

Two compassionate use programs are also still ongoing.

Redacted confidential commercial information

COPAXONE® initiates its immunological activity at the site of injection Tissue homogenates reveal that copolymer-1 is actively degraded to smaller peptides at the site of administration *In vivo* demonstration of bioavailability of COPAXONE® in humans rests upon 1) a decline in the *in vitro* proliferative response of peripheral blood mononuclear cells to the drug following chronic administration, 2) formation of non-neutralizing antibodies following chronic administration of the drug, and 3) demonstration of efficacy in adequate and well-controlled clinical trials Thus, there are no clinical studies in this NDA which measure classical pharmacokinetic parameters

2.3 Demographics and Baseline Disease Characteristics

The population of patients with relapsing MS who received copolymer-1 in the clinical program was representative in terms of demographic and disease characteristics of those likely to receive the drug after it is approved for marketing Both a controlled clinical trial population (Trials 01-9001/9001E and BR-1) and a less restricted population (Trials 01-9002, 1110-1, 1110-2, and the RR cohort in BR-3) of relapsing MS patients received copolymer-1 Patients with relapsing MS between 18 and 68 years of age participated in these trials Each of the trials had more females than males, consistent with the overall population of relapsing MS patients The vast majority of relapsing MS patients for whom race was recorded were Caucasian Prior two-year relapse rate and mean (E)DSS scores at baseline were consistent with those that would be expected from a population of patients with relapsing MS of 5-9 years duration The demographic characteristics of the relapsing MS patients and their baseline disease characteristics are summarized in Table 1 and Table 2 in Appendix B

The method of selecting patients for participation in Trial BR-1 was more restrictive than that used in Trial 01-9001/9001E Trial BR-1 was a single center trial, conducted in a localized setting A large number of patients were initially questioned This led to a group of prospective participants, from which 50 were enrolled into the trial In contrast, Trial 01-9001/9001E included 11 centers with a broad geographic distribution

Although the number of CP MS patients studied was relatively small, the CP MS sample studied was representative of the population at risk and expands the safety database for copolymer-1 As this trial was designed and conducted prior to the new terminology and classification of the clinical course of MS published in 1996, no data are available on whether these patients had primary or secondary progressive MS Ages of patients with CP MS ranged from 23 to 58 years Where race of trial participants was recorded, most treated CP MS patients were Caucasian, but some Blacks participated, one Hispanic with unspecified MS also participated (Trial BR-3)

2.4 Summary of Efficacy in Adequate and Well-Controlled Pivotal Studies (Trials 01-9001/9001E and BR-1)

COPAXONE® is safe, slows progression of disability and reduces the frequency of relapses in patients with relapsing MS The evidence to support this claim is substantiated by each of the two adequate and well controlled Trials, BR-1 and 01-9001/9001E This Briefing Document focuses primarily on these trials and the more encompassing data available for safety As described previously, BR-1 was conducted under an investigator IND and was supported by a grant from the NINCDS A copy of Dr Bornstein's publication of Trial BR-1 in the New England Journal of Medicine is provided in Appendix D and a copy of Dr Johnson's publication of Trial 01-9001/9001E in Neurology, July 1995 is contained in Appendix C A more detailed description of the procedures taken to assure quality of the data from Dr Bornstein's trial appears under Section 2 0

2 4 1 Study Design

Both Trial BR-1 and Trial 01-9001/9001E were double-blind, randomized, placebo-controlled, long-term, fixed dose studies In both studies, the objective was to assess the safety, tolerability, and therapeutic efficacy of 20 mg copolymer-1 self-administered subcutaneously daily in patients with relapsing MS Both studies were designed to last 24 months, and the double-blind period of Trial 01-9001/9001E was extended to up to 35 months. In Trial 01-9001/9001E, once patients completed 24 months, they were immediately entered into the double-blind extension All patients were offered participation in the extension and investigators remained blinded throughout the dosing period (extension as well as core) Two additional differences in design are worth mentioning Trial BR-1 was single-center, while Trial 01-9001/9001E was multi-center Trial BR-1 employed a matched-pair randomization scheme, while Trial 01-9001/9001E used a centralized dynamic randomization methodology

2 4 2 Study Conduct

Each subject signed a written informed consent and oversight of each trial was provided by an Institutional Review Board In addition, both studies were overseen by a steering committee, and safety issues were reviewed by an independent safety committee

2 4 3 Patient Selection

The methods of subject selection provided adequate assurances that the patients had MS Dr Bornstein enrolled patients with definite MS based on diagnostic criteria similar to those being proposed by Poser in his publication of 1983 In 01-9001/9001E, a diagnosis of definite MS was established according to the criteria of Poser et al (1983), prior to randomization These criteria

included a requirement for objective neurologic evidence of CNS disease and a differentiation of MS from other neurologic disorders. To ensure that patients in each trial had relapsing MS, patients were to have a history of at least two well-documented relapses during the two years before entry into the trial. Although chronic progression of MS at the time of entry into the trial was a reason for exclusion, patients who had what was called at the time relapsing-progressive MS were not excluded. Today these patients would all fall into the category of relapsing MS. Subjects were required to be ambulatory (ambulatory with assistance in Trial BR-1) with a baseline Kurtzke EDSS score (See Appendix L) of 0-5 in Trial 01-9001/9001E or DSS score of 0-6 in Trial BR-1. Two patients were enrolled in Trial BR-1 who were later determined to have symptoms considered psychogenic in nature that might interfere with the evaluation of the treatment effect. These patients were not included in Dr. Bornstein's analysis.

2.4.4 Dosage Regimen

In both trials patients received either 20 mg/day of copolymer-1 or placebo by subcutaneous injection.

2.4.5 Blinding

Adequate measures were taken to minimize bias on the part of the patients, observers, and analysts of the data in both studies. The investigators, other trial personnel, and patients were all blinded throughout each of the two pivotal trials. To fully maintain blinding in the multicenter Trial (01-9001/9001E) and Trial Br-1, each patient was evaluated by a blinded Examining Neurologist and each patient's medical condition, including MS-related events, was managed by a Treating Neurologist and a blinded trial coordinator. The Examining Neurologist performed the neurologic examinations but did not discuss symptoms or adverse experiences with the patient. The Treating Neurologist managed the patient's care including adverse experiences and treatment of relapses. Trial 01-9001/9001E had an independent safety advisory committee that reviewed data from the trial in a blinded fashion. In both trials, copolymer-1 and placebo were supplied in identical single-dose vials and the labeling either concealed (Trial 01-9001/9001E) or in no way contained (Trial BR-1) the identity of trial medication.

2.4.6 Assessment of Efficacy

For both trials, pre-established relapse criteria were used and included a requirement for objective neurologic change. Relapse end-point criteria included relapse rate (the number of observed relapses during the 24 months - the primary efficacy endpoint in Trial 01-9001/9001E), proportion of relapse-free patients (the primary efficacy endpoint in Trial Br-1), and time to first relapse. Progression of disability was also defined and based on the published, validated

Kurtzke Disability Status Scale (DSS) in Trial BR-1 and the Kurtzke Expanded Disability Status Scale (EDSS) score in Trial 01-9001/9001E For a complete description of this scale, see Appendix L. In addition, Dr John Kurtzke, originator of the Kurtzke scale for MS assessment, served on an external advisory committee that monitored the progress of Trial BR-1 The end-point criteria for assessing progression of disability included proportion of progression-free patients (progression was defined as an increase of at least one point in the Kurtzke (Expanded) Disability Status Scale (EDSS) score from baseline maintained for at least 3 months), time to progression and change in Kurtzke (E)DSS score from baseline

2 4 7 Statistical Methods

In both Trial 01-9001/9001E and Trial BR-1, all statistical testing was conducted at the two-sided $\alpha = 0.05$ level of significance

For Trial 01-9001/9001E, the "all patients" (Intent-to-Treat, ITT) cohort was considered the primary cohort for inferences for the core 24 month trial and it is the basis for the results presented for the core plus extension data An "evaluable" cohort of patients who were considered as having not violated the protocol was analyzed as a secondary cohort A number of additional manifestations of the data were analyzed at 24 months, including last observation carried forward, patients treated at least 24 months (730 days), retrieved dropouts, and patients treated for at least 6 months (183 days)

For Trial BR-1, TEVA confirmed Dr. Bornstein's published analysis ("Publication cohort") and also performed a post-hoc analysis using the ITT or all patient cohort Both analyses are included in this briefing document

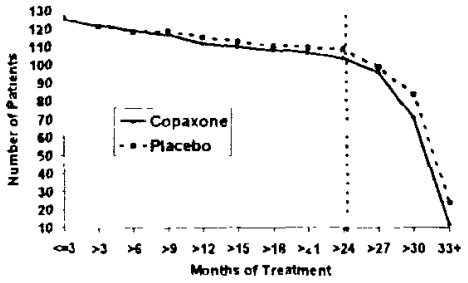
2 4 8 Study Population

The two trials were similar with respect to the patient selection criteria, resulting in similar demographics and baseline disease characteristics between studies The treatment groups within each trial were comparable with regard to demographics and baseline disease characteristics. The population studied in both trials was characteristic of the general population of patients with relapsing MS with respect to age (mean 30-35 years), sex (F M >1), race (mostly Caucasians) and baseline disease characteristics (Appendix C, Table 1)

2.4.9 Exposure

In Figures 5 and 6, duration of exposure is presented for patients who participated in Trial 01-9001/9001E and BR-1, respectively. In both studies time to withdrawal and the number of patients who withdrew were comparable for those patients treated with placebo and COPAXONE®.

Figure 5 Extent of Exposure 01-9001/9001E

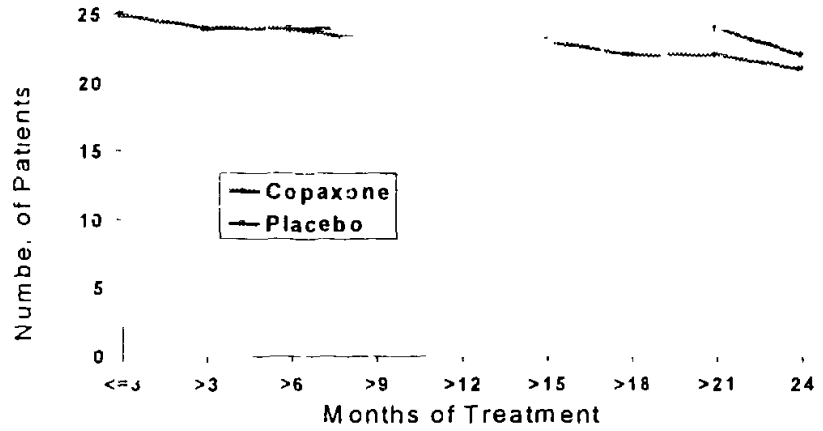


Core Protocol Extension

Mos in Trial	0-3	>3-6	>6-9	>9-12	>12-15	>15-18	>18-21	>21-24	>24-27	>27-30	>30-<33	≥ 33
Copaxone (N=125)	125	122	119	117	112	110	108	107	104	96	71	12
Placebo (N=126)	126	122	119	119	116	113	111	110	109	99	84	24

A total of 91 (73%) Copaxone and 94 (75%) placebo patients completed the extension, which lasted anywhere from 3 to 11 months, depending on the time the patient was randomized in the core 24-month protocol

Figure 6 Extent of Exposure BR-1



Mos in Trial	0-3	>3-6	>6-9	>9-12	>12-15	>15-18	>18-21	>21-24	24+
Copaxone (N=25)	25	24	24	24	24	24	24	24	22
Placebo (N=25)	25	24	24	23	23	23	21	22	21

Table 6 presents, for both trials, the number of patients randomized to receive placebo or COPAXONE®, the number of patients included in the safety analysis and the number of patients included in several of the efficacy cohorts

Table 6 Patient Disposition Trials 01-9001/9001E and BR-1

	01-9001/9001E		BR-1	
	Number of Patients		Number of Patients	
	COPAXONE®	Placebo	COPAXONE®	Placebo
Randomized	125	126	25	25
Included in Safety Analyses	125	126	25	25
Included in Efficacy Analyses				
All Patients (Intent to Treat)[a]	125	126	25	25
Evaluable[b]	105	115	25	23[d]
Completers[c]	99	109	-	-

[a] All Patients (ITT) includes all randomized patients

[b] Evaluable patients includes
- patients treated for at least 6 months of double-blind treatment,
- patients who received at least 90% of the total expected doses or at least 95% of consecutive doses
- patients who had no documented use prior to entry or continuous concomitant use of the following cytotoxic drugs or treatments azathioprine, cyclophosphamide, cyclosporin, total lymphoid radiation,
- patients who had at least 70% of scheduled neurologic evaluation follow-up visits, and had missed no more than 2 consecutive scheduled neurologic evaluation visits

[c] Completers includes patients treated for at least 730 days

[d] For Trial BR-1
- Excludes two patients who were unable to comply with the protocol

2 4 10 Results Efficacy

A number of primary and secondary endpoints were described in the protocols for Trials 01-9001/9001E and BR-1 For Trial 01-9001/9001E, the primary endpoint was the number of observed relapses during the 24 months of double-blind randomized treatment Secondary endpoints included the proportion of relapse-free patients, time to first relapse in days, progression of disease (an increase of at least one point in EDSS score maintained for 3 months), and change in disability score as measured by change from baseline in Kurtzke EDSS score.

For Trial BR-1, the proportion of relapse-free patients was denoted as the primary endpoint in both the publication and in Dr Bornstein's grant proposals Additional analysis specified in the grant proposal included a comparison of the frequency of relapses per year and the change in the number of relapses from the two years prior to study Also considered were changes in DSS and changes in duration and severity of relapses In Dr Bornstein's publication, results are presented for the primary efficacy endpoint (proportion of relapse-free patients), change in DSS (using a categorical approach), and confirmed progression of disease The sponsor's analysis of the BR-1 results was limited to those presented in the publication

FDA has produced additional analyses which are also presented in this document

2 4 10 1 Relapse Results

Relapse end-point criteria included relapse rate (the number of observed relapses during the 24 months - the primary efficacy endpoint in Trial 01-9001/9001E), proportion of relapse-free patients (the primary efficacy endpoint in Trial BR-1), and time to first relapse

2 4 10 1 1 Relapse Rate

The mean number of relapses for both Trials 01-9001/9001E and BR-1 appear in Table 7 The figures presented in Table 7 represent the mean number of relapses observed over 24 months or 24 months plus the time spent in the extension In both trials, the mean number of relapses was lower for the copolymer-1-treated patients, when compared to placebo treated patients, whether relying on the core 24 month trial or the core+extension of Trial 01-9001/9001E, whether relying on the publication cohort or the all patient cohort of Trial BR-1

Table 7 Mean Number of Relapses Trials 01-9001/9001E and BR-1

	Trial 01-9001/9001E (All Patient Cohort)		Trial BR-1	
	Core 24 Month Trial	Core + Extension	Publication Cohort	All Patient Cohort
Copolymer-1	1 29	1 47	0 6	0 6
Placebo	1 67	1 97	2 6	2 4

For Trial BR-1, the publication includes a categorical analysis of the frequency of relapses per patient, classified as 0, 1-2 and 3 more Fisher's exact test of the equality of the distribution between copolymer-1 and placebo patients was 0 002 for the publication cohort and 0 004 for the all patients cohort

For Trial 01-9001/9001E, the analysis specified in an amended protocol was a linear model accounting for the effect of drug (D), center (C), and any lack of homogeneity of treatment effect among the centers The p-value for the effect of copolymer-1 was 0 056 Four (4) covariates were then examined to assess their relation to the on-study relapse rate baseline EDSS, prior 2-year relapse rate, sex and duration of disease Of those, only baseline EDSS and prior two-year relapse rate were found to be significant covariates The resulting model including the effect of D, C, and the two covariates yielded a p-value of 0 007 for treatment effect Details of results from various model fittings can be found in Appendix M It should be noted that selecting covariates from the data of the trial may not control the false positive rate when evaluating a treatment effect

FDA produced supplementary analyses of treatment effect which did not rely on a linear model A simple t-test produced p=0 04 A categorical analysis in which each category was the number of relapses was also done Controlling for center (Cochran-Mantel-Haenszel (CMH)) produced p=0 02 and controlling for baseline EDSS (CMH) produced p=0 02

Several additional cohorts were evaluated to assess the effect of COPAXONE® at the end of 24 months in Trial 01-9001/9001E The results of these analyses are

described in Table 2 of Appendix M, and are consistent with those findings already presented

In summary the findings demonstrate a statistically significant difference between treatment groups which is essentially consistent among the various models and cohorts for the primary efficacy endpoint, i e , mean number of relapses

The results demonstrate that there are two adequate and well-controlled clinical trials showing substantial evidence that copolymer-1 is effective in reducing the frequency of relapses

2 4 10 1 2 Proportion of Relapse-Free Patients

Table 8 provides summary statistics for the proportion of relapse-free patients

Table 8 Proportion of Relapse-Free Patients for Trials 01-9001/9001E and BR-1

	Trial 01-9001/9001E					
	24 Months			Up to 35 Months		
	Copolymer-1 (N=125)	Placebo (N=126)	P-Value[a]	Copolymer-1 (N=125)	Placebo (N=126)	
Proportion of relapse-free patients	33 6%	27 0%	0 188 (CMH) 0 098 (Logistic)	33 6%	24 6%	
	Trial BR-1 Publication Cohort			Trial BR-1 All Patient Cohort		
	Copolymer-1 (N=25)	Placebo (N=23)	P-Value[b]	Copolymer-1 (N=25)	Placebo (N=25)	P-Value
Proportion of relapse-free patients	56%	26 1%	0 039	56 0%	32 0%	0 180

[a] CMH Cochran-Mantel-Haenszel, Logistic - Logistic regression adjusted for covariates used in the ANCOVA of the number of relapses
[b] Fisher's Exact Test

The proportion of relapse-free patients was the primary endpoint of Trial BR-1 and a secondary endpoint in the Trial 01-9001/9001E In Trial BR-1, the publication cohort revealed that significantly more patients on copolymer-1 were relapse-free compared to those on placebo The all patient cohort showed a numerical but not statistically significant difference in proportion of relapse-free patients between treatment groups

In Trial 01-9001/9001E, two methods of analysis were used in the comparison of relapse-free proportions The Cochran-Mantel-Haenszel (CMH) analysis is the multicenter analog of Fisher's exact test used in BR-1 Using this method, the difference in proportions between treatments was not significant for the core 24-

month trial The logistic model, a binary analog to the ANOVA/ANCOVA model, which included the full set of covariates fit in the analysis of mean number of relapses (prior 2-year relapse rate, baseline EDSS, sex, and duration of disease), also showed a numerical but not statistically significant difference favoring copolymer-1

2 4 10 1 3 Time to First Relapse

Time to first relapse was evaluated in Trial 01-9001/9001E by the log-rank test of treatment effect The BR-1 publication did not include an analysis of time to first relapse, but this was undertaken by the sponsor for the all patients treated cohort Table 9 summarizes the time to first relapse findings by trial

Table 9 Time to first Relapse for Trials 01-9001/9001E and BR-1

Trial 01-9001/9001E

	24 Months			Up to 35 Months	
	Copolymer-1 (N=125)	Placebo (N=126)	P-Value[a]	Copolymer-1 (N=125)	Placebo (N=126)
Median time to first relapse (days)	287	198	0 233	287	198

Trial BR-1 All Patient Cohort

	Copolymer-1 (N=25)	Placebo (N=23)	P-Value[a]
Median time to first relapse (days)	312[b]	156	0 008

[a] Log Rank Test
[b] 312 days are the 25 percentile Median times estimated to be over 700 days

Figures 7 and 8 give the survival curves for the all patients cohorts of Trials 01-9001 (24-month core trial), 01-9001E (core+extension) and BR-1, respectively In all cases, copolymer-1 patients demonstrated longer times until onset of a first relapse, no crossing over of survival distributions was observed In Trial BR-1, the log-rank test gave a p-value of 0 008 which was statistically significant in favor of copolymer-1

Figure 7 Kaplan-Meier Survival Function of Time to First Relapse(Core+Extension)
Trial 01-9001/9001E All Patients

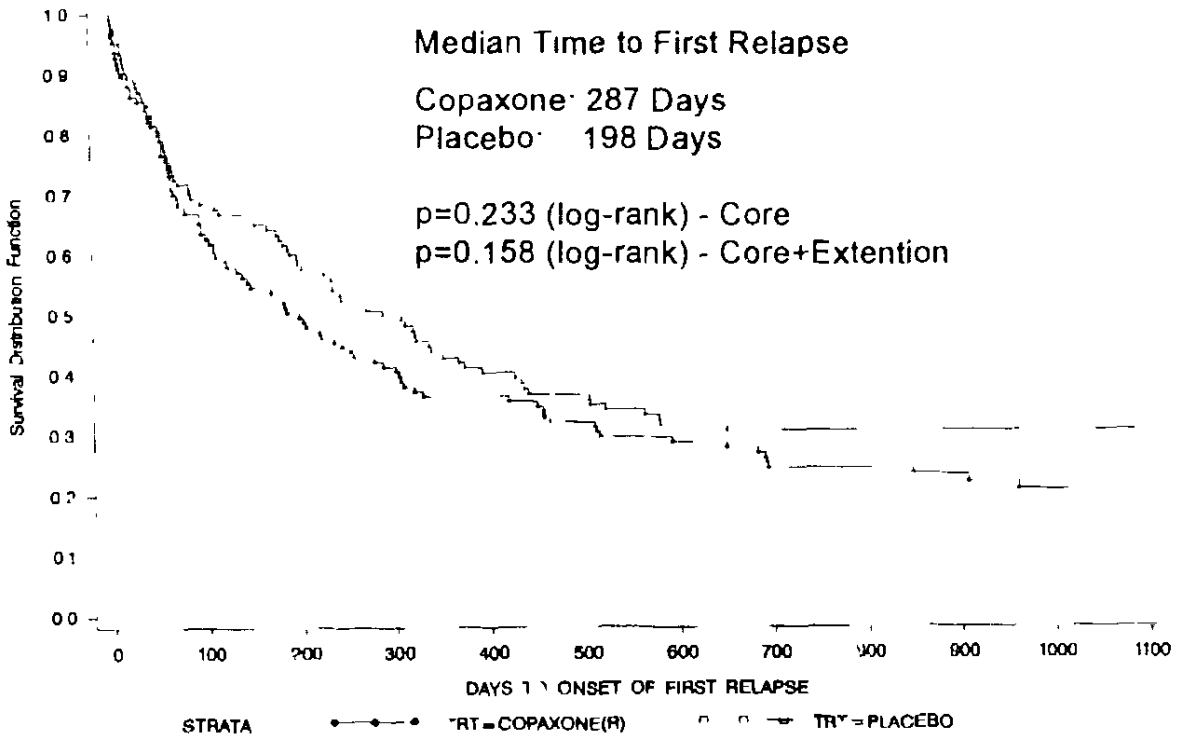
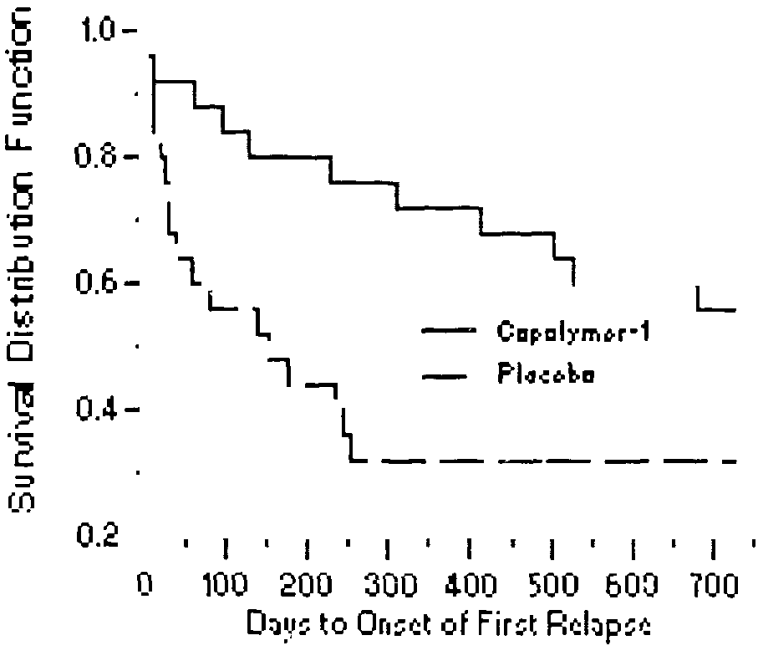


Figure 8 Kaplan-Meier Curve of Time to First Relapse for Trial BR-1
P=0 008 (log-rank)



2 4 10 1 4 Relapse Rate by Baseline Kurtzke (E)DSS Score Category

For Trial 01-9001/9001E, the frequency of relapses by baseline Kurtzke EDSS score is displayed in Figures 9 and 10 The mean number of observed relapses for both treatment groups was higher with increasing baseline Kurtzke EDSS score category For all three EDSS score categories, the number of relapses was lower for copolymer-1-treated patients compared to placebo-treated patients. The percent reduction was greatest in patients with a baseline EDSS score of 0-2

Figure 9 Mean Number of Observed Relapses Over 24 Months by Baseline EDSS Score
Trial 01-9001/9001E

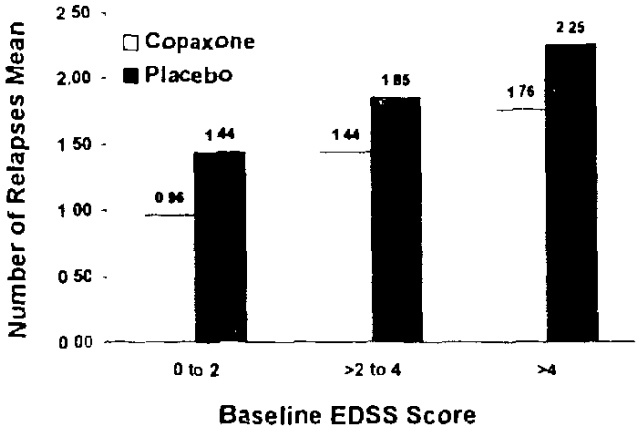
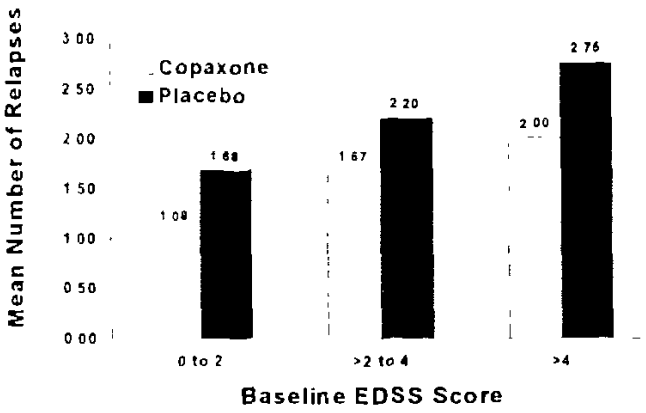


Figure 10 Mean Number of Observed Relapses (Core+Extension) By Baseline EDSS Score: Trial 01-9001/9001E



Si . arly, in BR-1, the greatest differential effect of copolymer-1 was observed in patients with a baseline Kurtzke DSS score of 0-2 Relapse rates in patients with a baseline Kurtzke DSS score of 0-2 were 0.3 and 2 6 for copolymer-1 and placebo-treated patients, respectively

2 4 10 1 5 Progression of Disability Results

Progression of disability was defined and based on the published, validated Kurtzke Disability Status Scale (DSS) in Trial BR-1 and the Kurtzke Expanded Disability Status Scale (EDSS) score in Trial 01-9001/9001E Several endpoints were evaluatede to assess progression of disability These included mean change in Kurtzke (E)DSS score from baseline, categorical change in Kurtzke disability score from baseline, proportion of progression-free patients (progression was defined as an increase of at least one point in the from baseline maintained for at least 3 months), and time to progression

2 4 10 1 5 1 Mean Change in Kurtzke Disability Score from Baseline

In Trial 01-9001/9001E two basic methods of analysis were performed First, a repeated measures analysis (RMA) was conducted on the entire profile of changes observed at each 3 monthly visit in which the EDSS score was determined The purpose of this approach was to evaluate the average treatment effect across visits

while assessing the constancy of the effect from visit-to-visit The second approach was a simple ANCOVA of the baseline to last visit EDSS score change, using a last observation carried froward (LOCF) procedure for patients who withdrew prior to completing 24 months (or 33 months for the core +extension analysis)

Figures 11 and 12 illustrate the profile of EDSS score changes from baseline in both the 24-month core trial and the core+extension During the 24-month treatment phase, repeated measures analysis indicated a significant overall effect in favor of copolymer-1 which was evident at all visits The simple change between baseline and last visit, although numerically favoring copolymer-1, was not statistically significant

Figure 11 EDSS Change from Baseline Over 24 Months, Trial 01-9001/9001E

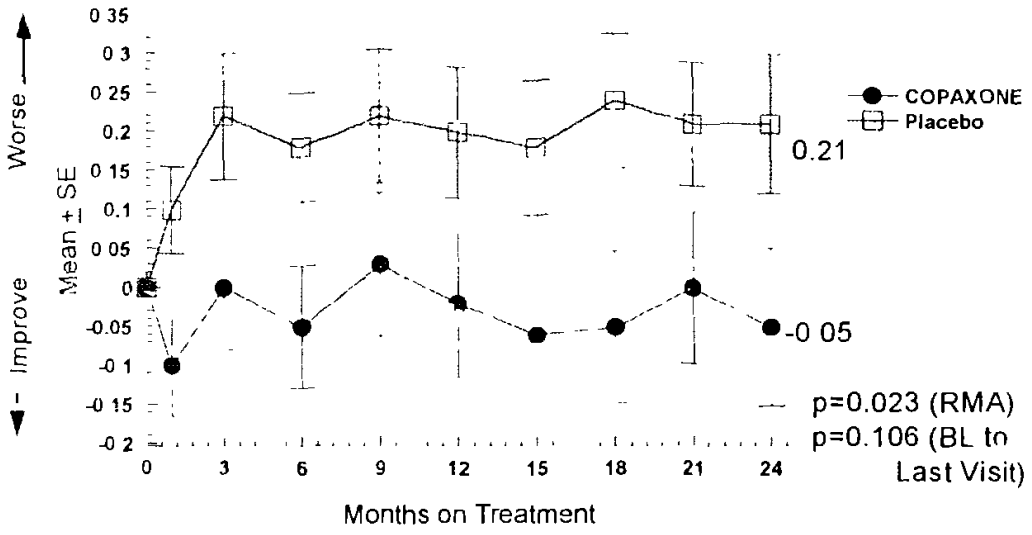
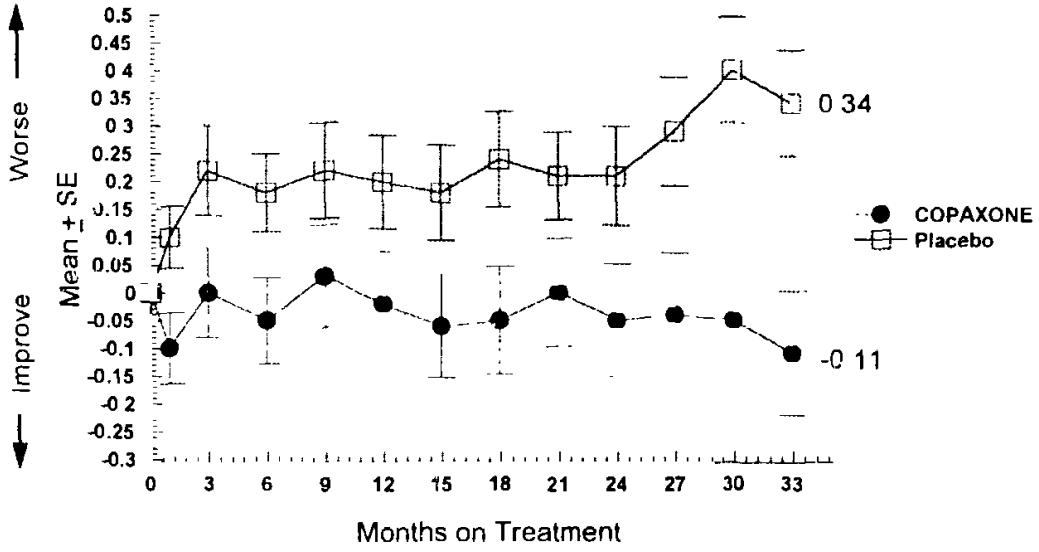


Figure 12 EDSS Change From Baseline (Core+Extension): Trial 01-9001/9001E



2 4 10 1 5 2 Categorical Change in Kurtzke Disability Score from Baseline

Based on the natural history of disease, a large proportion of patients with Kurtzke disability scores of 0-6, would be expected to remain stable over a 2-3 year period, and, as expected, the mean (E)DSS change from baseline is, therefore, relatively small Thus, another clinically relevant and useful analysis is based upon an individual patient's response, i e., the distribution of patients by change in Kurtzke (E)DSS score from baseline See Figures 13 and 14

Accordingly, progression of disability during Trial 01-9001/9001E was also evaluated by categorization of the change in EDSS score from baseline as showing improvement (EDSS change $\leq$ -1), no change (EDSS change $\pm$ 0.5), or worsening (EDSS change $\geq$ 1) There was a statistically significant effect in favor of COPAXONE® at both 24 months. At the end of the 24-month core trial period, 24 8% of COPAXONE® and 15.2% of placebo patients showed improvement, while 20 8% of COPAXONE® and 28 8% of placebo patients showed worsening Both the categorical repeated measures and simple baseline to last visit analyses demonstrated that the distribution of patients across these three categories was significantly different between COPAXONE® treated patients and those receiving placebo At the end of the extension, the proportion of improved and worsened patients with COPAXONE® were improved=27.2%, worsened=18 4%, placebo improved=12 0%, worsened=31 2%

Figure 13 Categorical Change in EDSS at Last Visit (24 Months) Trial 01-9001/9001E All Patients

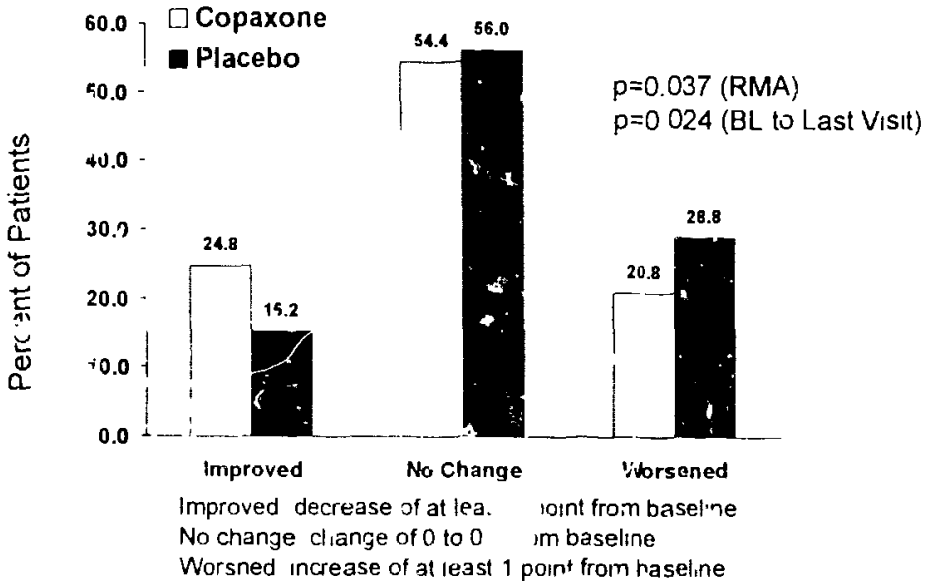
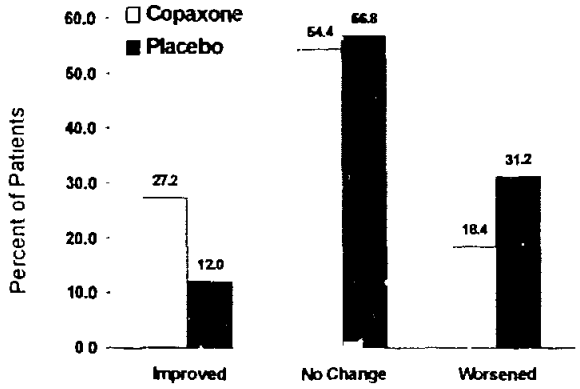
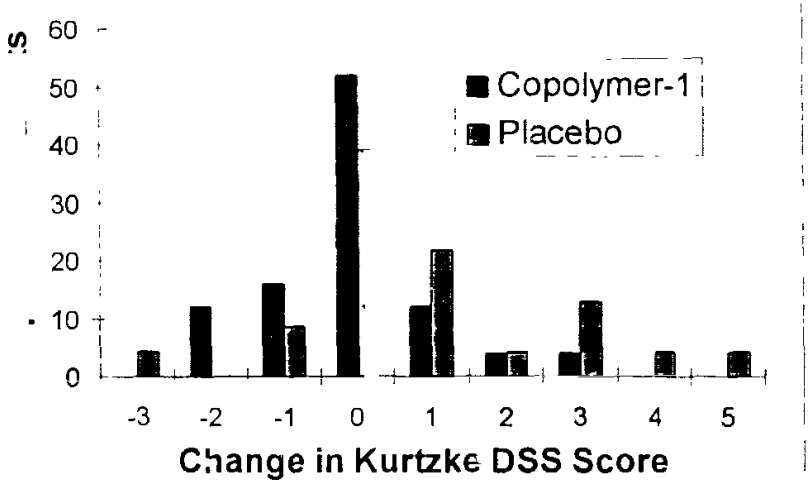


Figure 14 Categorical Change in EDSS at Last Visit (Core+Extension)
Trial 01-9001/9001E: All Patients



The distribution of patients by change in Kurtzke DSS score from baseline to final assessment is depicted in Figure 15 for the Bornstein cohort in Trial BR-1. Negative values indicated improvement, zero implied no change and positive values denoted worsening Five (20%) of the copolymer-1-treated patients had worsening in their Kurtzke DSS score compared with 12 (52 2%) of the placebo-treated patients The p-value for this difference was p=0 066. In the Trial BR-1 All Patient cohort, the copolymer-1 proportion remained at 20%, whereas the placebo proportion of worsening patients fell to 44% (p=0.128)

Figure 15 Distribution of Patients by Change From Baseline in Kurtzke DSS Score Trial BR-1 Bornstein Cohort



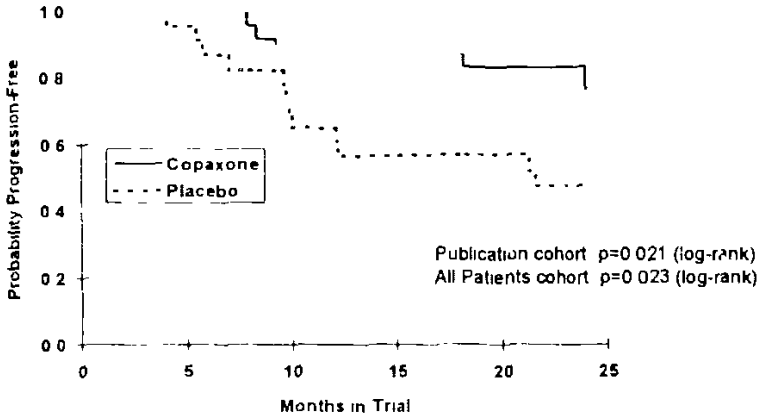
2 4 10.1.5.3 Progression-Free Patients

Progression was defined as an increase of at least one EDSS unit from baseline that was maintained for 3 months. In Trial BR-1, a positive, statistically significant effect of copolymer-1 on the proportion of progression-free patients at 24 months was obtained In the publication cohort, the proportion of progression-free patients in the copolymer-1 group was 80% compared with 47.8% in the placebo group; (p = 0 034) In the all patient cohort, the placebo percentage increased to 52% (p=0 072) An analysis taking into account the paired randomization for Trial BR-1 (McNemar's Test) gives the same result In Trial 01-9001/9001E, over three-fourths of all patients did not have confirmed progression of disease as defined in the protocol, no significant differences between treatments were observed in that trial

2 4 10 1 5 4 Time to Progression

Time to progression was evaluated in both trials. The Kaplan-Meier survival curve of time to progression for each treatment group is shown in Figure 16, for the Trial BR-1 publication and the ITT cohorts

Figure 16 Kaplan-Meier Survival Curve of Time to Progression Trial BR-1



Over the two year period, the placebo group showed progression sooner than the copolymer-1 group A statistically significant difference in favor of copolymer-1 was obtained in Trial BR-1 in both the publication and the ITT cohorts for this end-point

In Trial 01-9001/9001E, no statistically significant differences between treatment groups were seen with respect to time to progression Moreover, no values for the median time to progression could be derived, since in both groups, most of the patients did not progress by the end of the trial

2 4 11 Efficacy Conclusions From Controlled Trials

Two adequate and well-controlled studies provide substantial evidence of the efficacy of copolymer-1 in patients with relapsing MS Specifically, the trials demonstrate that COPAXONE®, at a daily dose of 20 mg by the subcutaneous route, slows progression of disability and reduces the frequency of relapses in this population

The frequency of relapses was reduced in both trials. The greatest differential effect of copolymer-1 was observed in patients with baseline Kurtzke (E)DSS scores of 0-2 Patients receiving COPAXONE® tended to remain stable as measured by Kurtzke EDSS, while patients receiving placebo tended towards an increase in EDSS

2 4 12 MRI Findings

MRI studies were carried out as adjunct research at the University of Pennsylvania, one of the participating centers in the 01-9001/9001E trial MRI evaluations were undertaken at months 0, 1, 3, 6, 12, 18, 22 and 24 All MRI measurements were obtained on General Electric 1 5T Sigma MR imagers. Fourteen COPAXONE®-treated patients and 12 placebo-treated patients were included in the analysis Since MRI has not yet been validated as a primary measure of outcome in multiple sclerosis, the data can only be used as supportive information However, they are consistent with the clinical results

2.5 Summary of Safety

The summary of safety includes data for 893 patients exposed to copolymer-1, 49 in clinical pharmacology trials and 844 in the clinical program (controlled, uncontrolled, and compassionate use trials). Safety data were unavailable for 13 of the 857 patients treated with copolymer-1 in the clinical program 779 patients had relapsing MS

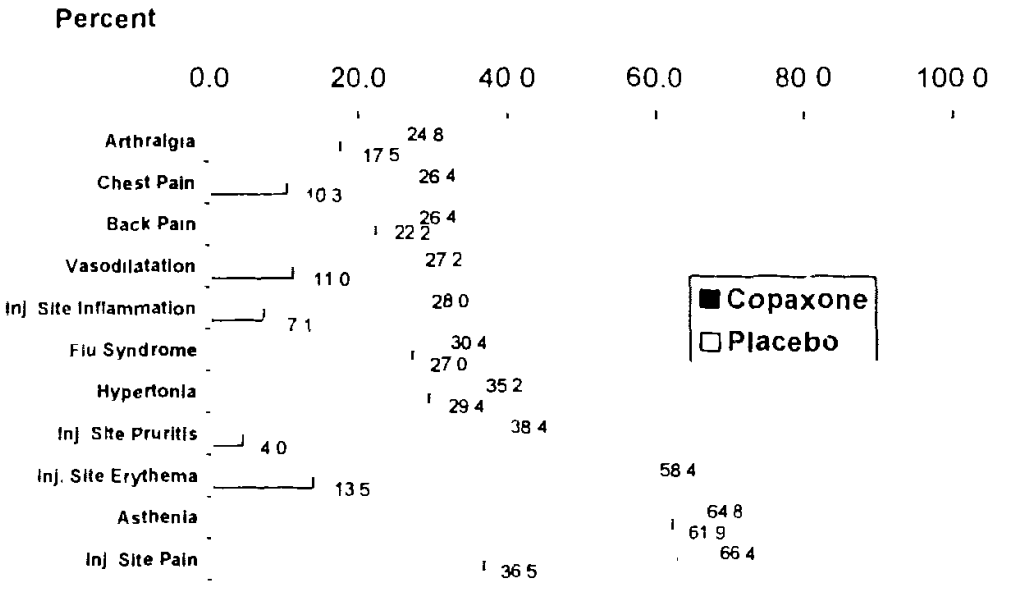
COPAXONE®, 20 mg injected subcutaneously once daily is safe for use in the treatment of patients of relapsing MS. This data package represents a cumulative exposure in excess of 1000 patient years and demonstrates that COPAXONE® is well tolerated in this population

2 5 1 Adverse Experiences

2 5 1 1 Overall Adverse Experience Summary

Figure 17, from Trial 01-9001/9001E, the larger and more recently completed of the pivotal trials, lists the adverse experiences that occurred at an incidence of at least 2% among patients who received copolymer-1 and at an incidence that was at least 2% more than that observed in the same trial for placebo patients The ten most common adverse experiences meeting these criteria were injection site pain (66 4% copolymer-1 vs 36 5% placebo), asthenia (64 8% copolymer-1 vs 61 9% placebo), injection site erythema (58 4% copolymer-1 vs 13 5% placebo) injection site pruritus (38 4% copolymer-1 vs 4 0% placebo), hypertonia (35 2% copolymer-1 vs 29 4% placebo), flu syndrome (30 4% copolymer-1 vs 27 0% placebo), injection site inflammation (28 0% copolymer-1 vs 7 1% placebo), vasodilatation (27 2% copolymer-1 vs 11 1% placebo), chest pain (26 4% copolymer-1 vs 10 3% placebo), and injection site mass (26.4% copolymer-1 vs 7 9% placebo) No laboratory adverse experiences that met these criteria were reported

FIGURE 17 Adverse Events Largest COPAXONE® Frequencies and Greater than Placebo Trial 01-9001/9001E



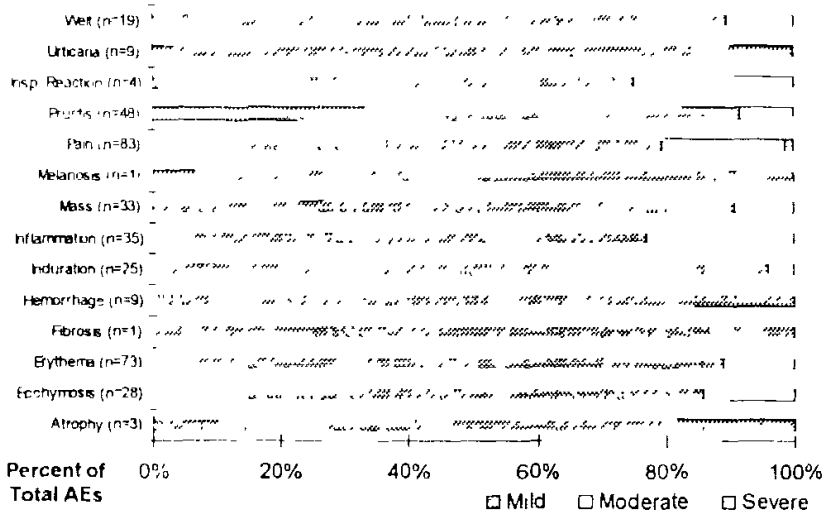
Injection site inflammation, injection site pruritus, injection site erythema, and injection site pain, chest pain, vasodilatation, were much more common in copolymer-1 treated patients Injection site inflammation, pruritus, erythema, and pain are all addressed in Section 2 5.1.2 on local adverse events Chest pain is

addressed in Section 2 5 1 3 and again in Section 2 5 1 4 , as it relates to the systemic reaction Finally vasodilatation is also discussed in Section 2 5 1 3.

2 5 1 2 Local Adverse Events

The most commonly observed adverse experiences associated with the use of copolymer-1 were local reactions at the site of injection Some of the most common of these local reactions were erythema, pain, inflammation, pruritus, and mass The majority of these reactions were reported as mild, and although common in patients treated with copolymer-1, were also observed in patients treated with placebo (see Figure 18) In Trial 01-9001/9001E, injection site pain (66 4%), erythema (58 4%), and pruritus (38 4%) occurred most frequently among copolymer-1-t ated patients, whereas injection site pain (36 5), ecchymoses (34 9%), and erythema (13 5%) occurred most frequently in placebo patients

Figure 18 Injection Site Reactions Severity for Trial 01-9001/9001E



As can be seen from Figure 18, only one report of injection site pain was considered severe, while most complaints were mild Only two patients discontinued from the trial due to injection site reactions

2 5 1 3 Systemic Adverse Events

Definition a systemic reaction was prospectively defined prior to code opening for Trial 01-9001/9001E as a cluster of symptoms associated with an individual injection In order for an event to qualify as a systemic reaction a patient had to report the occurrence of either chest pain or vasodilatation (flushing) in association with palpitations, anxiety and/or dyspnea (Refer to Appendix E) This reaction occurred sporadically and within minutes of injection and resolved after 15-30 minutes

In Trial 01-9001/9001E 19 (15 2%) patients treated with Copaxone® and 4 (3 2%) patients treated with placebo reported events consistent with the prospective definition (See Table 10) It must be noted that 10 of the 19 patients experienced a reaction only once and that patients received daily injections for 24 months

Table 10 Transient, Self-Limiting Systemic Reactions - Trial 01-9001/9001E

COPAXONE®	19 patients (15 2%) 10 with 1 episode 4 with 2 episodes 3 with 3 episodes 2 with 4 or more episodes
Placebo	4 patients (3 2%) All with 1 episode

In addition, these reactions resolved without intervention or sequelae From the available data, although the etiology of these reactions is not fully understood, they do not seem to be associated with either short or long term implications

Data comparing changes in blood pressure for those patients having experienced at least one systemic reaction to the general population of treated patients are presented in Appendix F

2 5 1 4 Chest Pain

As can be seen, the incidence of chest pain in this population is higher in the copolymer-1 treated patients A review of ECG's performed at baseline and at 24 months does not reveal any evidence of myocardial damage or clinically significant change Vital signs including an assessment of blood pressure and heart rate also did not reveal evidence of clinically significant

change Due to the sporadic and transient nature of the chest pain, it is difficult to obtain ECG data during the events Patients experiencing chest pain were no more likely to discontinue than those not reporting chest pain Thirty-three patients, treated with COPAXONE®, reported chest pain while participating in Trial 01-9001/9001E Thirteen patients treated with placebo experienced chest pain while participating in the same trial Six out of the thirty-three patients in the COPAXONE® treated group (18 2 %) withdrew ,for any reason, prematurely from the trial Three out of the thirteen (23 1 %) placebo treated patients withdrew, for any reason, prematurely from this trial With the exception of the report of chest pain, these patients had similar adverse event profiles Most commonly the chest pain requires no treatment and resolves without sequelae (Refer to Appendices F and J)

2 5 1 5 Deaths

Of the 893 copolymer-1-treated patients evaluated for safety, a total of 7 deaths were reported, all in uncontrolled trials No deaths occurred in the controlled trials or in the treatment IND Two of the deaths occurred in non-US, TEVA sponsored Trial 1110-1 These patients had relapsing multiple sclerosis One patient died due to respiratory arrest This patient did not receive COPAXONE® on the day of her death The second patient died as a result of massive broncho-pneumonia and generalized sepsis Five patients with CP MS died, one in Trial BR-2 and four in Trial ER-3 The patient in Trial BR-2 died due to sepsis and pneumonia Data on the patients who died while participating in the compassionate use program conducted by Dr. Bornstein, Trial BR-3, is limited The causes of death for these patients are listed in Appendix G The cause of death is unavailable for one of these patients None of the deaths appeared to be reasonably associated with the use of copolymer-1

2 5 1 6 Premature Withdrawals Associated With Adverse Experiences

A total of 72 (8 0%) of the 893 copolymer-1-treated patients and 5 (2 4%) of the 206 placebo-treated patients evaluated for safety withdrew from therapy specifically due to adverse experiences or reported one or more adverse experiences at the time of their premature discontinuation from a trial, this includes the two patients in Trial 1110-1 who died, but does not include the four deaths reported in Trial BR-3, which were not recorded as adverse experiences by the investigator

Reasons for premature withdrawal reported by 1% or more of the 893 patients evaluated for safety included dyspnea (17 patients, 1 9%), vasodilatation (17 patients, 1 9%), injection site erythema (10 patients,

1 1%), injection site inflammation (9 patients, 1 0%), asthenia (9 patients, 1 0%), chest pain (9 patients, 1 0%), and rash (9 patients, 1 0%) None of the withdrawals was due to a laboratory abnormality A complete list, by study, of adverse experiences associated with withdrawal is provided in Appendix H

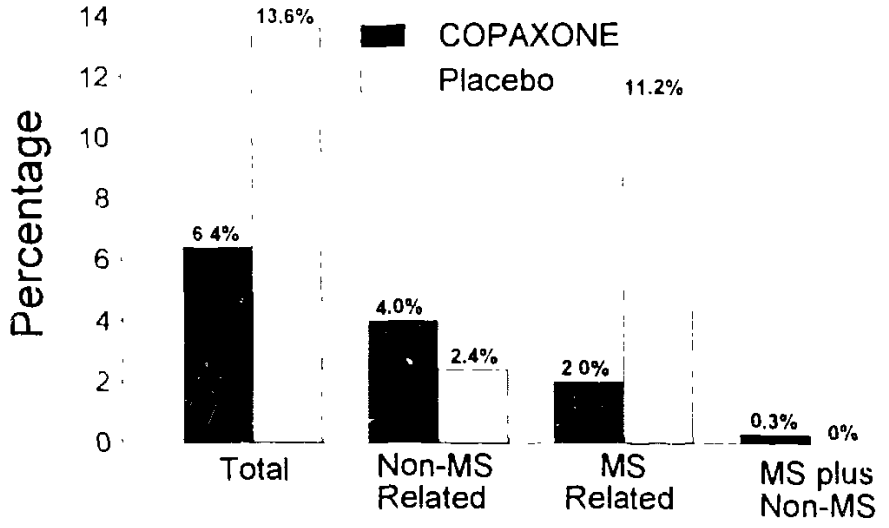
2 5 1 7 Serious Adverse Experiences

A total of 55 copolymer-1-treated patients and 16 placebo-treated patients evaluable for safety reported one or more serious adverse experiences Those serious or potentially serious adverse experiences considered (by the investigators) to be related to copolymer-1 are listed in Appendix I

2 5 1 8 Hospitalizations in All Trials

Among all 893 copolymer-1 and 206 placebo patients exposed in clinical trials (including clinical pharmacology trials) and considered evaluable for safety, 85 patients (copolymer-1, 57, 6 4%; placebo, 28, 13 6%) were hospitalized (Figure 19)

Figure 19 Hospitalizations across all patients exposed to copolymer-1



Forty-one (41) patients (copolymer-1, 36, 4 0%, placebo, 5, 2 4%) were hospitalized only for reasons unrelated to MS Of the 36 hospitalized copolymer-1 patients, 30 (3 4%) had relapsing MS and 6 (0 7%) had CP MS

Of the 5 hospitalized placebo patients, 4 (1 9%) had relapsing MS and 1 (0 5%) had CP MS

Forty-one (41) patients (copolymer-1, 18, 2 0%, placebo, 23, 11 2%) were hospitalized only for MS related events All 18 (2 0%) of the hospitalized copolymer-1 patients had relapsing MS Of the 23 hospitaliz placebo patients, 20 (9 7%) had relapsing MS and 3 (1 5%) had CP MS

Three (3, 0 3%) patients, all treated with copolymer-1, had hospitalization(s) for reasons other than MS as well as hospitalization(s) for MS related events, one (0 1%) of these patients had relapsing MS, one (0 1%) had CP MS, and one (0 1%) had MS unspecified

Of the patients hospitalized, there were many more placebo treated patients hospitalized for MS related events than COPAXONE® treated patients

2 5 1 9 Laboratory Results

Laboratory parameters evaluated in all or some of the clinical trials included hemoglobin, hematocrit, red blood cell count (RBC), platelet count, white blood cell count (WBC), white blood cell differential (neutrophils [segs], lymphocytes, monocytes, eosinophils, and basophils), hematocrit, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, mean corpuscular volume, sodium, potassium, chloride, bicarbonate, alkaline phosphatase, SGOT, SGPT, total bilirubin, creatinine, BUN and urea Other blood chemistry parameters included glucose, total protein, albumin, calcium, phosphorus, cholesterol, triglycerides, CPK, uric acid, LDH and gamma globulin.

Based on the laboratory data available in these trials, no laboratory abnormality was directly attributable to copolymer-1

2 5 2 Vital Signs

Vital signs (blood pressure and heart rate) were systematically measured in a total of 492 patients who participated in Trial 01-9001/9001E and in the US uncontrolled clinical trial, 01-9002 In all, 366 of these patients were treated with copolymer-1 and 126 were treated with placebo. Vital signs were not systematically measured in any other clinical trial except clinical pharmacology Trial BR-0A

Overall, the vital signs data showed no changes of clinical significance attributable to copolymer-1 Additional data regarding changes in blood pressure are presented in Appendix F

2 5 3 Electrocardiograms

Electrocardiograms (ECGs) were systematically done in Trial 01-9001/9001E, in which they were performed at baseline and at 24 months (or at time of early discontinuation) Overall the results revealed no adverse effects of copolymer-1 on the heart Additionally, electrocardiograms were done in clinical pharmacology Trial BR-OA, a trial with 7 patients (4 with unspecified MS and 3 with ADE), and there were no changes reported Listings of ECG findings are found in Appendix J

2 5 4 Pregnancies in Clinical Trials

During the clinical trials with copolymer-1, seven women conceived while being treated with the active drug Three of the patients electively discontinued pregnancy, three patients withdrew from treatment after 411, 459, and 751 days of treatment and delivered healthy babies No information was available regarding the seventh case

2 5 5 Drug-Drug Interactions

Interactions between copolymer-1 and other drugs have not been formerly evaluated Results from existing clinical trials which include the concurrent use of corticosteroids for up to 28 days for acute relapses in Trial 01-9001/9001E, do not suggest any significant interactions of copolymer-1 with therapies commonly used in MS patients Copolymer-1 has not been formally evaluated in combination with interferon beta. However, 10 patients in Trial 01-9002, who switched from therapy with interferon beta-1b to copolymer-1, have not reported any unexpected adverse experiences.

2 5 6 Overdosage

At the time of the NDA submission, there was one known case of overdosage. This was a 27-year-old Hispanic male who had a history of anxiety and depression After approximately 3½ months of treatment with copolymer-1, the patient was admitted to a psychiatric hospital for suicidal ideation The patient had not used study medication for several days and had self-injected four doses of study medication at once prior to the admission Forty-eight days after his hospital admission, the patient reported for his termination visit and was discontinued from the study

2 5 7 Withdrawal Effects, Drug Abuse and Dependence

No evidence or experience suggests that abuse or dependence occurs with COPAXONE® therapy, however, the risk of dependence has not been systematically evaluated

2 5 8 Conclusion

COPAXONE® is well tolerated with the most common adverse events being local injection site reactions of a mild nature and systemic reactions that do not require intervention and resolve without sequelae Although there were 7 deaths, none of these deaths appeared to be related to the use of COPAXONE® Limited data is available for those patients who died while participating in Dr Bornstein's program

COPAXONE® 20 mg administered subcutaneously is safe for use in patients with relapsing multiple sclerosis

3 SAFETY CONSIDERATIONS FROM NONCLINICAL STUDIES

3.1 Nonclinical Findings Relevant to Use of Copolymer-1 in Pregnancy

Reproduction trials included a multi generation trial in rats, two teratogenicity trials in rats (one as part of the multi generation trial, and a second independent trial) and one in rabbits, and two peri- and post-natal developmental trials in the rat (one included in the multi generation trial and one independent). The doses used in these trials were as high as 37.5 mg/kg

Copolymer-1 had no potential for fetotoxicity or teratogenicity in rats or rabbits at doses up to 37 5 mg/kg/day In a multi generational fertility and reproduction trial in rats, copolymer-1 at doses up to 36 mg/kg/day did not interfere with the reproductive performance of treated males or females or of their offspring. In addition, no effect on peri- and post-natal development of the F1 and F2 generations of treated animals was noted except for a small reduction, relative to control, in body weight gain of F1 pups observed in one trial at 6 and 36 mg/kg copolymer-1, which was not corroborated in the second trial.

Based on all these trials, the no observed adverse effect level (NOAEL) for the effects of copolymer-1 on reproduction and teratogenicity was established as higher than 36 mg/kg

3.2 Nonclinical Findings from Other Toxicology Studies

Based on the absence of any structural similarity of copolymer-1 to any known carcinogen and the mechanism of action of copolymer-1, as well as on results clinical and pathological findings in chronic toxicological studies in animals and humans, COPAXONE® has shown no potential for carcinogenicity Still, two life-span carcinogenicity studies in animals are ongoing and will be completed by the end of 1997

Anaphylaxis, mediated by Ig G1, was demonstrated following intravenous administration of high doses of COPAXONE® to sensitized guinea pig This mechanism has not been shown to correlate with anaphylaxis in humans, which is usually mediated by Ig E A few patients have, however, experienced urticaria, rash, and angioedema The events in some cases were treated with antihistamines and resolved without sequelae None resulted in death or hospitalization

4 DETERMINATION OF COPOLYMER-1 REACTIVE ANTIBODIES

Once daily dosing with COPAXONE® has been shown to result in the production of copolymer-1 reactive antibodies in man and animals, but all evidence suggest that these antibodies are not neutralizing More detail can be found in Appendix K

5 RISK BENEFIT ASSESSMENT

Benefits:

Slowing the progression of disability and reducing the frequency of relapses

In patients with relapsing MS, substantial evidence based on adequate and well-controlled clinical trials demonstrated that COPAXONE® once daily slows the progression of disability and reduces the frequency of relapses The relapse finding was maintained across all levels of disability, and was most pronounced in the less disabled patients. As measured by changes in EDSS scores, more patients on COPAXONE® remained stable or improved compared to patients receiving placebo

Neutralizing Antibodies

There is no evidence that daily treatment with COPAXONE® induces the formation of neutralizing antibodies Although data from clinical trials showed that copolymer-1-reactive antibodies were formed in almost all patients treated with COPAXONE® , the clinical efficacy of COPAXONE® was maintained throughout the dosing period regardless of changes in antibody titers

Safety and Tolerability

- 1092 patient years of exposure, over 10 years of treatment in some patients
- Fewer MS-related hospitalizations for COPAXONE® patients
- No known product-related lab abnormalities in 844 patients evaluated across all studies
- The incidence of flu-like symptoms and depression or attempted suicide, was similar in COPAXONE® and placebo-treated patients
- No product related seizures or tissue necrosis were reported

•COPAXONE® showed no potential for fetotoxicity or teratogenicity in rats or rabbits at doses up to 37 5 mg/kg

•In addition, in the multicenter phase III trial with COPAXONE®, five women treated with COPAXONE® conceived after being treated for prolonged periods (up to two years) Three of these elected to continue their pregnancies, and all delivered healthy babies

•No abnormal ECG changes seen

•No significant overall changes in vital signs.

Risks:

Local Site Reactions

•Most commonly observed adverse experience in patients receiving COPAXONE® Included erythema, pain, inflammation, pruritus and mass (also observed in patients receiving placebo). Majority were reported as mi'd

Systemic Reactions

•Self-limited, occurring following subcutaneous injection Defined as chest pain or vasodilatation and one or more of the following palpitations, anxiety or dyspnea Unpredictable in occurrence. Majority of patients who reported a systemic reaction experienced it only once Resolution occurred within 15 minutes in all patients No therapy required; no sequelae have been reported

Anaphylaxis

•Anaphylaxis can be associated with the administration of almost any foreign substance Based on the protein nature of copolymer-1, the risk for anaphylaxis can not be excluded However, in 844 patients treated to date, no anaphylactic shock was reported In addition, IgE antibodies were not identified in those patients treated A few patients experienced urticaria rash, and angioedema None has been associated with death or long-term sequelae

Conclusion

MS is a serious chronic disorder with no known prevention or cure for which treatment options are limited COPAXONE® represents a valuable clinical option due to its unique mechanism of action specific for multiple sclerosis, its excellent tolerability profile, and its potential for maintaining efficacy long-term

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APPENDIX A

Autoimmune Processes in Multiple Sclerosis

New lesions are characterized by perivenous inflammation with increased numbers of
' ' phocytes and plasma cells, macrophage infiltration, and proliferation of certain glial
s, supportive cells of the nervous system. Macrophages contain degradation
.ducts of myelin. It is thought that macrophages are a principal source of damage to
myelin, with additional harm from antibody-complement activity, direct cytokine action,
and cytotoxic T cells as well as apoptosis of oligodendrocytes

The presence of leukocyte infiltrates in the CNS lesions of MS provides a critical clue to a basic pathological process of the disease -- the breakdown of the blood-brain barrier The term blood-brain barrier (BBB) refers to a property of the endothelial lining of postcapillary venules in the CNS The endothelial cells of micro vessels in the CNS differ from those of other organ systems in that, instead of facilitating free passage of molecules and immune cells into surrounding tissues, they function to provide a barrier between many components of the blood supply and brain tissue (see Fig 1)

Fig 1 The blood-brain barrier (BBB) restricts the passage of lymphocytes from the blood into the central nervous system (CNS)

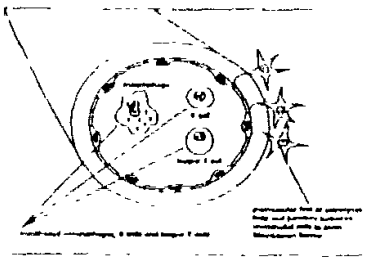


Fig 2 Activation of pro-inflammatory and suppressor lymphocytes outside the CNS results in the expression of adhesion molecules on the surface of the lymphocytes and the secretion of cytokines that act upon endothelial cells to permit passage of the lymphocytes into the CNS

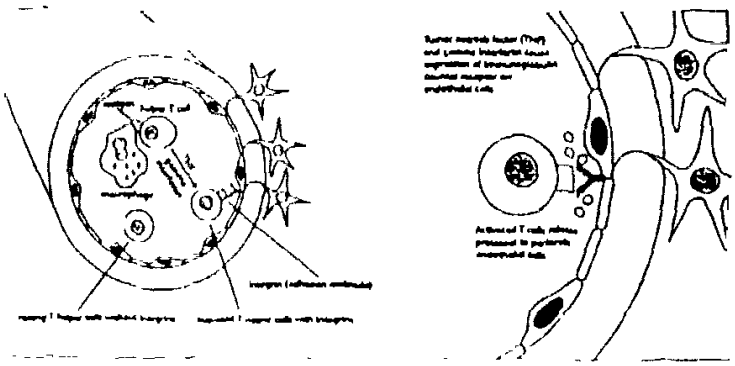
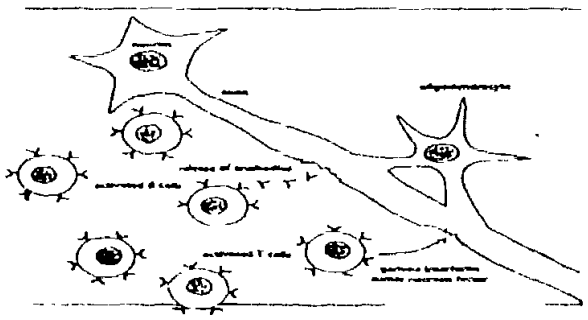


Fig 3. In MS, it is thought that the BBB is breached by an inflammatory process that allows myelin-sensitive lymphocytes into the CNS The inflammatory response widens the breach in the BBB and permits more lymphocytes into the CNS

Fig 4. These lymphocytes effect the demyelination seen in MS lesions (plaques). Lymphocyte proliferation occurs at the demyelinating lesion site. Lymphocytes release cytokines and antibodies to further damage myelin

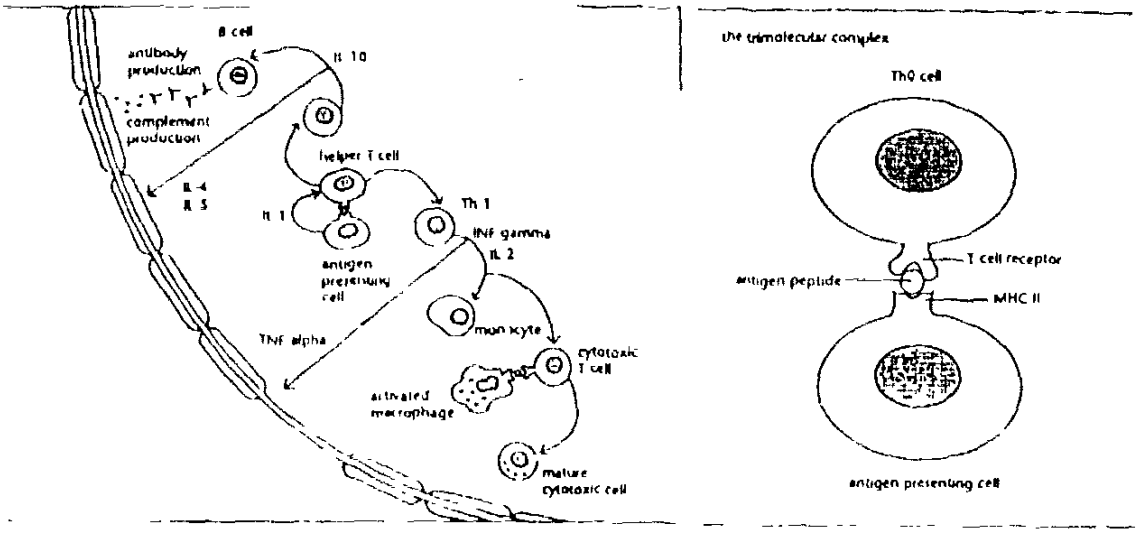


Normally, the BBB excludes most immune cells from the CNS. However, a limited number of activated lymphocytes will pass through the BBB (see Fig 2) to invade CNS tissue.[2] [Hickey, 1991] If these T cells encounter antigen-presenting cells with the specific antigen to which they are programmed to respond, they could initiate an inflammatory response. One theory of MS etiology is that some T cells may become activated to respond to myelin-associated protein components by an event outside the CNS. If those cells then gain passage into the CNS, they could initiate an inflammatory response (Fig 3, 4) that develops into a demyelinating lesion. The inflammatory response is characterized by a wide breach in the BBB and the passage of leukocytes (including both T and B cells) from the blood into brain tissue.

It is not yet known exactly what protein components of myelin are primary involved in the disease's etiology; nor is it known with certainty how the protein(s) becomes antigenic. Peptide fragments of myelin basic protein, proteolipid protein, and myelin oligodendrocyte glycoprotein have been considered as possible autoantigens. The inflammatory response is activated

when T-cell receptors (TCR) on the surface of a helper T cell form a trimolecular complex with MHC class II molecules on the surface of an antigen-presenting cell (APC) and an antigenic peptide, a moiety of a myelin protein, that is nestled between the two cells (see Fig 5, inset) This activation is also dependent upon the secretion of interleukin 1 by the APC When activated via the trimolecular complex, the helper T cell begins to secrete interleukins that influence other lymphocytes In addition, it undergoes replication, thus producing more helper T cells that can be activated upon presentation with the same antigen. This is a major positive feedback system within the inflammatory response

Fig 5 Larger drawing shows the demyelinating inflammatory response; inset shows the trimolecular complex



The activation and proliferation of helper T cells with the consequent increased cytokine secretion induce the proliferation of macrophages, cytotoxic T cells, and B cells as part of the autoimmune response (see Fig 5). Helper T cells may differentiate into either Th1 or Th2 cell types [Mosmann and Sad, 1996] The two are differentiated chiefly by the types of cytokines they secrete, and current evidence suggests that they are mutually inhibitory [Liblau, Singer, & McDevitt, 1995] Type Th1 secretes the lymphokines gamma interferon (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), and interleukin-2 (IL-2) Type Th2 secretes IL-4 and IL-5, IL-6, IL-10, TGF-β and IL-13 (see Table1) . Type Th1 cells mediate the activation of macrophages and cytotoxic T cells, the cell-mediated inflammatory response Th2 cells mediate the activation of B cells and the subsequent production of antibodies The cytokine pattern produced by each cell type seems to inhibit the activation of the other type For example, IFN-gamma inhibits the proliferation of Th2 cells, and IL10 inhibits cytokine release by Th1 cells [Mosmann and Sad, 1996]

Table 1. Th1 and Th2 Cytokine Secretion Patterns

Th1	Th2
Pro-inflammatory Cytokines	Anti-Inflammatory Cytokines
IL-2	IL-4
TNF-alpha	IL-5
IFN-gamma	IL-6
	IL-10
	IL-13
	TGF-beta

Both T-cell- and B-cell-mediated damage are thought to be important to the demyelination seen in MS. Cytokines produced by Th1 cells are central to the T-cell inflammatory process. IL-2 is required for T-cell growth, while IFN-gamma has deleterious effects in MS. TNF-alpha and IFN-gamma both induce the expression of MHC class II molecules on the membranes of astroglia and microglia in the CNS. Normally, neither of these types of glial cells carry MHC molecules on their surfaces Expression of MHC class II molecules on their surfaces allows the glial cells to function as antigen-presenting cells, further reinforcing the activation of helper cells. Secondly, IFN-gamma acts upon endothelial cells of blood vessels to enable the opening of the blood-brain barrier, thus facilitating the migration of lymphocytes into the CNS. TNF-alpha may be directly toxic to oligodendroglial cells that produce the myelin sheath Thus, helper T-cell activation and proliferation not only constitutes a positive feedback loop central to the inflammatory response, but cytokine production from activated helper T cells may produce direct damage to myelin TNF-alpha and IFN-gamma both stimulate the maturation of infiltrating monocytes into macrophages which attack myelin and, in turn, present fragments of myelin as antigens within the trimolecular complex to activate helper cells (see Fig 4) Cytotoxic T cells are triggered to proliferate and mature by IL-2. These cytotoxic T cells are also thought to participate in the attack upon myelin

Type Th2 activation of B cells is mediated by the Th2-specific pattern of cytokine secretion Activation of antigen-specific B cells by IL-4 and IL-5 results in the production of antibodies that may participate in demyelination However, recent research has suggested that the role of antibody production in MS demyelination may be more complex than a simple pathogenic one Research in an animal model of MS suggests that Th1 cells act to produce inflammatory responses and demyelination while Th2 cells damp the response and prevent damage [Liblau, Singer, & McDevitt, p 1995]In such a case, Th2 cells would function as suppressor cells that interrupt the inflammatory response and demyelination It is not immediately clear why presumably antimyelin antibody formation fostered by

Th2 cells would not continue to pursue a pathological demyelinating course. However, there is evidence that antibodies against myelin basic protein actually aid in remyelination and recovery of function in an animal model of MS. [Rodriguez, Miller and Lennon, p. 1996] It may be that the specific pattern of antigenicity of the Th2 responses is important to defining clinical consequences.

In summary, the MS lesion inflammatory response produces damage to myelin from four sources:

- Macrophages
- B-cell antibodies
- Cytotoxic T cells
- Direct cytokine damage (tumor necrosis factor)

All of these types of damage are dependent upon the activation and proliferation of helper T cells. That activation is, in turn, dependent upon continued formation of trimolecular complexes between the helper cells, antigen-presenting cells, and fragments of myelin protein.

APPENDIX B

Table 1: 01-900 ...al Type and Trial Number (Covers ...RR Cohort in BR-3)

	RR MS Trials							RR Cohort Compassionate Use (BR-3)
	Controlled (US)				Uncontrolled			
					US	non-US		
	01-9001/9001E		BR-1		01-9002	1110-1	1110-2	
	Cop-1 (n=125	Pbo (n=126)	Cop1 (n=25)	Pbo (n=25)	Cop-1 (n=241)	Cop-1 (n=282)[a]	Cop-1 (n=63)[b]	Cop-1 (n=43)
Age (years)								
Mean (SD)	34 6 (6 0)	34 3 (6 5)	30 0 (3 2)	31.0 (3 5)	39 7(9 1)	36 7(10 0)	35 (9.7)	34 7 (9 5)
Min - Max	19-46	19-46	20-33	25-35	20-68	18-59	19-61	18-54
Sex [n (%)]					(n=234)			
Male	37 (29 6)	30 (23 8)	11 (44 0)	10 (40 0)	61 (26 1)	118 (41 8)	17	11 (25 6)
Female	88 (70 4)	96 (76 2)	14 (56 0)	15 (60.0)	173 (73.9)	164 (58.2)	46	32 (74 4)
Race [n (%)]					(n=233)			
Caucasian	118 (94 4)	118 (93.6)	23 (92.0)	25 (100 0)	222 (95.3)			3 (7 0)
Black	7 (5 6)	8 (6 3)	2 (8.0)	0 (0)	11 (4 7)			
Other								
Unknown/ NA								40 (93 0)
Weight (kg)					(n=233)	(n=276)	(n=62)	
Mean (SD)	70 5 (17 0)	67 4 (16 1)			70.0 (15 6)	66 5 (13.2)	64 3 (14 8)	
Min - Max	41 7-126 8	40 9-136.8			41.8-131 8	43-120	33-115	

[a] Safety data are available for 272 of the 282 patients in Trial 1110-1
[b] Safety data are available for 61 of the 63 patients in Trial 1110-2

Table 2 [illegible]eristics by Trial Type and Trial Number (Covers 01-9[illegible]01-900[illegible]0-2 and RR Cohort in BR-3)

	RR MS Trials							RR Cohort Compassionate Use (BR-3)
	Controlled (US)				Uncontrolled			
					US	non-US		
	01-9001/9001E		BR-1		01-9002	1110-1	1110-2	
	Cop-1 (n=125)	Pbo (n=126)	Cop-1 (n=25)	Pbo (n=25)	Cop-1	Cop-1	Cop-1	Cop-1
Duration of Disease								U
Mean (SD)	7 3 (4 9) yr	6 6 (5 1) yr	4 9 (2 7) yr	6 1 (3 9) yr	8 9 (7 5) yr	103 0 (80 2) mos *[mean = 8 6 yrs]*	84 2 (73 2) mos *[mean = 7 0 yrs]*	N
Min - Max	0 6-21 2 yr	1 0-23 0 yr	2 0-10 0 yr	1 0-13 0 yr	0 2-45 0 yr	6-480 mos	10-328 mos	✓
Prior 2-Year Relapse Rate						(n=278)	(n=62)	N
Mean (SD)	2 9 (1 3)	2 9 (1 1)	3 8 (1 4)	4.0 (1.2)	3 0 (1 9)	2 9 (1 5)	2 9 (1 6)	O
Min - Max	2-11	0-6	2-8	2-7	0-12	0-10	1-12	W
Baseline Kurtzke								N
Mean (SD)	2 8 (1 2)	2 4 (1 3)	2 8 (1 9)	3.2 (2 0)	3 2 (1 7)	3 3 (1 8)	2 6 (1 4)	
Min - Max	0-5	0-5	1-6	0-6	0-6 5	0-7 5	1-7 5	
Baseline Kurtzke Category								
0-2 (Number of Patients)	51	68	13	11	86			
3-4 (Number of Patients)	57	46	5	7	93			
5-6 (Number of Patients)	17	12	7	7	62			

APPENDIX C

expedited publication

Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis:

Results of a phase III multicenter, double-blind, placebo-controlled trial

K.P. Johnson, MD; B R Brooks, MD; J.A Cohen, MD; C.C. Ford, MD; J. Goldstein, MD; R.P. Lisak, MD; L W. Myers, MD; H.S. Panitch, MD, J.W. Rose, MD; R B. Schiffer, MD, T. Vollmer, MD; L.P. Weiner, MD, J.S Wolinsky, MD, and the Copolymer 1 Multiple Sclerosis Study Group*

bstract—We studied copolymer 1 (Copaxone) in a multicenter (11-university) phase III trial of patients with re-mitting multiple sclerosis (MS) Two hundred fifty-one patients were randomized to receive copolymer 1 (n = acebo (n = 126) at a dosage of 20 mg by daily subcutaneous injection for 2 years. The primary end point was a in the MS relapse rate. The final 2-year relapse rate was 1.19 ± 0.13 for patients receiving copolymer 1 and 3 for those receiving placebo, a 29% reduction in favor of copolymer 1 ($p = 0.007$) (annualized rates = 0. · 1 and 0 84 for placebo). Trends in the proportion of relapse-free patients and median time to first relaj olymer 1. Disability was measured by the Expanded Disability Status Scale (EDSS), using a two-neurologi nd treating) protocol When the proportion of patients who improved, were unchanged, or worsened by ≥1 baseline to conclusion (2 years) was evaluated, significantly more patients receiving copolymer 1 were fo oved and more receiving placebo worsened ($p = 0.037$) Patient withdrawals were 19 (15.2%) from the copo nd 17 (13.5%) from the placebo group at approximately the same intervals. The treatment was well tole common adverse experience was an injection-site reaction. Rarely, a transient self-limited systemic reactic injection in 15 2% of those receiving copolymer 1 and 3 2% of those receiving plucebo. This reaction was cl flushing or chest tightness with palpitations, anxiety, or dyspnea and commonly lasted for 30 seconds This rigorous study confirmed the findings of a previous pilot trial and demonstrated that copolymer 1 ignificantly and beneficially alter the course of relapsing-remitting MS in a well-tolerated fashion.

NEUROLOGY 1995;45:1268

Progress in identifying effective therapies for multiple sclerosis (MS) has accelerated during this decade as pathogenic factors active in the disease have been identified We now report that treatment with copolymer 1 (Copaxone), given subcutaneously (s.c.) at a dosage of 20 mg per day in a rigorously controlled 2-year trial, significantly reduced the relapse rate in patients with relapsing-remitting MS. Neuro-

See also page 1245

*See pages 1275 and 1276 for the Copolymer 1 Multiple Sclerosis Study Group participants

From the Department of Neurology (Drs Johnson and Panitch), University of Maryland Baltimore, MD, the Department of Neurology (Dr Brooks), University of Wisconsin, Madison, WI, the Department of Neurology (Dr Cohen), University of Pennsylvania, Philadelphia, PA, the Department of Neurology (Dr Ford) University of New Mexico, Albuquerque, NM the Department of Neurology (Drs Goldstein and Vollmer), Yale University, New Haven, CT the Department of Neurology (Dr Lisak) Wayne State University, Detroit, MI the Department of Neurology (Dr Myers), University of California, Los Angeles CA, the Department of Neurology (Dr Rose), University of Utah and the Veterans Administration Medical Center, Salt Lake City, UT, the Department of Neurology (Dr Schiffer) University of Rochester, Rochester NY, the Department of Neurology (Dr Weiner), University of Southern California Los Angeles CA, and the Department of Neurology (Dr Wolinsky), University of Texas, Houston, TX

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Address correspondence and reprint requests to Dr Kenneth P Johnson Department of Neurology N4W46 University of Maryland Hospital 22 South Greene Street Baltimore MD 21201

logic impairment, as measured by the Expanded ... Disability Status Scale (EDSS),[1] was also favorably ... lerated treatment well, with ... effects. Thus, copolymer 1 ... (IFNB-1b) (licensed in 1993) ... positively alter the natural ...ting MS.[2]

...cetate salt of a mixture of ... composed of four amino ...mic acid, L-lysine, and L-ty... of 4.2, 1.4, 3.4, and 1.0, re... average molecular weight ...ons. First synthesized in ...non, D. Teitelbaum, and ...Weizmann Institute of Sci... 1 suppresses or modifies ...cephalomyelitis (EAE)[3] in ...nals including nonhuman ...[3] suggest that copolymer 1 ...vity with myelin basic pro... ...n of the cell-mediated im... ...tigen.

...al findings encouraged ...a small number of patients ...r acute disseminated en... ...olymer 1. They used a low ...icity. Bornstein et al[7] then ...in the relapsing-remitting ...gressive stages of disease ...ed fewer relapses or neu... ...five. They used various ...ministration for up to 6 ...as later extended and the ...i.m. to 20 mg s.c. daily for ...nificant side effects or lab... ...oratory abnormalities.

These early human studies indicated that copolymer 1 could be given safely and prompted a 2-year, placebo-controlled, double-blind pilot trial to evaluate its effects on the MS relapse rate, disability, and patient tolerance.[8] Forty-eight patients with relapsing-remitting MS, a high mean annual relapse rate of 1.9, and a mean disability status scale (EDSS) score of 3.0 were entered. Twenty-five received 20 mg of copolymer 1 s.c. daily and 23 received s.c. placebo. During 2 years, there were 62 relapses in the placebo group but only 16 in the copolymer 1 group, a highly significant difference. Fifty-six percent of the copolymer 1 group and 26% of those receiving placebo remained relapse-free. The effect was most pronounced in patients with the lowest EDSS ratings at entry, and there was a trend toward benefit of copolymer 1 over placebo in terms of progression of disability, especially in the patients with the lower EDSS scores at entry. Patient tolerance was very good, and there were no laboratory abnormalities.[8]

Copolymer 1 was then studied in patients with chronic-progressive MS at two centers, the Albert Einstein College of Medicine, Bronx, NY, and the Baylor College of Medicine, Houston, TX.[9] Patients with EDSS ratings from 2.0 to 6.5, inclusive, were observed for at least 12 months before randomization to document progression of their disease. One hundred six patients (mean age 42 years, mean EDSS score 5.6) were treated in a double-blind trial. They received either placebo or 25 mg of copolymer 1 twice daily by s.c. self-injection, and tolerated the therapy well. The combined results showed a trend toward benefit with copolymer 1 treatment, which was, however, not statistically significant.[9]

To further evaluate copolymer 1 treatment of patients with relapsing-remitting MS, we conducted a large, placebo-controlled, multicenter trial and have observed patients in a blinded fashion for 2 years.

Table 1 Participating universities and the number of patients randomized to each treatment group

Center	Copolymer 1	Placebo
University of California, Los Angeles	16	14
University of Maryland*	14	14
University of New Mexico	13	14
University of Pennsylvania	14	13
University of Rochester	15	13
University of Southern California	6	8
University of Texas, Houston	9	11
University of Utah	12	12
Wayne State University	12	12
University of Wisconsin	6	7
Yale University	8	8

* National coordinating center

Methods. The objectives of the current study were to compare the patient tolerance and therapeutic impact of daily s.c. injections of 20 mg of copolymer 1 or placebo over 24 months, using the number of MS relapses as the primary variable. The study was designed and the patients recruited to confirm the conclusions of the previously published pilot trial.[8]

Participants. Eleven universities with active MS centers and experience in conducting clinical neurologic research participated in the trial (table 1). The University of Maryland served as the administrative and clinical coordinating center. After an intensive training session for neurologists and study coordinators, the trial began in October 1991.

Study design. The primary end point, determined prospectively in this phase III study, was a comparison of the mean number of relapses experienced by copolymer 1- or placebo-treated relapsing-remitting MS patients during 2 years of treatment. A relapse was defined as the appearance or reappearance of one or more neurologic abnormalities persisting for at least 48 hours and immediately preceded by a relatively stable or improving neurologic state of at least 30 days. A relapse was confirmed only when the patient's symptoms were accompanied by objective changes on the neurologic examination consistent with an increase of at least a half a step on the EDSS, two points on one of the seven functional systems,[1] or one point on two or more of the functional

systems. Events associated with fever were excluded. A [illegible] played by the [illegible]
change in bowel/bladder or [illegible]

[illegible] at least one step) or
[illegible] therapy was em[illegible] "no change"

Results. *Baseline characteristics of subjects* Between October 1991 and May 1992, 284 patients were screened and 251 randomized to the two treatment groups The demographics of the randomized cohort are shown in table 2 The two groups were well matched for age, sex, race, duration of disease, mean relapse rate in the prior 2 years, EDSS, and ambulation index. As expected, the majority of randomized patients were women (73%) and white (94%). Among the patients randomized to receive copolymer 1, 51 were in the 0 to 2, 57 in the 2 to 4, and 17 in the >4 EDSS range. Of those randomized to receive placebo, 68 were in the 0 to 2, 46 in the 2 to 4, and 12 in the >4 EDSS range.

Patient exposure and withdrawals. The total patient exposure and duration of treatment is shown in table 3. The total patient exposure to copolymer 1 was 227 years and to placebo 232 years. Nineteen patients (15%) withdrew from the copolymer 1-treated group and 17 (13.5%) from the placebo group The proportion of patients who withdrew and the time to withdrawal as shown in table 3 were statistically similar over the duration of the study Three patients in the copolymer 1 group withdrew when they became pregnant, and one stopped medication because of disease progression. Two patients in the placebo group failed to comply with the protocol Two copolymer 1 patients withdrew for serious adverse events: one, after 50 days on treatment, developed immediate flushing, chest tightness, dyspnea, nausea, and vomiting (see below), which lasted for more than 90 minutes after the injection, and one, after 131 days on treatment, developed generalized lymph node enlargement. Lymph node biopsy from that patient revealed only chronic inflammatory change. Three other patients receiving copolymer 1 and one patient receiving placebo withdrew because of transient self-limited systemic reactions that were brief and not considered serious

MS relapse rates. During the 2-year trial, the copolymer 1-treated patients had 161 confirmed relapses and the placebo group had 210 confirmed relapses (table 4). The mean relapse rate (2 years) was 1.19 in the copolymer 1 group and 1.68 in the placebo group, a 29% reduction, which was statistically significant at the $p = 0.007$ level Annualized relapse rates were 0.59 for the copolymer 1 group and 0.84 for those receiving placebo. The median time to first relapse from baseline for the copolymer 1 group was 287 days and for the placebo group it was 198 days, a difference that approached statistical significance ($p = 0.097$). Forty-two patients receiving copolymer 1 (33.6%) and 34 placebo patients (27.0%) were relapse-free throughout the trial ($p = 0.098$). This result also approached statistical significance. When the relapse data were summarized in relation to baseline EDSS scores, it was found that patients with greater disability at entry had more relapses during the trial (figure 1). However, the therapeutic effect appeared to be most pronounced in patients with the lowest EDSS scores at entry (0 to 2), in

Table 2. Demographics and MS characteristics at baseline (number screened = 284)

	Copolymer 1 (n = 125)	Placebo (n = 126)
Age (yr; mean ± SD)	34.6 ± 6.0	34.3 ± 6.5
Sex		
Women	88 (70.4%)	96 (76.2%)
Men	37 (29.6%)	30 (23.8%)
Race		
White	118 (94.4%)	118 (93.6%)
Other	7 (5.6%)	8 (6.3%)
Prior 2-year relapse rate (mean ± SD)	2.9 ± 1.3	2.9 ± 1.1
EDSS (mean ± SD)	2.8 ± 1.2	2.4 ± 1.3
Ambulation index (mean ± SD)	1.2 ± 1.0	1.1 ± 0.9
Duration of MS (yr; mean ± SD)	7.3 ± 4.9	6.6 ± 5.1

EDSS Expanded Disability Status Scale

Table 3. Patient exposure and duration of treatment

Duration of treatment (mo)	Copolymer 1 (n = 125) n	%	Total patient months	Placebo (n = 126) n	%	Total patient months
≤3	3	2.4	5.6	4	3.2	9.8
>3-6	3	2.4	13.6	3	2.4	13.6
>6-9	2	1.6	13.9	0	0.0	0
>9-12	5	4	49.4	3	2.4	31.6
>12-15	2	1.6	27.0	3	2.4	41.2
>15-18	2	1.6	33.1	2	1.6	31.4
>18-21	1	0.8	18.9	1	0.8	20.5
>21-24	1	0.8	21.3	1	0.8	23.5
>24	106	84.8	2,376.0	109	86.5	2,615.9
Total	125	100	2,725.3	126	100	2,781.5

Table 4. Relapse experience of copolymer 1 and placebo groups

	Copolymer 1 (n = 125)	Placebo (n = 126)	Reduction vs placebo	p Value
Primary end points				
Relapse rate over 24 mo (covariate adjusted mean)	1 19	1 68	-29%	0 007
Annualized relapse rate	0 59	0 84		
Observed relapses over 24 mo	161	210		
Secondary end points				
Proportion of relapse-free patients	33 6%	27 0%		0 098
Median time to first relapse (days)	237	198		0.097
Number of relapses per patient				
0	42	34		
1-2	60	55		0 023
≥3	23	37		

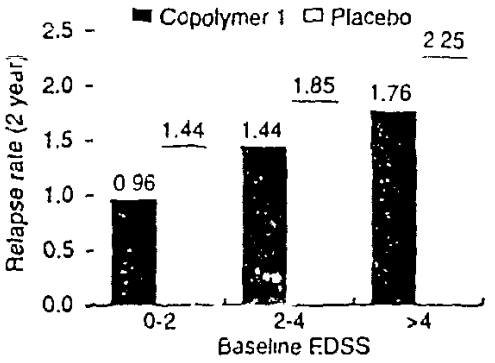


Figure 1. Changes in relapse rate observed over 2 years, by baseline EDSS score The numbers above each bar represent the mean 2-year relapse rate for each group

whom there was a 33% difference in the relapse
r of copolymer 1.

c disability. The effect of copolymer 1
neurologic disability was evaluated in a
condary end points (table 5) based on
nd ambulation index, and determined
ths by the examining neurologist. Fig-
that more patients receiving copolymer
oved whereas more patients on placebo
by one or more EDSS steps when com-
en baseline and 24 months Thus find-
istically significant in favor of copoly-
ith the categorical repeated-measures
0 037) and the analysis from baseline
s (p = 0 024) The repeated-measures
ean change in EDSS also significantly
ymer 1 (p = 0 023) When progression
disability was defined as an increase
in EDSS steps maintained for more
- that is, for two consecutive sched-
little difference was noted between
ose patients treated with copolymer 1,
ree of progression while of those re-

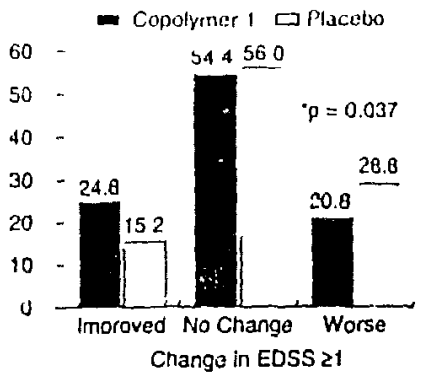
Table 5 Disability experience measured by EDSS and ambulation index of copolymer 1 and placebo groups

	Copolymer 1	Placebo	p Value
Proportion of patients with a change in disability between baseline and conclusion			
Improved (EDSS decrease ≥1)	24 8%	15 2%	
No change	54 4%	56 0%	0 037*
Worse (EDSS increase ≥1)	20 8%	28 8%	
EDSS change from baseline (mean ± SD)	-0 05 ± 1 13	0 21 ± 0 99	0 023†
Proportion of progression-free patients	78.4%	75 4%	NS
Ambulation index (mean ± SD)	0 27 ± 0 94	0 28 ± 0 93	NS

EDSS Expanded Disability Status Scale
NS Not significantly different.
* Categorical repeated measures
† Repeated-measures analysis of covariance

ceiving placebo, 75.4% showed no progression (NS). The mean ambulation index scores were also similar between groups, 0.27 for copolymer 1-treated patients and 0.28 for those on placebo (NS).

Adverse events. No clinically significant differences in vital signs were noted during the trial. The most commonly recognized adverse event was a localized injection-site reaction consisting of mild erythema and induration, which sometimes persisted for several days (table 6). It was observed at least once during 730 days of treatment in 90% of the copolymer 1-treated patients and in 59% of the patients receiving placebo The other adverse event clearly related to therapy was a transient self-limited systemic reaction (table 7), which also was recognized in earlier copolymer 1 studies[9] This reaction was sporadic and unpredictable, occurred within minutes of an injection, and was characterized by a variable combina-



...percent of patients who improved, were unchanged, or were worse by one or more EDSS steps between baseline and the last (24-month) measurement (repeated-measures ANCOVA). The numbers above the bars represent the percent of patients in the respective copolymer 1 or placebo group

Table 6. Observations on injection-site changes

	Copolymer 1		Placebo	
	n	%	n	%
Pain	80	64 00	46	36 51
Erythema	71	56.80	16	12.70
Pruritus	48	38 40	5	3 97
Inflammation	34	27 20	8	6 35
Mass	33	26 40	10	7 94
Ecchymosis	27	21 60	45	35 71
Induration	24	19 20	1	0 79

tion of flushing and chest tightness, accompanied at ... anxiety. It lasted ..., resolved sponta... ely was witnessed ... ed at least once in ...ients and in 3% of ...xperienced seven ...d with copolymer ... placebo (table 8). ...uation of therapy ... group and one in ...ents occurred ap... ...r 1- and placebo-

..., pregnancy oc... ...ourse of the trial, ... One elected to ...ntinue, while two ... normal infants ...mmon metabolic ...s showed no dif... ...seline or during ... he conclusion of ... unchanged in both groups

Table 7. Incidence of transient self-limited systemic reactions

	Copolymer 1 (n = 125)		Placebo (n = 126)	
	n	%	n	%
Systemic reaction	19	15 2	4	3 2
Primary symptoms				
Flushing without chest pain	6		2	
Chest pain without flushing	6		2	
Both chest pain and flushing	7		0	
Secondary symptoms				
Palpitation	6		0	
Anxiety	2		2	
Dyspnea	16		2	

Table 8. Number of episodes of transient self-limited systemic reactions experienced per patient over 2 years

	Copolymer 1 (n = 125)		Placebo (n = 126)	
No. episodes*	n	%	n	%
1	10	8 0	4	3 2
2	4	3 2	0	0
3	3	2 4	0	0
4	1	0 8	0	0
7	1	0 8	0	0

* Over an average of 680 injections

Discussion. This large multicenter trial successfully confirmed the findings of an earlier pilot trial[8] showing that daily s.c. injections of 20 mg of copolymer 1 significantly reduced the relapse rate in relapsing-remitting MS patients. In addition, repeated-measures analysis of the mean EDSS scores showed significant differences in disability between the treatment groups in favor of those receiving copolymer 1. Finally, the benign patient tolerance profile of earlier trials was maintained.

The difference in mean relapse rate was the primary end point in this 2-year study. Very few relapses were not confirmed by the examining neurologist within 7 days of onset of symptoms (as mandated in the protocol), so we believe this is a true picture of the clinical course experienced by these two well-matched groups. The difference in mean relapse rate was highly significant (p = 0.007). This clinical effect persisted through each 6-month interval of the study. The observations on the median number of days to first relapse and the proportion of relapse-free patients, although not statistically significant, did show strong trends in favor of copolymer 1 therapy.

Figure 1 shows that patients with low EDSS scores at baseline were more likely to have had fewer relapses during the trial. A similar finding was evident in the copolymer 1 pilot study.[8] Of in-

terval, there appeared to be a correlation between EDSS at baseline and the subsequent relapse experience (figure 1). Patients with higher EDSS scores at entry may have had more active or virulent MS, showing not only more disability at baseline but also continued higher relapse activity during the course of the trial. This suggests that any large MS cohort is rather heterogeneous and that improved methods of patient classification must be found to aid in the design of future MS therapy trials.

The difference in the mean relapse rate between groups in this study, although highly significant, was less pronounced than in the earlier copolymer 1 pilot study.[8] The reason for this is unknown, but one possible reason may be the obvious difference in the patient populations studied. In this investigation, patients had a lower pre-study frequency of relapses and there were proportionally fewer patients at the low end of the EDSS scale. One could argue that the cohort for this trial was more representative of the majority of relapsing-remitting MS populations.

Now that both copolymer 1 and IFNB-1b[2] have been shown to positively influence the relapse rate in relapsing-remitting MS, it is tempting to compare the magnitude of effect. The difference between the high-dose IFNB-1b group and a placebo group was highly significant at the 0.0001 level. However, the annual relapse rate for IFNB-1b was 0.84 whereas in this copolymer 1 study it was 0.59. The IFNB-1b high-dose group and the copolymer 1 groups were of similar size (IFNB-1b = 115 and copolymer 1 = 124), yet during 2 years of observations, those receiving IFNB-1b experienced 173 relapses whereas the copolymer 1-treated group experienced only 161 relapses. Are such differences due to a different therapeutic effect or to inequalities in the populations selected for study? Probably only improved information on the natural history of MS, improved protocol design, and comparison of other measures of effect in future studies will answer this question.

A positive influence on neurologic disability was suggested in earlier copolymer 1 clinical studies where there were encouraging trends but no significant differences.[8,9] In the current investigation, several methods of analysis, based on the EDSS, showed that copolymer 1 had a significant effect on neurologic disability even though the patient population was not selected primarily to measure such differences. Figure 2 shows evidence of neurologic improvement for patients receiving copolymer 1 whereas patients receiving placebo were more likely to be worse (disability defined as a change of one or more full steps on the EDSS determined repeatedly between baseline and 24 months, $p = 0.037$). In another analysis of repeated measures, the mean EDSS, determined at 3-month intervals (table 5) was also significantly improved in favor of copolymer 1 ($p = 0.023$). The ability in this trial to demonstrate significant therapeutic benefits both on the relapse rate and on neurologic disability suggests that these two fundamental measures of MS activity are linked.

Two predetermined measures of neurologic disability failed to demonstrate significant differences between the treatment groups. The proportion of patients without sustained progression for 90 or more days (EDSS ≥ 1 step) was similar, 78.4% in the copolymer 1 group and 75.4% in the placebo group after 2 years (table 5). This is not dissimilar to the findings in the IFNB-1b study[2] of similar size, where 80% of patients receiving the high dose and 72% of those receiving placebo were progression-free after 3 years when the same definition of progression was used. The effect of copolymer 1 treatment on the ambulation index was also not significant (table 5). These findings are not surprising, in that patients relatively early in the course of their MS were selected for both studies and relapse activity was the primary criterion for selection and therapeutic effect. A treatment effect on sustained progression can be documented only if the placebo group shows measurable worsening during the course of the trial. Patients with the MS characteristics used for selection to these two studies (copolymer 1 and IFNB-1b) clearly are unlikely to progress by defined criteria in 2 or 3 years.

Patient tolerance to long-term dosing and the safety of copolymer 1 were positive in this trial, in line with previous experience. Injection-site reactions were common, appearing at least once during 730 injections in 90% of patients receiving copolymer 1 and 59% in patients given placebo. The high rate observed in the placebo group in this investigation compared with previous copolymer 1 clinical studies may have been due to the inclusion of mannitol in both copolymer 1 and placebo preparations. In fact, the substantial number of injection-site reactions noted by patients receiving placebo probably improved investigator and patient blinding.

The transient, self-limited, systemic reaction we observed has been a consistent finding in each copolymer 1 clinical trial. The increased size and duration of this study provide additional evidence that the reaction is benign, even though its cause is unknown. Fifteen percent of patients receiving copolymer 1 and 3% of patients receiving placebo experienced between one and seven similar episodes at unpredictable times throughout the trial. Four patients treated with copolymer 1 and one receiving placebo withdrew from the study because of this reaction. Rarely was its duration long enough for it to be observed by any health professional, and in no case were there persisting sequelae. Because of its unpredictable and sporadic nature, it is unlikely to have an allergic basis.

No other adverse event appeared significantly more often in copolymer 1 than in placebo treated patients. Similar numbers withdrew from each group at approximately the same intervals throughout the 2-year study (table 3). An experienced safety committee meeting independently to review all safety issues at 3 month intervals was

at no time concerned about the continuation of the trial. There was no evidence of any laboratory or ECG abnormalities [illegible]

[illegible] molecules on antigen presenting cells. More recently, these investigators[19] demonstrated direct binding of copolymer 1 to human antigen-presenting cells of various HLA haplotypes. Using biotinylated antigens, they showed that copolymer 1 could inhibit binding of MBP or the MBP peptide p84-102 to these cells, probably through competition for MHC class II surface molecules.

Despite recent progress in defining the mechanism of action of copolymer 1, its inhibitory specificity for MBP seems paradoxic in view of its random amino acid sequence and striking lack of specificity for species, MBP epitope, or MHC restriction. Fridkis-Hareli et al[20] proposed that copolymer 1, as a complex mixture of polypeptides, can bind "promiscuously" to a variety of MHC molecules, while it resembles MBP sufficiently to inhibit activation of T cells with many different peptide specificities and MHC restrictions. To some extent, the apparent specificity for MBP may be a function of limited testing, as suggested by a study[21] in which copolymer 1 inhibited the in vitro responses of T-cell hybridomas specific for ovalbumin and insulin. As additional antigens are investigated, it may become clear why immune responses to some can be inhibited by copolymer 1 while responses to others cannot. Of particular interest in this regard would be the effect of copolymer 1 on T-cell reactivity to myelin proteolipid protein and myelin-oligodendrocyte glycoprotein, both of which are encephalitogenic in experimental animals and could play a role in the pathogenesis of MS.

The clinical results reported here confirm the provocative findings from the pilot trial[8] of copolymer 1 published in 1987. Additionally, they indicate that there are now two treatments proven to alter the natural course of relapsing-remitting MS, interferon beta-1b and copolymer 1. Of interest, laboratory studies indicate that interferon beta and copolymer 1 produce their effects by different immunologic mechanisms, suggesting that they could be used in combination. In vitro studies do, in fact, show that the two agents produce at least additive effects on human lymphocytes[22] sensitized to MBP. The concept of combined therapy must be carefully investigated to rule out the possibility of unexpected adverse reactions. Pending regulatory approval, copolymer 1 will become available as one of the unique agents capable of influencing the long-term course of relapsing-remitting MS. Physicians will then have the opportunity of selecting the most appropriate treatment for the patients in their care considering the extent of therapeutic effect, and patient tolerance and safety.

The Copolymer 1 Multiple Sclerosis Study Group comprises the following investigative teams: *Hospital of the University of Pennsylvania*—Shawn J. Bird, MD, Christian Constantinescu, MD, Dennis L. Kolson, MD, PhD, Francisco Gonzalez-Scarano, MD, Daniel Brennan, RN, Dorothea Pfohl, RN, *University of New Mexico School of Medicine*—Ralph N. Mandler, MD, Gary A. Rosenberg, MD, Carol Jeffrey, RN, *Wayne State University School of Medicine*—Geoffrey R. Barger, MD, Balbir Gandhi, MD, Patricia M. Moore, MD, Lisa R. Rogers, DO, Deena Lisak, RN, Lisa Smith, *UCLA School of Medicine*—George W. Ellison, MD, Robert W. Baumhefner, MD, Sharon L. Craig, RN, *University of Maryland School of Medicine*—Suhayl S. Jalbut, MD, Eleanor Katz, RN, Kathleen L. Conway, RN, *University of Utah Veterans Administration Medical Center*—James B. Burns, MD, Connie Shiba, RN, *University of Rochester Medical Center*—Daniel W. Giang, MD, Mary O. Petrie, RN, *Yale University*—Joseph B. Guarnaccia, MD, Susan Anderson, RN, Anne McKeon, *University of Texas at Houston*—Micheline McCarthy, MD, PhD, Azreena B.

Thomas, MD, Francine J. Vriesendorp, MD, Sara G. Austin, MD, John W. Lindsey, MD, Mazen Dimachkie, Cerreta, RN, *USC School of Medicine*—Nor-ck, MD, Kathleen A. McCarthy, RN; *Univer-onsin*—John Fleming, MD, Jennifer H. Par-nnifer Tamulevich, BA, Christy Wessler, BA. naceutical Industries, Ltd—Shaul Kadosh, d Hait, MS, Yafit Stark, PhD, Irit Pinchasi, inal Medical Research Corporation—Nina

mittee Chairman, Stanley van den Noort, s, Irvine; Aaron Miller, MD, , New York, NY; David Mel-Hospital, Baltimore, MD; ional Multiple Sclerosis So-ing H. Gomolin, MDCM, FACP, FACP, Gurwin Jewish Geriatric Center, New York, NY

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APPENDIX D

A PILOT TRIAL OF COP 1 IN EXACERBATING–REMITTING MULTIPLE SCLEROSIS

MURRAY B. BORNSTEIN, M.D., AARON MILLER, M.D., SUSAN SLAGLE, M.P.H., MURIEL WEITZMAN, M.S.W., HOWARD CRYSTAL, M.D., ELLEN DREXLER, M.D., MARSHALL KEILSON, M.D., ARNOLD MERRIAM, M.D., SYLVIA WASSERTHEIL-SMOLLER, PH.D., VINCENT SPADA, M.Sc., WILLIAM WEISS, B.A., RUTH ARNON, PH.D., ISRAEL JACOBSOHN, DVORA TEITELBAUM, PH.D., AND MICHAEL SELA, PH.D.

Abstract Cop 1 is a random polymer (molecular weight, 14,000 to 23,000) simulating myelin basic protein. It is synthesized by polymerizing L-alanine, L-glutamic acid, L-lysine, and L-tyrosine. It suppresses but does not induce experimental allergic encephalomyelitis, an animal model of multiple sclerosis. It is not toxic in animals.

In a double-blind, randomized, placebo-controlled pilot trial, we studied 50 patients with the exacerbating–remitting form of multiple sclerosis, who self-injected either 20 mg of Cop 1 dissolved in 1 ml of saline or saline alone daily for two years.

Six of 23 patients in the placebo group (26 percent) and 14 of 25 patients in the Cop 1 group (56 percent) had no exacerbations ($P = 0.045$). There were 62 exacerbations in the placebo group and 16 in the Cop 1 group, yielding two-year averages of 2.7 and 0.6 per patient, respectively. Among patients who were less disabled on entry (Kurtzke disability score, 0 to 2), there were 2.7 exacerbations in the placebo group and 0.3 in the Cop 1 group over two years. Among patients who were more affected (Kurtzke disability score, 3 to 6), there was an average of 2.7 exacerbations in the placebo group and 1.0 in the Cop 1 group. Over two years, less disabled patients taking Cop 1 improved an average of 0.5 Kurtzke units; those taking placebo worsened an average of 1.2 Kurtzke units. More disabled patients worsened by 0.3 (Cop 1 group) and 0.4 (placebo group) unit. Irritation at injection sites and rare, transient vasomotor responses were observed as side effects.

These results suggest that Cop 1 may be beneficial in patients with the exacerbating–remitting form of multiple sclerosis, but we emphasize that the study is a preliminary one and our data require confirmation by a more extensive clinical trial. (N Engl J Med 1987; 317:408-14.)

COP 1 is synthesized by the random polymerization of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine in the ratio of 6.0:1.9:4.7:1.0 (molecular weight, 14,000 to 23,000). It was one of a series of polypeptides prepared to simulate myelin basic protein, a natural component of the myelin sheath.[1-3] Myelin basic protein in Freund's complete adjuvant induces experimental allergic encephalomyelitis, an animal model of multiple sclerosis. In saline, it suppresses the response in challenged animals.[1,3] Some of the polypeptides simulating myelin basic protein, particularly Cop 1, proved incapable of inducing experimental allergic encephalomyelitis, yet suppressed the disease in rabbits, guinea pigs, mice, and nonhuman primates.[1,6-9] Studies in mice suggest that it acts through the production of antigen-specific suppressor T cells.[10,11] Cop 1 is also nontoxic during short-term and longer-term (three to six months) administration in mice, rabbits, and dogs (Meshorer A: personal communication)

In view of these characteristics and the reported

From the Saul R. Korey Department of Neurology and the Department of Epidemiology and Social Medicine at the Albert Einstein College of Medicine, Bronx, N.Y., and the Weizmann Institute of Science, Rehovot, Israel. Address reprint requests to Dr. Bornstein at the Albert Einstein College of Medicine, 1300 Morris Park Ave., Kennedy Center 401, Bronx, NY 10461.

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first on: 4 severely affected patients with multiple sclerosis[16] and later on 12 patients with the chronic, progressive form of the disease and 4 patients with the exacerbating–remitting form.[17] Those studies led to this double-blind, randomized, matched-pair, placebo-controlled pilot trial of Cop 1 in patients with the exacerbating–remitting form of the disease.

METHODS

The trial was approved by the Committee on Clinical Investigations of the Albert Einstein College of Medicine and by the Food and Drug Administration (Cop 1 was assigned the investigational-new-drug number 14,115).

Preparation and Characterization of Cop 1

Cop 1 was first prepared at the Weizmann Institute of Science, Rehovot, Israel,[1] and later by the Bio-Yeda Company in Rehovot. All batches were analyzed for their amino acid composition, molecular weight, cross-reactivity with myelin basic protein, and suppression of experimental allergic encephalomyelitis in guinea pigs. Suppression was expressed as the difference in the percentage of diseased animals between the group treated with Cop 1 and the controls. The 12 batches from the Weizmann Institute had a suppression rate ranging from 10 to 80 percent (average, 33.5 percent), the rate for 14 batches produced by Bio-Yeda ranged from 10 to 75 percent (average, 40.6 percent). In an attempt to reduce inflammatory reactions at injection sites, we used an in vitro method to evaluate cell damage (basophil degranulation) by serotonin release.[18] All the batches in this study produced releases of less than 30 percent.

Cop 1 was dissolved in bacteriostatic saline at a concentration of 20 mg per milliliter. Sterile single-dose vials containing 1 ml of bacteriostatic saline alone or the Cop 1 solution were stored at −20°C until they were used. Each patient received a monthly supply of 32 vials of the appropriate solution. The preparation and distribution of vials and patient compliance were monitored by a clinical assistant under the direction of the statistician responsible for the randomization of patients (see Study Design below).

Patient Recruitment and Enrollment

To be eligible for the study, patients had to fulfill all the diagnostic criteria for definite multiple sclerosis,[19] be 20 to 35 years of age, have an above-average exacerbation rate, consisting of at least two well-demarcated and well-documented episodes of exacerbation in the two years before admission, have a score no higher than 6 (ambulatory with assistance) on the Kurtzke Disability Status Scale, and be emotionally stable as determined by psychosocial evaluation. The Kurtzke Disability Status Scale[20] represents degrees of neurologic dysfunction in units from 0 (no disability) to 10 (death from multiple sclerosis); a related scale measures functioning in eight areas: pyramidal, cerebellar, brain-stem, sensory, bowel and bladder, visual, mental, and other.

Questionnaires completed by 932 volunteers were reviewed; 140 of these candidates were evaluated in neurologic and psychosocial examinations. Ninety of the 140 were excluded — 23 because of age; 21, low frequency of exacerbations; 19, lack of documentation; 15, psychosocial inadequacy; 8, transition to a chronic, progressive course; 3, distance from the clinic; and 1, pregnancy. Fifty patients were accepted into the trial.

Study Design and Data Collection

Study patients were matched according to sex, number of exacerbations per year within ±1 exacerbation, and degree of disability as measured by the Kurtzke Scale in three strata: 0 to 2, 3 to 4, and 5 to 6. The random assignment of the first patient of a pair determined the assignment of both. Treatment assignments were made known to the clinical assistant responsible for the production, labeling, and dr

is enrolled in the study after another explanation of the trial, instruction in the method of self-injection, and signing of a consent form.

Eight patients who had an exacerbation between screening and acceptance into the study were enrolled after their conditions had become stable. One patient was enrolled after being weaned from corticosteroids over a period of a month.

Data from a personal and disease history and a neurologic examination and status evaluation using Kurtzke's Disability Status Scale and Eight Functional Groups were recorded at the time of screening and on the patient's entry into the study. Patients visited the clinic one month later and every three months thereafter for two years. At each visit, a neurologist unaware of the patient's treatment group completed a neurologic examination and status evaluation. The patient's self-evaluation of local or generalized side effects and changes in neurologic status were reported to the clinical assistant, who was not blinded to treatment.

Patients were also seen at the times of suspected exacerbations — i.e., when reporting the rapid onset of new symptoms or a worsening of preexisting symptoms that persisted for 48 hours or more. The neurologist verified exacerbations on the basis of study criteria. An event was counted as an exacerbation only when the patient's symptoms were accompanied by observed objective changes on the neurologic examination involving an increase of at least one grade in the score for one of the eight functional groups or the Kurtzke Scale. Sensory symptoms unaccompanied by objective findings or transient neurologic worsening were not considered to [illegible] exacerbation. Patients experiencing an acute exacer[illegible] evaluated at frequent intervals — usually every tw[illegible] new, stable neurologic base line had been establis[illegible] percent of 62 exacerbations in the placebo group [illegible] 16 exacerbations in the Cop 1 group were treat[illegible] Symptomatic medications, such as cholinergic and a[illegible] drugs, were permitted.

Laboratory Tests

Blood and urine samples were obtained from each patient upon entry into the trial and at each three-month visit. Routine urinalyses, blood chemistry (SMA 20) determinations, and complete blood counts were performed. Aliquots of serum and cells were stored in a deep freezer or in liquid nitrogen (at −90° or −180°C, respectively) for future studies.

HLA typing of HLA-A, B, C, and DR was performed by the tissue-typing laboratory of the Department of Surgery, Montefiore Medical Center, Bronx, New York.

Statistical Methods

The base-line characteristics of the study population in the two treatment arms were compared with use of two-tailed t-tests for continuous variables and chi-square tests with Yates' correction for discrete variables. Differences in side effects according to treatment arm were evaluated with a chi-square test.

The principal end point was the proportion of exacerbation-free patients. The other end points were frequency of exacerb[illegible] change in Kurtzke score from that at base line, and length o[illegible] before progression, as defined below.

The study design included planned subgroup analyses acc[illegible] to the disability status of the patients when they were rando[illegible] (Kurtzke units 0 to 2, 3 to 4, and 5 to 6). However, only one p[illegible] entered with a score of 4, and three with a score of 5. Therefo[illegible] combined two of the three strata (3 to 4 and 5 to 6), creatin[illegible] strata (0 to 2 and 3 to 6) with approximately equal numb[illegible] patients for subgroup analyses.

For the matched-pair analysis, the difference between[illegible] ment arms was tested with use of a McNemar's statist[illegible] the 22 matched pairs. A two-tailed Fisher's exact test was[illegible] for other two-by-two contingency tables. The chi-square tes[illegible] used to test two-by-three contingency tables for frequency of exacerbations.

Survival curves were calculate[illegible]

Table 1 Base-Line Characteristics of the Study Population

Characteristic	Treatment Group		
	Placebo		Cop 1
	randomized	included in analysis	
No. entered	25	23	25
Average age (yr)	31.0	31.1	30.0
Average duration of disease (yr)	6.1	6.4	4.9
Sex			
Male	10	10	11
Female	15	13	14
Race/ethnic group			
White	25	23	23
Black/Hispanic	0	0	2
Disability score (Kurtzke Scale)			
0–2	11	10	13
3–4	7	7	5
5–6	7	6	7
Average disability score	3.2	3.1	2.9
Prior exacerbation rate (over 2-yr period)	3.9	3.9	3.8

noted at the time of the visit during which it was observed; however, it had to be maintained for at least three months to be counted. Data on patients lost to follow-up were censored at the time of withdrawal. The log-rank statistic was used to test for comparability of the survival curves for each treatment arm. The curves were also tested for a difference at the discrete point of 24 months.[21]

Multiple logistic-regression analyses were undertaken to test the effect of treatment on the outcome, with adjustment for other variables, including sex, the duration of disease, the previous exacerbation rate, disability at the time of entry into the study, and various interactions of these variables. Odds ratios were calculated from the regression coefficients.[22]

Study Population

Fifty patients were enrolled: 48 in 24 matched pairs, and 2 unmatched patients, 1 randomly assigned to each study group. Table 1 shows the base-line characteristics of the total study population and of the 48 patients included in the analyses. The distributions of these characteristics were similar in the two treatment arms.

In order to guard against any possible bias that might be introduced by subjects dropping out of the study, we tried to include all the randomized patients in the analyses. There were seven patients who did not complete the two years of the trial. Of these, two patients in the placebo group were excluded from all the analyses because of unusable data. Both had been dropped from the trial for psychological reasons. The partial data obtained from the other five patients were included in the analyses. One patient taking Cop 1 dropped out during a period of exacerbation after two months of treatment. This patient had a second exacerbation shortly after stopping medication. Both were counted as study exacerbations in the data analyses.

Results

The design of the study specified the recruitment of patients in matched pairs, one patient randomly assigned to each treatment arm, with the proportion of exacerbation-free patients as the principal end point.* The matched analysis of the principal end point included 22 pairs, or 44 patients. An unmatched analysis permitted the inclusion of an additional four patients — two who were unmatched and two who had been matched to two patients who were subsequently excluded (Fig. 1). Analyses of exacerbation data are reported both as matched and unmatched. Subsequent analyses were performed on an unmatched basis.

Exacerbations during the Two-Year Study Period

In the 22 matched pairs, there were 12 discordant pairs: 2 patients in the placebo group had no exacerbations, whereas their matches in the Cop 1 group did, 10 patients in the Cop 1 group had no exacerbations, whereas their matches in the placebo group did. The remaining 10 pairs had concordant results. The difference in discordant pairs between treatment groups was significant ($P = 0.039$). An unmatched analysis of the presence or absence of exacerbations was also significant ($P = 0.045$).

Figure 1 shows the occurrence and time of exacerbations in each patient during the two years of the trial. There were 62 exacerbations among 23 patients in the placebo group (average, 2.7) and 16 among the 25 patients in the Cop 1 group (average, 0.6). The effect of treatment was also examined according to the base-line Kurtzke score. In the 0 to 2 stratum, there were 27 exacerbations in two years among 10 placebo-treated patients (average, 2.7) and 4 exacerbations among 13 Cop 1–treated patients (average, 0.3). In the 3 to 6 stratum, there were 35 exacerbations in the two years among 13 placebo-treated patients (average, 2.7) and 12 exacerbations among 12 Cop 1–treated patients (average, 1.0).

The distributions of exacerbations among the 48 patients are shown in Table 2. Fourteen of the 25 patients in the Cop 1 group (56 percent) were free of exacerbations, as compared with 6 of the 23 patients in the placebo group (26 percent). By contrast, 12 patients in the placebo group (52 percent) had three or more exacerbations, as compared with 1 in the Cop 1 group (4 percent). Patients were grouped according to whether they had no exacerbations, one to two, or three or more. The comparison between groups was significant at $P<0.001$.

Multiple logistic-regression analyses were carried out to evaluate the effect of a number of covariates. These included treatment, sex, duration of disease, prior exacerbation rate, Kurtzke score at base line, and various interactions of these variables. Only the treatment group and Kurtzke score at base line had a significant effect. The multiple logistic-regression analyses showed that treatment with Cop 1 independently increased the likelihood that a patient would be free of exacerbations ($P = 0.036$), as did a lower disability score at base line ($P = 0.003$). An esti-

*See NAPS document no. 04120 for supplementary material. Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163-3513. Remit in advance for NAPS copies of the subjects $7.75 for

greater for a patient taking placebo than for a patient taking Cop 1.

There was a decrease in the number of exacerbations among the patients in the placebo group, from 41 in the first year to 21 in the second. The ratio of the number of exacerbations in the placebo group to that in the Cop 1 group was 4.9 for year 1 and 3.3 for year 2.

Fifteen patients were treated throughout the trial with Cop 1 supplied by the Weizmann Institute, and 10 with Cop 1 supplied by Bio-Yeda. Ten of the patients receiving the Weizmann product (67 percent) were free of exacerbations, there were seven exacerbations among the remaining 5 patients. Of the 10 patients receiving the Bio-Yeda product, 4 (40 percent) were exacerbation-free, the remaining 6 patients had nine exacerbations. This difference was not statistically significant.

Change in Disability Status

Table 3 shows the distribution of the two-year changes in Kurtzke score according to treatment group for the entire study population. A negative score indicates improvement, a positive score worsening, and zero no change. Eleven patients in the placebo group (48 percent) and 5 in the Cop 1 group (20 percent) had disease progression over the two-year period. The difference between treatment groups in the proportion of patients whose disability status worsened as compared with the proportion who remained stable or improved was of borderline significance ($P = 0.064$).

The change in disability status in the patients treated with the Weizmann product was similar to that in the patients treated with the Bio-Yeda product.

Table 3 also shows the distribution of the changes in Kurtzke score according to treatment group for each Kurtzke-score stratum. In the 0 to 2 stratum, Cop 1 had a significantly beneficial effect on disability status: 84.6 percent of the patients in the Cop 1 group were stable or improved, as compared with 30 percent of those in the placebo group ($P = 0.012$). The average change in Kurtzke score favored Cop 1 by 1.7 units (there was a worsening of 1.2 with placebo and an improvement of 0.5 with Cop 1). In the 3 to 6 stratum, the proportions of patients whose conditions were stable, improved, and worse were comparable in both treatment groups, as were the average changes in Kurtzke score (there was a worsening of 0.4 with placebo and of 0.3 with Cop 1).

The effect of the previously identified covariates on the comparison of worsening with the absence of change or improvement was evaluated with use of multiple logistic-regression analyses. These analyses demonstrated a beneficial effect of Cop 1 on disability status ($P = 0.033$). A patient taking placebo was four times more likely to have progression of disease.

For the end point length of time before progression, the survival curve for each treatment group is shown in Figure 2. Progression was defined as an increase of at least 1 unit in the Kurtzke score that was maintained for at least three months. Over the two-year period the curves were significantly different ($P = 0.05$), with the placebo group having progression sooner than the Cop 1 group. Fifty percent of the

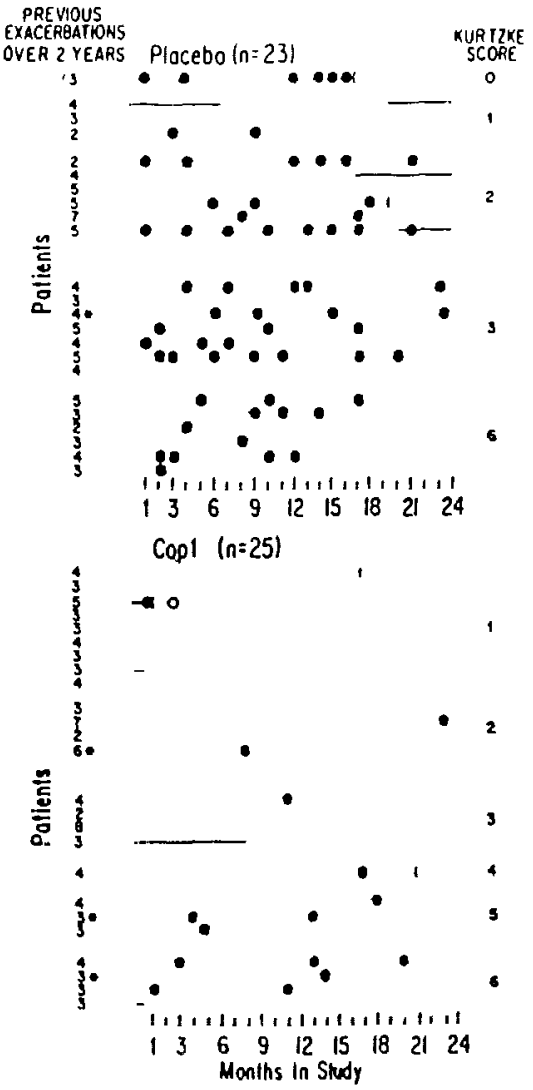

Figure 1. Exacerbations Occurring during the Two Years of the Trial

Each line represents a patient, and each circle an exacerbation. Patients are grouped according to their Kurtzke score on entry. The number of pretrial exacerbations are indicated to the left. Discontinued lines represent patients who withdrew before com-

Table 2. Exacerbations According to Treatment Group

No. of Exacerbations per Patient	Treatment Group			
	Placebo		Cop 1	
	No.	%	No.	%
0	6	26.1	14	56.0
1	3	13.1	7	28.0
2	2	8.7	3	12.0
3	5	21.8	1	4.0
4	2	8.7	0	0.0
5	1	4.3	0	0.0
6	2	8.7	0	0.0
7	1	4.3	0	0.0
8	1	4.3	0	0.0
Totals	23	*100.0*	25	*100.0*

patients in the placebo group had progression by the end of 18 months, whereas only 20 percent of those in the Cop 1 group had progression by the end of 24 months. At 24 months, there was a significant difference ($P<0.005$) favoring the group treated with Cop 1.

Laboratory Studies and Side Effects

The HLA characteristics of the 48 patients were unrelated to the effects of treatment. Patient reactions were monitored during each routine clinic visit by means of urinalysis, blood examination, and the patient's evaluation of symptoms. Urinalyses and blood examinations revealed no apparent changes in the functions of the liver, spleen, kidney, bone marrow, gastrointestinal tract, heart, or lungs.

Table 4 shows the percentage of patients in each group who reported reactions at the injection sites and other reactions.

More patients taking Cop 1 reported reactions at the injection site involving soreness ($P<0.001$), swelling ($P<0.001$), and itching ($P<0.01$). In addition, soreness was reported during at least half the visits in 32 percent of the Cop 1 group as compared with 9 percent of the placebo group, itching was reported in 40 percent as compared with 4 percent, swelling in 36 percent as compared with none, and redness in 40 percent as compared with 9 percent.

Other reactions were reported with comparable frequencies in each group (Table 4). No symptom was a persistent problem in more than 12 percent of either group. Dizziness, constipation, and joint pain were the most common symptoms in the Cop 1 group, whereas headache, dizziness, constipation, and joint pain were the most common in the placebo group.

Two patients had a patterned, transient reaction to Cop 1. It began during or immediately after an injection and consisted of a flush, sweating, palpitations, a feeling of tightness around the chest, difficulty breathing, and associated anxiety. It lasted from 5 to 15 minutes and passed with no residual difficulties. In one patient, the reaction occurred three times in 21 months, and in the other, twice in 17 months. Medication was discontinued in these two patients, who remained under observation for the balance of the trial. The remaining patients were alerted to the possibility of such reactions, informed of precautionary measures, and given a kit containing epinephrine and antihistamine tablets.

After the trial was completed, one of the two patients who had had a reaction volunteered to take Cop 1 in an unblinded manner. This patient reported a hypersensitivity reaction that included urticaria, itching, and marked discomfort and that was controlled with epinephrine and steroids.

Blinding

Considerable efforts were made to maintain the blinding of this trial. The examining neurologist and the patients avoided discussing side effects. Patients reported such effects to the unblinded clinical coordinator.

After the trial, the effectiveness of the blinding was evaluated. The patients and the examining neurolo-

Table 3. Changes in Disability Status over Two Years According to Base-Line Kurtzke-Score Strata.

Change in Kurtzke Score	All Cases				Base-Line Kurtzke Stratum 0–2				Base-Line Kurtzke Stratum 3–6			
	Placebo		Cop 1		Placebo		Cop 1		Placebo		Cop 1	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Worse												
4	1	4.4	0		1	10.0						
3	3	13.0	1	4.0	1	10.0			2	15.4	1	8.3
2	2	8.7	1	4.0	1	10.0			1	7.7	1	8.3
1	5	21.7	3	12.0	4	40.0	2	15.4	1	7.7	1	8.3
Subtotal	*11*	*47.8*	*5*	*20.0*	*7*	*70.0*	*2*	*15.4*	*4*	*30.8*	*3*	*25.0*
Stable (0)	9	39.1	12	48.0	2	20.0	5	38.4	7	53.8	7	58.4
Improved												
−1	2	8.7	5	20.0	1	10.0	4	30.8	1	7.7	1	8.3
−2	0		3	12.0			2	15.4				
−3	1	4.4	0									
Subtotal	*12*											

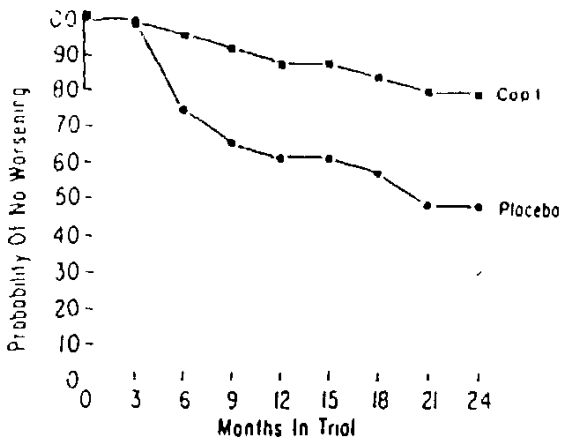

Figure 2 Curves Representing the Probability of No Worsening from the Base-Line Kurtzke Score

Worsening was determined when first observed, but was counted only if it continued for three months

gist were asked to guess treatment assignments. Fourteen of 18 patients in the placebo group who responded (78 percent) and 15 of 22 in the Cop 1 group (68 percent) guessed correctly. The neurologist correctly identified 70 percent of those taking placebo and 78 percent of those taking Cop 1. He based his evaluation on the clinical status of the patient, as did the majority of the patients (68 percent of the Cop 1 group and 61 percent of the placebo group). Approximately 20 percent of the patients based their guesses on the occurrence or absence of side effects. This suggests that the ability to guess treatment assignment correctly was influenced by the effect of treatment rather than by side effects.

Discussion

The pathophysiologic mechanisms that produce multiple sclerosis remain unknown, but many investigators agree that an altered immune mechanism is an essential element. Consequently, most drug treatments and clinical trials have involved attempts at immunomodulation.[23]

The mode of action of Cop 1 in multiple sclerosis is undetermined. Cop 1 was originally synthesized to simulate the immunochemical and immunobiologic properties of myelin basic protein.[1-3] Immunologic cross-reactions between Cop 1 (and several related copolymers) and myelin basic protein have been observed in guinea pigs and rabbits at the level of antibodies, delayed hypersensitivity, and lymphocyte stimulation.[2] All the polymers that cross-reacted also suppressed experimental allergic encephalomyelitis, whereas those incapable of suppression were immunologically not cross-reactive. The latter group included an analogue of Cop 1, similar in composition and size, but composed exclusively of D-amino acids.[3] Some laboratory

al.[24] observed no cross-reactivity between Cop 1 and myelin basic protein nor any correlation between the inhibition of experimental allergic encephalomyelitis by Cop 1 and cell-mediated immunity to myelin basic protein.

Three clinical trials attempting to treat multiple sclerosis with myelin basic protein failed to reveal any beneficial effects.[25-27] Perhaps the explanation for the difference between Cop 1 and myelin basic protein will be found in some unrecognized factor in trial design, such as dosage schedules, or the influence of Cop 1 on some mechanism other than immunologic cross-reactivity or suppressor-cell involvement. Such an explanation is supported by the lack of cross-reactivity between Cop 1 and myelin basic protein in helper phenotype T-cell lines isolated from human peripheral blood by in vitro exposure to Cop 1 or myelin basic protein.[28]

Nevertheless, on the basis of previous clinical evidence of the effects of Cop 1 on presumed autoallergic disease of the human central nervous system,[16,17] we proceeded to carry out another study. This pilot trial examined the effects of Cop 1 on a selected sample of patients with actively exacerbating multiple sclerosis.

The principal end point was the occurrence of exacerbations. It was selected as an outcome specifically germane to the type of patient in this study. Changes in the patients' disability status were also of major concern and were therefore evaluated.

The results show that Cop 1, administered subcutaneously for two years at a daily dose of 20 mg, produced clinically important and statistically significant beneficial effects, particularly in the patients who had less clinical involvement when treatment began.

Table 4. Percentages of Patients Reporting Side Effects.

Symptom	Placebo (N = 23)	Cop 1 (N = 25)
Local		
Soreness*	35	92
Itching†	22	64
Swelling*	17	88
Redness	48	76
Other	35	36
Other		
Headache	39	32
Nausea	17	24
Vomiting	4	4
Dizziness	30	40
Constipation	30	40
Sweating	26	28
Rash	17	24
Palpitations	13	24
Cramps	9	12
Faintness	13	20
Joint pain	39	40
Gastrointestinal discomfort	22	12
Appetite loss	13	20
Drowsiness	26	20
Other	17	1

Undesirable side effects — primarily local irritation at injection sites and rare transient vasomotor responses — were well tolerated.

The beneficial effects of Cop 1 demonstrated in this study should not be extrapolated to other patients with multiple sclerosis. Rather, we conclude that these results warrant further evaluation of Cop 1 in a full-scale, multicenter clinical trial.

We are indebted to the members of the External Advisory Committee — Drs. John Kurtzke, Herbert Scheinberg, and Joel Verter — for their criticisms and advice during the course of the trial.

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APPENDIX E

SYSTEMIC ADVERSE EVENTS

Background In Dr Bornstein's early trials with COPAXONE® he described an event which he labeled a "vasomotor" reaction Two patients in the BR-1 trial experienced flush, sweating palpitations, a feeling of tightness in the chest, difficulty breathing and associated anxiety The events as described by Dr Bornstein in his New England Journal of Medicine article (Appendix E) lasted 5 to 15 minutes and passed without residual difficulties Based on the clinical picture, TEVA launched into the larger multicenter trial and attempted to better assess the incidence and nature of these reactions

Some patients participating in Trial 01-9001/9001E reported symptoms consistent with a limited systemic reaction that occurs immediately following an individual injection This reaction is characterized by vasodilatation or chest tightness with palpitations, anxiety, and/or dyspnea These symptoms generally appeared within minutes of an injection and lasted up to 15 minutes Most patients who had this reaction reported one episode The maximum number of episodes per patient was 7 after approximately 845 injections (i e , <1%) Most of the component AE's were either mild or moderate These events are unpredictable in their occurrence and most often are not experienced a second time by the same individual Resolution occurs without any therapy and no sequelae have been reported to be associated with the events As a result of the sporadic nature and short duration of the systemic reactions obtaining ECG and vital sign data during the acute event has proven to be difficult There have also been anecdotal observations of blood in the syringe following the inciting injection Thus, some hypothesize an association with an inadvertent intravascular injection This has not been confirmed

The following discussion attempts to provide additional data on the systemic reaction as described by investigators and patients through clinical observations and a review of the available data Prior to breaking the blind in 01-9001/9001E an operational definition was created based on Dr Bornstein's original description and on those of our investigators TEVA requested two of the investigators describe a "typical" systemic reaction Although data from the complete database (both controlled and uncontrolled trials) will be presented, the analysis below will focus on the data for Trial 01-9001/9001E, as this is the largest controlled trial to date First, a description of the events is provided, followed by demographic data comparing the subset of patients who experience these reactions and were treated with COPAXONE® to those placebo, treated patients who also experienced reactions and to the overall COPAXONE® treated population (those patients who did not experience a reaction) Also provided long-term follow-up In addition, an assessment of the severity and available long term follow up is provided

Definition. a systemic reaction was prospectively defined for Trial 01-9001/9001E as a cluster of symptoms associated sporadically with an individual injection In order for an event to qualify as a systemic reaction a patient had to report the occurrence of either chest pain or vasodilatation in association with palpitations, anxiety and/or dyspnea

In Trial 01-9001/9001E 19 (15 2%) patients treated with COPAXONE® and 4 (3 2%) patients treated with placebo reported a total of 42 events consistent with the prospective definition The distribution of those events in both populations is shown in Table 1

Table 1 Systemic Reactions - Trial 01-9001/9001E

COPAXONE®.	19 patients (15 2%) 10 with 1 episode 4 with 2 episodes 3 with 3 episodes 2 with 4 or more episodes
Placebo	4 patients (3 2%) All with 1 episode

The component adverse experiences of these reactions were reported as presented in Fig 1 "V" represents vasodilatation, "CP" represents Chest Pain

Figure 1 Components of Systemic Reactions - Trial 01-9001/9001E

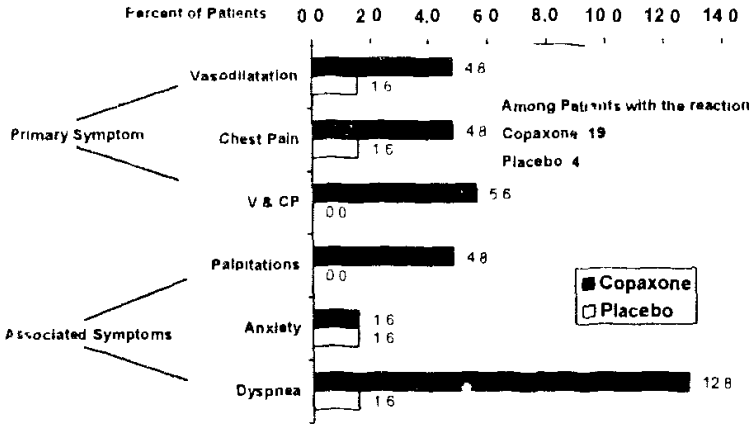
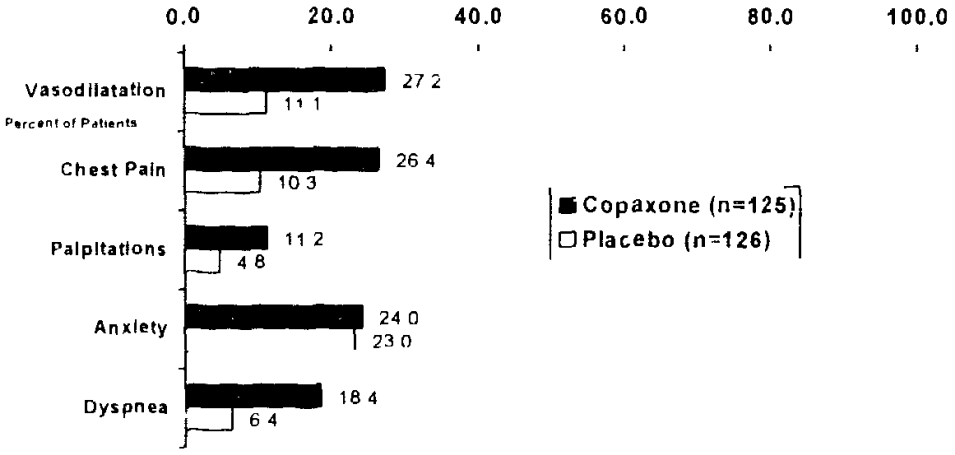


Figure 1 presents the components of the systemic reaction as they occurred in the 19 patients The percentage is calculated based on all patients in the treatment group (125 for COPAXONE® and 126 for placebo). Vasodilatation as the sole primary symptom for all reported systemic reactions for a given patient accounted for 4 8% in patients receiving COPAXONE® and 1 6% in the placebo group Chest pain as the sole primary symptom for all reported systemic reactions for a given patient also accounted for 4 8% in patients receiving COPAXONE® and 1 6% in the placebo group Either chest pain or vasodilatation as the primary symptom of any defined systemic reaction for a given patient was reported in 5 6% of patients treated with COPAXONE® and none treated with placebo The most commonly reported secondary symptom was dyspnea and was reported in 12 8% of patients receiving COPAXONE® compared to 1 6% of patients receiving placebo Palpitations and anxiety accounted for 4 8% and 1 6% respectively of those patients in the COPAXONE® treated group and 1 6% and 1 6% respectively in the placebo treated group

Figure 2 provides the overall incidence of these symptoms irrespective of whether they were part of an operationally defined reaction As is evident from this Figure, dyspnea and chest pain occurred more frequently in the COPAXONE® treated patients than in the placebo treated patients The overall incidence of chest pain and dyspnea is greater than that described in association with the predefined criteria This may suggest that partial reactions with the same etiology do occur The outcome of these isolated events was no different than those occurring in association with the other symptoms described Although patients may have been treated, most commonly with antihistamines, all seemed to resolve with or without treatment and without sequelae

Figure 2 Systemic Reactions Incidence of Individual Terms Among All Patients - Trial 01-9001/9001E



The number of episodes occurring in the 19 COPAXONE® treated patients was 38 and in the 4 placebo treated patients was 4 This is presented in Table 2

Table 2 Frequency of Symptoms Reported During Systemic Post-Injection Reactions

	Trial 01-9001/9001E	
	COPAXONE®	Placebo
Number of Patients with Systemic Reactions	19	4
Number of Episodes of Systemic Reactions	38	4
Component		
Chest Pain	12	2
Vasodilatation	14	2
Chest Pain and Vasodilatation	12	0
Palpitation	5	0
Anxiety	3	2
Dyspnea	32	2

As can be readily seen from this table, the predominant symptoms associated with this predefined reaction are dyspnea, chest pain and vasodilatation Anxiety and palpitations appear to play a less prominent role This is consistent with the data presented in Figure 1

In addition to reviewing the incidence of the symptoms included in the operational definition other symptoms reported concurrently were reviewed Table 3 lists the events that occurred in conjunction with the operationally defined systemic reactions

Table 3 Other Adverse Experiences Reported in Conjunction with Systemic Reactions - Trial 01-9001/9001E

	COPAXONE®	Placebo
Number of Patients with Systemic Reactions	19	4
Adverse Experience		
Nausea	9	0
Dizziness	6	0
Sweating	5	0
Paresthesia	3	1
Asthenia	2	0
Dysphagia	2	1
Erythema	2	0
Face Edema	2	0
Injection Site Urticaria	2	0
Tachycardia	2	0

* Other events seen in only one patient.
COPAXONE®. Diarrhea, Injection Site Erythema, Eye Pain, Injection Site Reaction, Injection Site Ecchymosis, Syncope, Pallor, Laryngismus, Rash, Headache, Urinary Incontinence, Myalgia, Abdominal Pain, Chills
Placebo. Amblyopia, Hypesthesia, Injection Site Pain, Task Perversion, Increased Salivation, Tinnitis

As can be seen from this table, nausea, dizziness, and sweating occur more frequently in association with this reaction than do other events and may be part of the symptom complex Also of note is the low frequency of dyspnea in the placebo group as presented in Table 2 From Table 2 and Table 3 it appears that the complex described by the placebo treated patients may have a different character and thus may not have the same etiology

Table 4 presents the occurrence of systemic reactions by gender, race, weight and age.

Table 4 Demographics of Patients Experiencing Systemic Reactions - Trial 01-9001/9001E

	Patients Reporting Systemic Reactions		All Patients	
	Cop-1	Placebo	Cop-1	Placebo
Total Number of Patients	19	4	125	126
Sex				
Male	5	2	37	30
Female	14	2	88	96
Race				
White	17	4	118	118
Black/Other	2	0	7	8
Age (yrs)				
Mean	32 5	37 3	34 6	34 3
Standard Deviation	5 7	4 1	6 0	6 5
Min	22 0	32 0	19	19
Max	42 0	42 0	46	46
Weight (lbs)				
Mean	143 6	137 5	155 1	148 3
Standard Deviation	24 7	14 1	37 4	35 5
Min	100 0	127 0	91 7	90 0
Max	188 0	158 0	279 0	301 0

As can be seen from the table, the average age, race, sex, and average weight of patients having experienced a systemic reaction is not different from the overall population of patients treated

Outcome and Follow-up

To evaluate outcome for patients who experienced at least one systemic reaction, duration of treatment and reason for withdrawal were compared to the general study population Data are presented in Table 5 and Table 6.

Table 5 Duration of Treatment for Patients with Systemic Reactions Compared to All treated Patients - Trial 01-9001/9001E

	Patients with Systemic Reactions		Patients Without Systemic Reactions	
Time Interval to Withdrawal (Months)	COPAXONE® (n = 19)	Placebo (n = 4)	COPAXONE® (n = 106)	Placebo (n = 122)
0 - 3	3	1	0	3
> 3 - 6	1	0	2	3
> 6 - 12	0	0	7	3
> 12 - 18	1	0	3	5
> 18 - 24	0	0	4	2
> 24*	14 (73 7 %)	3 (75 %)	90 (84 9%)	106 (86.9%)

* Includes Patients who completed the ful term of treatment

The above demonstrates that patients who experience at least one systemic reaction were no more likely to discontinue the trial prematurely compared to those who reported no events consistent with a systemic reaction. Time to withdrawal was also similar between the two groups.

Table 6 Reasons for Withdrawal Among Patients with Systemic Reactions - Trial 01-9001/9001E

	COPAXONE® (n = 19)	Placebo (n = 4)
Number of Patients who Prematurely Withdrew	6 (31 6 %)	1 (25 %)
Reasons for Withdrawal		
Patient Decision - Wanted to be off drug until open label study	1	1
Pregnancy	1*	0
Adverse Event	4	1

* This patient completed 24 months but withdrew during the extension

Less than one third of those COPAXONE® patients with systemic reactions withdrew prematurely Of the four who withdrew due to adverse events, only two withdrew specifically as a result of events consisting of particular components of the systemic reaction. These patients all recovered without sequelae The other two patients withdrew due to general adverse event reports The particular adverse events noted on case report forms as the reason for treatment stoppage appear in Table 7.

Table 7 Specific AE's Cited as the Cause of Stopping Treatment among patients with systemic reactions who prematurely withdrew from the Trial - Trial 01-9001/9001E

	COPAXONE®	Placebo
Number of patients with systemic reactions	19	4
Number of patients who prematurely withdrew due to adverse expenence	4 (21 1 %)	1 (25 %)
Adverse Expenence - Number of Patients		
Dizziness	2	1
Dyspnea	2	1
Dysphagia	1	0
Depression	1	0
Suicidal Ideation	1	0
Urticaria	1	1
Vasodilatation	1	0
Face Edema	1	0
Syncope	1	0
Nausea	1	0
Vomiting	1	0
Rash	1	0
Anxiety	1	1
Sweating	0	1
Taste Perversion	0	1
Injection Site Pain	0	1

Tables 5, 6, and 7 demonstrate that there is no difference in time to withdrawal or the reason for withdrawal when patients experiencing systemic reactions were compared to the overall study population

Adverse events reported by patients who experienced at least one systemic reaction were compared to the adverse events reported in the overall population The 10 most common adverse events for each group are reported in Table 8 As would be expected, the lists are identical with the exception of the appearance of vasodilatation, dyspnea, chest pain, palpitation, dizziness and sweating, all symptoms thought to be associated with the systemic reaction

Table 8 Most Common (10) Adverse Events for Trial 01-9001/9001E

Patients with Systemic Reactions			Patients with No Systemic Reactions		
	Cop-1 (n = 19)	Placebo (n = 1)		Cop-1 (n = 106)	Placebo (n = 122)
Vasodilatation	16	2	Infection	82	96
Dyspnea	16	3	Injection Site Pain	72	43
Infection	15	1	Asthenia	69	75
Injection Site Erythema	15	1	Headache	63	74
Chest Pain	14	2	Injection Site Erythema	58	16
Headache	13	1	Pain	49	51
Asthenia	12	3	Hypertonia	41	36
Injection Site Pain	11	3	Injection Site Pruritus	40	4
Hypesthesia	9	3	Hypesthesia	39	54
Injection Site Pruritus	8	1	Urinary Tract Infection	37	44
Palpitation	8	0			
Dizziness	8	2			
Sweating	8	1			

Also reviewed were concomitant medications This analysis was performed to evaluate whether patients with systemic reactions were receiving a particular medication that could possibly be interacting with COPAXONE® or whether these patients could possibly had a concurrent disease process as evidenced by their therapeutic intervention that predisposes them to a systemic reaction. The most common concomitant medications for patients having experienced a systemic reaction and those for the overall population are presented in Table 9

Table 9 Most Frequently Used Concomitant Medications Among Patients With and Without Systemic Reactions - Trial 01-9001/9001E

Patients with Systemic Reactions			Patients with No Systemic Reactions		
	Cop-1 (n = 19)	Placebo (n = 4)		Cop-1 (n = 106)	Placebo (n = 122)
Acetaminophen	13 (68 4 %)	2 (50 %)	Prednisone	83 (78 3 %)	97 (79 5 %)
Prednisone	9 (47 4%)	4 (100 %)	Acetaminophen	78 (73 6 %)	93 (76 2 %)
Diphenhydramine	7 (36 8)	0	Methylprednisolone	51 (48 1%)	57 (46 7 %)
Pemoline	7 (36 8)	0	Baclofen	30 (28.3 %)	29 (23 8 %)
Amoxicillin	6 (31 6 %)	0	Diphenhydramine	30 (28 3 %)	32 (26 2 %)
Methylprednisolone	5 (26 3 %)	1 (25 %)	Amoxicillin	29 (27 4 %)	36 (29 5 %)

There is no difference between the groups in the types of concomitant medications being prescribed Thus, there is no evidence that concomitant medications impact the occurrence of the systemic reaction

Systemic Reactions - incidence all trials

From a more global perspective, symptoms consistent with the operational definition were reported at least once by 87 of the 844 patients (10 3%) treated with copolymer 1 The total number of episodes reported was 152 As in Trial 01-9001/9001E, most of the patients reported only one episode, the maximum being 7 episodes for one patient

Electrocardiograms

ECG's were obtained in Trial 01-9001/9001E upon entry into the trial and at the time of termination These studies revealed no clinically significant change from baseline A listing of all ECG comments is contained in appendix K In addition, although a single case, and thus anecdotal, a patient who had experienced her first systemic reaction recently called emergency personnel and was seen and

evaluated in the emergency room while still reporting chest pain Her ECG and chest X-ray were negative She was treated with IV Benadryl and her symptoms resolved

Vital Signs

Blood pressure and heart rate were evaluated (additional data Appendix G) and no clinically significant change in blood pressure was seen in either the overall population or those patients having experienced at least one systemic reaction

Conclusion

A transient self-limited systemic reaction occurs in between 10% and 15% of patients treated with COPAXONE® This reaction occurs sporadically, unpredectably, and almost immediately after the administration of the drug and is characterized by chest pain or vasodilatation with anxiety, palpitations and/or dyspnea It resolves within 15-30 minutes without therapeutic intervention After review of the data there may also be an association with nausea, dizziness and/or sweating There are no long-term sequelae Although only anecdotal data exists there may be an association with the inadvertent intravascular administration of COPAXONE®

Although the etiology of the systemic reaction is unknown, based on the transient nature of these events, the lack of a need for intervention, the fact that the clinical picture and laboratory data are not consistent with IgE mediated hypersensitivity, the lack of clinically significant change in ECG's and blood pressure, and finally the lack of any difference in the long-term dropout rates or adverse event profiles of patients having experienced a systemic reaction, an association with any long term sequelae seems highly unlikely In addition, data on 87 events and 844 patients including more than 100 patients treated for greater than 3 years with no clinically significant implications on sequelae suggests that th[illegible]e is no reason for concern

APPENDIX F

Blood Pressure

Summary statistics for vital signs for patients with systemic reactions in Trial 01-9001/9001E are given in Table 1

Table 1 Mean Systolic and Diastolic Blood Pressures and Heart Rate by Treatment Group: Patients with Systemic Reactions and All Treated Patients

	Patients with Systemic Reactions				All Treated Patients			
	COPAXONE®(N=19)		Placebo (N=3)*		COPAXONE®(N=125)		Placebo (N=123)**	
	Baseline	Last Observation	Baseline	Last Observation	Baseline	Last Observation	Baseline	Last Observation
Systolic BP (mm Hg)								
Mean	112 8	110 3	106 0	112 7	115 86	113 88	115 18	112 48
Standard Deviation	9 9	11 0	4 0	1 0	12 04	13 76	13 14	13 6
Min	92	90	102	106	90	80	82	80
Max	130	130	110	120	145	150	170	150
Diastolic BP (mm Hg)								
Mean	73 6	69 8	65 3	68 7	74 43	72 98	73 98	72,02
Standard Deviation	6 5	8 6	6 1	1 2	9 04	10 49	9 74	9 98
Min	58	50	60	78	50	40	46	50
Max	86	82	72	80	100	100	100	110
Heart Rate (Beats/Minute)								
Mean	72 7	77 1	83 3	70 7	77 35	75 99	77 49	76 80
Standard Deviation	10 3	8 8	21 4	8 3	11 19	10 29	10 97	10 85
Min	60	64	60	64	52	56	52	56
Max	96	100	102	80	110	10	120	119

* One placebo patient had incomplete vital sign data
** Three placebo patients had incomplete vital sign data

On average there were no clinically important changes in vital signs, including systolic and diastolic blood pressure and heart rate from baseline to endpoint in either group

For the entire sample of patients who were exposed to study drug and for whom vital sign assessments were available, the data were evaluated for potentially clinically significant abnormalities, according to pre-defined criteria

The number of patients with blood pressure and heart rate values of potential clinical significance for patients with systemic reactions and all treated patients in Trial 01-9001/9001E is presented in Table 2

Table 2

	Patients with Systemic Reactions				All Treated Patients			
Number of Patients Exceeding the Predetermined Criteria	COPAXONE® (N=19)		Placebo (N=4)		COPAXONE® (N=125)		Placebo (N=126)	
Systolic Blood Pressure					7	5 60	5	3 97
Diastolic Blood Pressure	2	10 5%	0	0	5	4 00	6	4 76
Heart Rate					1	0 80	0	0
Systolic and Diastolic Blood Pressure	2	10 5%	0	0	4	3 20	2	1 59
Diastolic Blood Pressure and Heart Rate					2	1 60	0	0

In all cases, blood pressures which fell to ≤90 mm Hg systolic and/or ≤50 mm Hg diastolic were considered having exceeded the criteria. For patients with systemic reactions, no patient fell below 50 mm Hg diastolic at any time during the trial; one patient had a recorded systolic reading of 80 mm Hg at one time during the trial. Among all treated patients, systolic readings outside the predefined criteria included a low of 72 mm Hg and a high of 180 mm Hg. Diastolic readings outside the predefined criteria for all treated patients included a minimum of 36 mm Hg and a maximum of 50 mm Hg.

In conclusion, similar distributions of vital signs were observed for patients with systemic reactions compared to all treated patients. Multiple factors that may have affected vital signs were identified for patients receiving both study drugs. Analysis of vital sign results revealed no change in vital signs of clinical concern attributable to copolymer-1.

APPENDIX G

Table 1 Patients Who Died in COPAXONE® Clinical Program (Covers 01-9001/9001E, BR-1, 01-9002, 1110-1, 1110-2, BR-2 and BR-3)

Trial Number	Patient #	Age (Yr)	Sex	Dosing Regimen (eg, mg/day)	Duration of Treatment	Cause of Death
BR-2	01-578	33	M	30 mg/day	11 Months	Complications of neuroglioblastoma, including pneumonia, sepsis and pancytopenia (6 months following premature termination
BR-3	2038	46	M	20 mg/day	22 Months	Complications of Tracheostomy Change
	2049	41	F		36 Months	Pneumonia
	2051	59	F		36 Months	Colon Malignancy
	2039	48	F		19 Months	Unknown
1110-1	8417	40	F	20 mg/day	796 Days	Unspecified, possible respiratory arrest
	8501	43	F			Unspecified Acute cardio-respiratory insufficiency in course of a massive bronchiolar pneumonia and generalized septic state

APPENDIX H

)NE® - Copolymer- Injection
Document Neuro macological Drug Proc ory Com

ble 1 Adverse periences Associa Discontinuation o tients

	ACROSS TRIALS	1110-1	1110-2	01-9001/9001E		01-9002 BR-08		BR-1		BR-2		BR-3		
	Cop-1	Placebo	Cop-1	Cop-1	Cop-1	Placebo	Cop-1	Cop-1	Cop-1	Placebo	Cop-1	Placebo	Cop-1
PREFERRED TERM													
Abdominal Pain	1	0	1	0	0	0	0	0	0	0	0	0	0
Abnormal Gait	1	1	1	0	0	1	0	0	0	0	0	0	0
Abscess	1	0	1	0	0	0	0	0	0	0	0	0	0
Accidental Injury	1	0	1	0	0	0	0	0	0	0	0	0	0
Allergic Reaction	1	0	0	0	0	0	1	0	0	0	0	0	0
Alopecia	1	0	1	0	0	0	0	0	0	0	0	0	0
Amblyopia	1	0	0	1	0	0	0	0	0	0	0	0	0
Anxiety	2	2	1	0	0	1	1	0	0	0	0	1	0
Asthenia	9	0	6	1	0	0	1	0	0	0	0	1	0
Asthma	1	0	1	0	0	0	0	0	0	0	0	0	0
Back Pain	1	0	1	0	0	0	0	0	0	0	0	0	0
Bacteria Infection	1	0	0	0	1	0	0	0	0	0	0	0	0
Chest Pain	9	0	7	0	1	0	1	0	0	0	0	0	0
Chills	2	0	1	0	0	0	0	0	0	0	1	0	0
Circumoral Paresthesia	1	0	1	0	0	0	0	0	0	0	0	0	0
Death	2	0	2	0	0	0	0	0	0	0	0	0	0
Decreased Blood Pressure	1	0	0	0	0	0	0	0	0	0	1	0	0
Depression	3	0	0	0	1	0	1	0	0	0	1	0	0
Dermatitis	1	0	1	0	0	0	0	0	0	0	0	0	0
Disease Progression	1	0	0	0	0	0	1	0	0	0	0	0	0
Dizziness	8	1	3	2	0	1	1	0	0	0	2	0	0
Dysphagia	0	1	0	0	0	1	0	0	0	0	0	0	0
Dyspnea	17	1	11	2	2	1	2	0	0	0	0	0	0
Dysuria	1	0	1	0	0	0	0	0	0	0	0	0	0
Face Edema	2	0	1	0	1	0	0	0	0	0	0	0	0
Fever	4	0	1	1	0	0	2	0	0	0	0	0	0
Flu-Like Syndrome	1	0	0	0	0	0	1	0	0	0	0	0	0
Headache	2	0	0	2	0	0	0	0	0	0	0	0	0
Hypertonia	1	0	0	0	0	0	0	0	0	0	1	0	0
Increased Salivation	0	1	0	0	0	1	0	0	0	0	0	0	0
Infection	2	0	0	0	1	0	1	0	0	0	0	0	0
Injection Site Atrophy	2	0	0	0	2	0	0	0	0	0	0	0	0
Injection Site Edema	4	0	3	1	0	0	0	0	0	0	0	0	0
Injection Site Erythema	10	0	7	1	1	0	1	0	0	0	0	0	0

Adverse periences Associa Discontinuation of tients

	ACROSS TRIALS		1110-1	1110-2		01-9001/9001E		01-9002 BR-3B		BR-1		BR-2		BR-3		
	Cop-1	Placebo	Cop-1	Cop-1	Cop-1	Placebo	Cop-1	Cop-1	Cop-1	Placebo	Cop-1	Placebo	Cop-1			
PREFERRED TERM																
Injection Site Hematoma	1	0	1	0	0	1	1	0	0	0	0		0			
Injection Site Hypersensitivity	5	0	4	1	0	0	0	0	0	0	0		0			
Injection Site Induration	8	2	5	1	2	0	0	0	0	0	0		0			
Injection Site Inflammation	9	0	3	3	1	0	0	0	0	0	0		0			
Injection Site Mass	3	0	1	1	0	0	0	0	0	0	0		0			
Injection Site Pain	8	2	2	2	2	1	1	0	0	0	0		0			
Injection Site Pruritis	0	1	0	0	0	1	0	0	0	0	0		0			
Injection Site Pruritus	3	0	2	1	0	0	0	0	0	0	0		0			
Injection Site Urticaria	1	0	0	0	1	0	0	0	0	0	0		0			
Injection Site Welt	1	0	0	0	0	0	1	0	0	0	0		0			
Insomnia	1	1	1	0	0	1	0	0	0	0	0		0			
Lack of Drug Effect	1	0	0	0	0	0	1	0	0	0	0		0			
Laparotomy	1	0	1	0	0	0	0	0	0	0	0		0			
Leg Pain	1	0	1	0	0	0	0	0	0	0	0		0			
Lymphedema	1	0	0	0	0	0	1	0	0	0	0		0			
Lymphadenopathy	1	0	0	0	1	0	0	0	0	0	0		0			
Malaise	1	0	0	0	0	0	0	0	0	0	1		0			
Menstrual Disorder	2	0	2	0	0	0	0	0	0	0	0		0			
Myalgia	2	0	1	0	0	0	1	0	0	0	0		0			
Nausea	4	0	3	0	1	0	0	0	0	0	0		0			
Neoplasm	1	0	0	0	0	0	0	0	0	0	1		0			
Nervousness	1	0	1	0	0	0	0	0	0	0	0		0			
Pain	1	0	1	0	0	0	0	0	0	0	0		0			
Palpitation	4	0	3	0	0	0	0	0	0	0	1		0			
Paranoid Reaction	1	0	1	0	0	0	0	0	0	0	0		0			
Peripheral Edema	1	0	1	0	0	0	0	0	0	0	0		0			
Pruritic	2	0	0	0	0	0	1	0	0	0	1		0			
Pruritus	5	0	4	1	0	0	0	0	0	0	0		0			
Psychotic Depression	1	0	0	0	1	0	0	0	0	0	0		0			
Rash	9	0	3	3	1	0	2	0	0	0	0		0			
Resp. Disorders	1	0	1	0	0	0	0	0	0	0	0		0			
Serum Sickness	1	0	1	0	0	0	0	0	0	0	0		0			
Skin Reaction	2	0	1	1	0	0	0	0	0	0	0		0			

Adverse periences Associat Discontinuation o tients

	ACROS	TRIALS	1110-1	1110-2	01-9001/9001E		01-9002	BR-0B	BR-1		BR-2		BR-3
	Cop-1	Placebo	Cop-1	Cop-1	Cop-1	Placebo	Cop-1	Cop-1	Cop-1	Placebo	Cop-1	Placebo	Cop-1
PREFERRED TERM													
Somnolence	2	0	1	0	0	0	1	0	0	0	0	0	0
Splenomegaly	1	0	0	0	1	0	0	0	0	0	0	0	0
Suicide Attempt	1	0	0	0	0	0	0	0	0	0	1	0	0
Sweating	2	1	2	0	0	1	0	0	0	0	0	0	0
Syncope	1	0	0	0	1	0	0	0	0	0	0	0	0
Tachycardia	3	0	1	0	0	0	0	0	0	0	2	0	0
Taste Perversion	0	1	0	0	0	1	0	0	0	0	0	0	0
Tremor	2	0	1	0	0	0	0	0	0	0	1	0	0
Unintended Pregnancy	4	0	0	0	3	0	0	0	0	0	0	0	1
Unspecified	6	2	0	0	2	1	1	1	1	1	0	0	1
Urticaria	5	0	1	2	2	0	0	0	0	0	0	0	0
Vaginitis	1	0	1	0	0	0	0	0	0	0	0	0	0
Vasodilatation	17	1	12	2	2	1	0	0	0	0	1	0	1
Vertigo	1	0	1	0	0	0	0	0	0	0	0	0	0
Vomiting	1	0	0	0	1	0	0	0	0	0	0	0	0

APPENDIX I

Table 1 Serious or Potentially Serious Adverse Experiences Related to Study Drug

DISTRACT	TRIAL	TREATMENT	CENTER	PATIENT NUMBER	DURATION (MINUTES
CHEST PAIN	85015	COP-1	4	403	
ABSCESS	01-9002	COP-1	4	4	
CHOLECYSTITIS	01-9002	COP-1	36	19	[illegible]
RASH	01-9002	COP-1	4		
SYNCOPE	01-9002	COP-1	36	1	
VOMITING	01-9002	COP-1	5	2	0.2
SERUM SICKNESS	1110-1	COP-1	MEIR	8428	NOT REPORTED
SYNCOPE	BR-2	COP-1		02-1	16
PNEUMONIA	BR-3	COP-1		2064	79
CLASS 4 PAP SMEAR	BR-3	COP-1		2015	
KIDNEY INFECTION	BR-3	COP-1		059	15
SEVERE REACTION	BR-3	COP-1			20

NOTE THE ACTUAL RELATIONSHIP TO TREATMENT WAS UNKNOWN FOR BR-3 AND WAS NOT REPORTED FOR 1110-1 PATIENTS.

APPENDIX J

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=COP-1

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL ECG EVALUATION	RHYTHM SPECIFICATION
1	101	33	Female	SCREENING	72	NORMAL	NORMAL	
				TERMINATION	91	NORMAL	NORMAL	
	104	28	Female	SCREENING	75	NORMAL	NORMAL	
				TERMINATION	81	NORMAL	NORMAL	
	106	34	Female	SCREENING	72	NORMAL	NORMAL	
				TERMINATION	82	NORMAL	NORMAL	
	108	39	Female	SCREENING	75	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	
	111	33	Male	SCREENING	63	NORMAL	NORMAL	
				TERMINATION	68	NORMAL	NORMAL	
	112	36	Female	SCREENING	67	NORMAL	NORMAL	
				TERMINATION	54	ABNORM	ABNORMAL	BRADYCARDIA
	114	42	Female	SCREENING	63	NORMAL	NORMAL	
				TERMINATION	61	NORMAL	NORMAL	
	115	44	Female	SCREENING	78	NORMAL	NORMAL	
				TERMINATION	82	NORMAL	NORMAL	
	117	37	Female	SCREENING	56	NORMAL	NORMAL	
				TERMINATION	54	NORMAL	NORMAL	
	119	34	Female	SCREENING	71	NORMAL	NORMAL	
				TERMINATION	77	NORMAL	NORMAL	
	121	37	Female	SCREENING	85	NORMAL	NORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	124	34	Male	SCREENING	70	NORMAL	NORMAL	
				TERMINATION	65	NORMAL	NORMAL	
	126	25	Female	SCREENING	76	NORMAL	NORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	128	44	Female	SCREENING	66	NORMAL	ABNORMAL	
				TERMINATION	73	NORMAL	NORMAL	
2	201	37	Male	SCREENING	84	NORMAL	NORMAL	
				TERMINATION	72	NORMAL	NORMAL	
	204	39	Female	SCREENING	79	NORMAL	NORMAL	
				TERMINATION	60	NORMAL	NORMAL	
	205	44	Female	SCREENING	73	ABNORM	ABNORMAL	NONSPECIFIC T WAVE ABNORMALITY
				TERMINATION	56	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	210	37	Male	SCREENING	64	NORMAL	NORMAL	
				TERMINATION	52	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	212	31	Male	SCREENING	73	NORMAL	ABNORMAL	
				TERMINATION	67	NORMAL	NORMAL	
	216	36	Male	SCREENING	67	NORMAL	NORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=COP-1

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
2	216	36	Male	TERMINATION	70	NORMAL	NORMAL	
	218	34	Female	SCREENING	64	NORMAL	NORMAL	
				TERMINATION	63	NORMAL	NORMAL	
	220	36	Male	SCREENING	51	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	50	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	224	46	Female	SCREENING	62	NORMAL	NORMAL	
				TERMINATION	67	ABNORM	ABNORMAL	NORMAL EKG WITH OCCASIONAL PRE
	223	35	Female	SCREENING	67	NORMAL	NORMAL	
				TERMINATION	71	NORMAL	NORMAL	
3	301	39	Female	SCREENING	76	NORMAL	ABNORMAL	
				TERMINATION	96	NORMAL	NORMAL	
	302	27	Male	SCREENING	90	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	
	307	38	Female	SCREENING	65	NORMAL	NORMAL	
				TERMINATION	71	NORMAL	NORMAL	
	309	39	Female	SCREENING	78	NORMAL	NORMAL	
				TERMINATION	65	NORMAL	NORMAL	
	309	41	Male	SCREENING	62	NORMAL	NORMAL	
				TERMINATION	72	NORMAL	NORMAL	
	312	39	Female	SCREENING	73	NORMAL	NORMAL	
				TERMINATION	80	NORMAL	NORMAL	
	315	40	Female	SCREENING	101	ABNORM	ABNORMAL	SINUS TACHYCARDIA
				TERMINATION	69	NORMAL	NORMAL	
	316	30	Female	SCREENING	70	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	317	31	Female	SCREENING	67	NORMAL	NORMAL	
				TERMINATION	64	NORMAL	NORMAL	
	320	22	Female	SCREENING	74	NORMAL	NORMAL	
				TERMINATION	67	NORMAL	NORMAL	
	321	35	Male	SCREENING	66	NORMAL	ABNORMAL	
				TERMINATION	58	NORMAL	NORMAL	
	323	31	Male	SCREENING	57	NORMAL	NORMAL	
				TERMINATION	64	NORMAL	NORMAL	
4	401	35	Male	SCREENING	58	NORMAL	ABNORMAL	
				TERMINATION	63	NORMAL	NORMAL	
	403	34	Female	SCREENING	79	NORMAL	NORMAL	
				TERMINATION	63	NORMAL	NORMAL	
	407	29	Female	SCREENING	54	ABNORM	ABNORMAL	SINUS BRADYCARDIA WITH SINUS A
				TERMINATION	61	NORMAL	NORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=COP-1

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
4	408	42	Female	SCREENING	70	NORMAL	NORMAL	
				TERMINATION	75	NORMAL	NORMAL	
	409	27	Male	SCREENING	56	NORMAL	ABNORMAL	
				TERMINATION	60	NORMAL	NORMAL	
	410	33	Female	SCREENING	56	NORMAL	ABNORMAL	
				TERMINATION	52	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	415	30	Female	SCREENING	57	NORMAL	NORMAL	
				TERMINATION	68	NORMAL	NORMAL	
	416	41	Male	SCREENING	63	NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	420	42	Female	SCREENING	85	NORMAL	NORMAL	
				TERMINATION	77	NORMAL	NORMAL	
	423	29	Female	SCREENING	65	NORMAL	NORMAL	
				TERMINATION	57	NORMAL	NORMAL	
	427	33	Male	SCREENING	62	NORMAL	NORMAL	
				TERMINATION	51	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	428	38	Male	SCREENING	79	ABNORM	ABNORMAL	OCCASIONAL PREMATURE ATRIAL CO
				TERMINATION	65	NORMAL	NORMAL	
	429	32	Female	SCREENING	74	NORMAL	NORMAL	
				TERMINATION	67	NORMAL	NORMAL	
	432	19	Female	SCREENING	55	ABNORM	ABNORMAL	OCCASIONAL PREMATURE SUPRAVENT
				TERMINATION	54	NORMAL	ABNORMAL	
5	503	22	Male	SCREENING	71	NORMAL	NORMAL	
				TERMINATION	67	NORMAL	NORMAL	
	507	36	Female	SCREENING	76	NORMAL	ABNORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	508	38	Female	SCREENING	83	NORMAL	NORMAL	
				TERMINATION	64	NORMAL	NORMAL	
	509	37	Male	SCREENING	57	NORMAL	NORMAL	
				TERMINATION	59	ABNORM	ABNORMAL	BRADYCARDIA
	512	29	Female	SCREENING	69	ABNORM	ABNORMAL	SINUS ARRHYTHMIA
				TERMINATION	66	NORMAL	NORMAL	
	514	42	Female	SCREENING	66	NORMAL	NORMAL	
				TERMINATION	65	NORMAL	NORMAL	
	516	23	Female	SCREENING	79	NORMAL	ABNORMAL	
				TERMINATION	56	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	517	37	Male	SCREENING	62	NORMAL	ABNORMAL	
				TERMINATION	54	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	518	33	Female	SCREENING	72	NORMAL	ABNORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=COP-1

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL E-G EVALUATION	RHYTHM SPECIFICATION
5	518	33	Female	TERMINATION	61	NORMAL	ABNORMAL	
	521	41	Female	SCREENING	74	NORMAL	NORMAL	
				TERMINATION	67	NORMAL	ABNORMAL	
	524	21	Male	SCREENING	120	ABNORM	ABNORMAL	TACHYCARDIA
				TERMINATION	89	NORMAL	NORMAL	
	525	32	Male	SCREENING	82	NORMAL	ABNORMAL	
				TERMINATION	73	NORMAL	ABNORMAL	
6	602	35	Female	SCREENING	75	NORMAL	NORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	604	35	Female	SCREENING	51	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	57	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	605	45	Female	SCREENING	71	NORMAL	NORMAL	
				TERMINATION	69	NORMAL	NORMAL	
	606	32	Male	SCREENING	61	NORMAL	NORMAL	
				TERMINATION	72	NORMAL	NORMAL	
	611	35	Female	SCREENING	57	NORMAL	ABNORMAL	
				TERMINATION	61	ABNORM	ABNORMAL	NORMAL SINUS RHYTHM WITH SINUS
	612	40	Female	SCREENING	62	NORMAL	NORMAL	
				TERMINATION	71	NORMAL	NORMAL	
	614	31	Female	SCREENING	71	NORMAL	NORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	615	38	Male	SCREENING	66	NORMAL	ABNORMAL	
				TERMINATION	75	NORMAL	ABNORMAL	
	617	38	Female	SCREENING	74	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	618	46	Male	SCREENING	69	NORMAL	NORMAL	
				TERMINATION	96	NORMAL	NORMAL	
	623	26	Female	SCREENING	75	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	
7	704	29	Female	SCREENING	81	NORMAL	NORMAL	
				TERMINATION	78	NORMAL	NORMAL	
	706	39	Female	MONTH 27	80	NORMAL	NORMAL	
				SCREENING	76	NORMAL	NORMAL	
				TERMINATION	82			
	711	31	Male	SCREENING	85	NORMAL	NORMAL	
				TERMINATION	66	NORMAL	NORMAL	
	719	40	Male	SCREENING	76	NORMAL	NORMAL	
				TERMINATION	64	NORMAL	NORMAL	
	723	29	Male	SCREENING	48	NORMAL	ABNORMAL	

COP-1 9001 US DOUBLE-BLIN TRIAL (INCLUDING EXTENSION)
APPENDIX L11. E_ TROCARDIOGRAM DATA

TREATMENT=COP-1

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL E/G EVALUATION	RHYTHM SPECIFICATION
7	723	29	Male	TERMINATION	48	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	725	21	Female	SCREENING	75	ABNORM	ABNORMAL	SINUS ARRHYTHMIA
				TERMINATION	72	NORMAL	NORMAL	
	727	35	Female	SCREENING	73	NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	731	19	Female	SCREENING	74	NORMAL	NORMAL	
				TERMINATION	92	NORMAL	NORMAL	
8	802	32	Female	SCREENING	49	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	59	NORMAL	NORMAL	
	804	44	Female	SCREENING	48	ABNORM	ABNORMAL	SINUS BRADYCARDIA, OLD ANTER
				TERMINATION	46	NORMAL	ABNORMAL	
	806	36	Female	SCREENING	74	NORMAL	NORMAL	
				TERMINATION	81	NORMAL	NORMAL	
	807	39	Female	OFF PROTO F				
				SCREENING	66	NORMAL	NORMAL	
	810	41	Female	SCREENING	75	NORMAL	NORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	812	42	Female	SCREENING	64	NORMAL	ABNORMAL	
				TERMINATION	76	NORMAL	ABNORMAL	
	814	38	Female	SCREENING	62	NORMAL	NORMAL	
				TERMINATION	51	NORMAL	NORMAL	
9	903	39	Male	SCREENING	59	NORMAL	NORMAL	
				TERMINATION	60	NORMAL	NORMAL	
	904	38	Female	SCREENING	81	NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	905	30	Female	SCREENING	51	NORMAL	ABNORMAL	
				TERMINATION	61	NORMAL	NORMAL	
	907	41	Female	SCREENING	58	NORMAL	NORMAL	
				TERMINATION				
	909	21	Male	SCREENING	52	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	62	NORMAL	NORMAL	
	912	36	Male	SCREENING	80	NORMAL	NORMAL	
				TERMINATION	61	NORMAL	NORMAL	
10	1002	30	Female	SCREENING	70	NORMAL	NORMAL	
				TERMINATION	56	NORMAL	ABNORMAL	
	1004	27	Male	SCREENING	77	NORMAL	NORMAL	
				TERMINATION	80	NORMAL	NORMAL	
	1007	33	Female	SCREENING	82	NORMAL	NORMAL	
				TERMINATION	75	NORMAL	NORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=COP-1

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
10	1008	38	Male	SCREENING	70	NORMAL	NORMAL	
				TERMINATION	68	ABNORM	ABNORMAL	SINUS RHYTHM WITH SINUS ARRHYT
	1011	28	Female	SCREENING	86	NORMAL	NORMAL	
				TERMINATION	71	NORMAL	NORMAL	
	1012	40	Female	SCREENING	65	NORMAL	NORMAL	
				TERMINATION	62	NORMAL	NORMAL	
	1013	30	Male	SCREENING	59	NORMAL	NORMAL	
				TERMINATION	58	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	1015	37	Female	SCREENING	63	NORMAL	NORMAL	
				TERMINATION	60	NORMAL	NORMAL	
	1024	46	Female	SCREENING	66	NORMAL	ABNORMAL	
				TERMINATION	86	ABNORM	ABNORMAL	ABNORMAL L AXIS DEVIATION
11	1102	33	Female	SCREENING	79	NORMAL	NORMAL	
				TERMINATION	94	NORMAL	NORMAL	
	1104	34	Female	SCREENING	64	NORMAL	ABNORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	1105	44	Female	SCREENING	77	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	1107	29	Male	SCREENING	63	ABNORM	ABNORMAL	SINUS ARRHYTHMIA
				TERMINATION	56	ABNORM	NORMAL	SINUS ARRHYTHMIA
	1109	32	Female	SCREENING	60	NORMAL	ABNORMAL	
				TERMINATION	62	NORMAL	NORMAL	
	1111	37	Female	SCREENING	90	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=PLACEBO

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
1	102	28	Female	SCREENING	84	NORMAL	NORMAL	
				TERMINATION	98	NORMAL	NORMAL	
	105	38	Female	SCREENING	82	NORMAL	NORMAL	
				TERMINATION	59	NORMAL	NORMAL	
	109	40	Female	SCREENING	94	NORMAL	ABNORMAL	
				TERMINATION				
	113	33	Female	SCREENING	84	NORMAL	NORMAL	
				TERMINATION	66	NORMAL	NORMAL	
	116	33	Female	SCREENING	66	NORMAL	NORMAL	
				TERMINATION	67	NORMAL	ABNORMAL	
	120	45	Female	SCREENING	58	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	54	ABNORM	NORMAL	SINUS BRADYCARDIA
	122	33	Female	SCREENING	82	NORMAL	ABNORMAL	
				TERMINATION	67	NORMAL	ABNORMAL	
	123	25	Male	SCREENING	94	NORMAL	ABNORMAL	
				TERMINATION	89	NORMAL	NORMAL	
	125	34	Female	SCREENING	68	NORMAL	NORMAL	
				TERMINATION	79	NORMAL	NORMAL	
2	202	25	Female	SCREENING	86	ABNORM	ABNORMAL	SINUS ARRHYTHMIA
				TERMINATION	73	ABNORM	ABNORMAL	NORMAL SINUS RHYTHM WITH SINUS
	203	21	Female	SCREENING	87	NORMAL	NORMAL	
				TERMINATION	59	ABNORM	ABNORMAL	SINUS BRADYCARDIA WITH SINUS A
	207	41	Male	SCREENING	80	NORMAL	NORMAL	
				TERMINATION				
	208	42	Male	SCREENING	67	NORMAL	NORMAL	
				TERMINATION	65	ABNORM	ABNORMAL	NORMAL SINUS RHYTHM WITH SINUS
	209	34	Female	SCREENING	54	ABNORM	ABNORMAL	BRADYCARDIA
				TERMINATION	58	ABNORM	ABNORMAL	SINUS BRADYCARDIA WITH SINUS A
	211	40	Male	SCREENING	54	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	58	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	213	39	Female	SCREENING	73	ABNORM	ABNORMAL	NORMAL RHYTHM WITH OCCASIONAL
				TERMINATION	75	NORMAL	NORMAL	
	215	25	Female	SCREENING	66	NORMAL	NORMAL	
				TERMINATION	71	NORMAL	NORMAL	
	217	44	Female	SCREENING	64	NORMAL	NORMAL	
				TERMINATION	64	NORMAL	NORMAL	
	222	36	Female	SCREENING	78	NORMAL	NORMAL	
				TERMINATION	81	NORMAL	NORMAL	
	224	35	Female	SCREENING	73	ABNORM	ABNORMAL	ABNORMAL RHYTHM

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=PLACEBO

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL E/G EVALUATION	RHYTHM SPECIFICATION
2	224	35	Female	TERMINATION	81	NORMAL	NORMAL	
	228	34	Female	SCREENING	83	NORMAL	NORMAL	
				TERMINATION	87	NORMAL	NORMAL	
3	303	33	Male	SCREENING	69	NORMAL	NORMAL	
				TERMINATION	80	NORMAL	NORMAL	
	304	27	Female	SCREENING	90	NORMAL	NORMAL	
				TERMINATION	96	NORMAL	NORMAL	
	305	23	Female	SCREENING	73	NORMAL	NORMAL	
				TERMINATION	66	NORMAL	NORMAL	
	306	44	Male	SCREENING	62	NORMAL	NORMAL	
				TERMINATION	59	NORMAL	NORMAL	
	310	39	Female	SCREENING	74	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	
	311	31	Female	SCREENING	68	NORMAL	NORMAL	
				TERMINATION	75	NORMAL	NORMAL	
	313	27	Female	SCREENING	63	NORMAL	NORMAL	
				TERMINATION	65	NORMAL	NORMAL	
	314	35	Female	SCREENING	91	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	
	318	38	Male	SCREENING	66	NORMAL	NORMAL	
				TERMINATION	64	NORMAL	NORMAL	
	319	39	Female	SCREENING	89	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	
	322	34	Male	SCREENING	65	NORMAL	NORMAL	
				TERMINATION	68	NORMAL	NORMAL	
	324	19	Female	SCREENING	71	NORMAL	NORMAL	
				TERMINATION	85	NORMAL	NORMAL	
4	402	32	Male	SCREENING	60	NORMAL	ABNORMAL	
				TERMINATION	67	ABNORM	ABNORMAL	OCCASIONAL PVC
	404	32	Female	SCREENING	79	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	405	22	Female	SCREENING	57	NORMAL	ABNORMAL	
				TERMINATION	79	ABNORM	ABNORMAL	MARKED SINUS ARRHYTHMIA
	406	40	Female	SCREENING	86	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	412	30	Female	SCREENING	68	NORMAL	NORMAL	
				TERMINATION	77	NORMAL	NORMAL	
	413	37	Female	SCREENING	53	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	49	ABNORM	ABNORMAL	MARKED SINUS BRADYCARDIA

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=PLACEBO

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
4	414	42	Female	SCREENING	105	ABNORM	ABNORMAL	SINUS TACHYCARDIC WITH OCCASIO
				TERMINATION	84	NORMAL	NORMAL	
	417	40	Female	SCREENING	69	NORMAL	NORMAL	
				TERMINATION	79	NORMAL	NORMAL	
	419	43	Male	SCREENING	53	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	62	NORMAL	NORMAL	
	421	21	Female	SCREENING	66	NORMAL	NORMAL	
				TERMINATION	63	NORMAL	NORMAL	
	422	33	Female	SCREENING	75	NORMAL	NORMAL	
				TERMINATION	68	NORMAL	NORMAL	
	426	37	Female	SCREENING	72	NORMAL	NORMAL	
				TERMINATION	60	NORMAL	NORMAL	
5	501	36	Female	SCREENING	65	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	504	34	Male	SCREENING	71	NORMAL	NORMAL	
				TERMINATION	67	NORMAL	NORMAL	
	505	37	Female	SCREENING	63	NORMAL	NORMAL	
				TERMINATION	75	NORMAL	NORMAL	
	506	26	Female	SCREENING	55	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	55	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	510	40	Female	SCREENING	85	NORMAL	NORMAL	
				TERMINATION	86	NORMAL	NORMAL	
	511	44	Male	SCREENING	58	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	65	NORMAL	NORMAL	
	513	36	Female	SCREENING	58	NORMAL	ABNORMAL	
				TERMINATION	57	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	515	23	Male	SCREENING	50	ABNORM	ABNORMAL	BRADYCARDIA
				TERMINATION	58	ABNORM	ABNORMAL	SINUS BRADYCARDIA WITH MARKED
	519	27	Female	SCREENING	79	ABNORM	ABNORMAL	SINUS ARRHYTHMIA
				TERMINATION	87	NORMAL	ABNORMAL	
	520	30	Female	SCREENING	97	ABNORM	ABNORMAL	SINUS ARRHYTHMIA
				TERMINATION	78	NORMAL	NORMAL	
	522	22	Female	SCREENING		NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	523	38	Female	SCREENING	63	NORMAL	ABNORMAL	
				TERMINATION	66	NORMAL	ABNORMAL	
	526	21	Female	SCREENING	65	NORMAL	ABNORMAL	
				TERMINATION	77	NORMAL	ABNORMAL	
	527	26	Male	SCREENING	59	NORMAL	ABNORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=PLACEBO

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
5	527	26	Male	TERMINATION	72	NORMAL	NORMAL	
6	601	36	Male	SCREENING	70	NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	603	39	Female	SCREENING	67	NORMAL	NORMAL	
				TERMINATION	62	NORMAL	ABNORMAL	
	607	38	Male	SCREENING	51	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	58	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	608	40	Female	SCREENING	71	NORMAL	NORMAL	
				TERMINATION	73	NORMAL	NORMAL	
	609	46	Male	SCREENING	50	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	65	ABNORM	ABNORMAL	NORMAL SINUS RHYTHM WITH SINUS
	610	33	Female	SCREENING	83	NORMAL	NORMAL	
				TERMINATION	91	NORMAL	NORMAL	
	613	29	Female	SCREENING	77	NORMAL	NORMAL	
				TERMINATION	80	NORMAL	NORMAL	
	616	32	Male	SCREENING	76	NORMAL	NORMAL	
				TERMINATION	81	NORMAL	NORMAL	
	619	38	Female	SCREENING	73	NORMAL	NORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	620	36	Female	SCREENING	69	NORMAL	NORMAL	
				TERMINATION	59	ABNORM	ABNORMAL	SINUS BRADYCARDIA WITH SINUS A
	622	24	Male	SCREENING	67	ABNORM	ABNORMAL	NORMAL SINUS RHYTHM WITH SINUS
				TERMINATION	54	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	624	35	Female	SCREENING	72	NORMAL	NORMAL	
				TERMINATION	78	NORMAL	NORMAL	
7	701	37	Female	SCREENING	88	NORMAL	NORMAL	
				TERMINATION	80	NORMAL	NORMAL	
	702	22	Female	SCREENING	67	NORMAL	NORMAL	
				TERMINATION	60	NORMAL	NORMAL	
	705	37	Female	SCREENING	75	NORMAL	NORMAL	
				TERMINATION	72	NORMAL	NORMAL	
	708	33	Male	SCREENING	52	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	54	NORMAL	ABNORMAL	
	709	37	Female	SCREENING	48	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	56	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	715	43	Female	SCREENING	8	NORMAL	NORMAL	
				TERMINATION	2	NORMAL	NORMAL	
	716	43	Female	SCREENING	7	NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=PLACEBO

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
7	717	25	Female	SCREENING	58	ABNORM	ABNORMAL	SINUS ARRHYTHMIA & BRADYCARDIA
				TERMINATION	66	NORMAL	NORMAL	
	718	30	Female	SCREENING	68	NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	721	36	Female	SCREENING	78	NORMAL	NORMAL	
				TERMINATION	74	NORMAL	NORMAL	
	724	41	Male	SCREENING	92	NORMAL	NORMAL	
				TERMINATION	90	NORMAL	NORMAL	
	726	39	Male	SCREENING	94	NORMAL	NORMAL	
				TERMINATION	80	NORMAL	NORMAL	
8	801	43	Male	SCREENING	65	NORMAL	ABNORMAL	
				TERMINATION	57	NORMAL	NORMAL	
	803	29	Female	SCREENING	62	NORMAL	NORMAL	
				TERMINATION	69	NORMAL	NORMAL	
	805	45	Female	SCREENING	81	NORMAL	ABNORMAL	
				TERMINATION	61	NORMAL	NORMAL	
	809	27	Female	SCREENING	83	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	811	27	Female	SCREENING	72	NORMAL	NORMAL	
				TERMINATION	78	NORMAL	NORMAL	
	815	26	Female	SCREENING	60	NORMAL	NORMAL	
				TERMINATION	50	NORMAL	NORMAL	
	816	26	Female	SCREENING	89	NORMAL	NORMAL	
				TERMINATION	74	ABNORM	ABNORMAL	SINUS ARRHYTHMIA
9	901	37	Female	SCREENING	66	NORMAL	NORMAL	
				TERMINATION				
	902	42	Female	SCREENING	55	ABNORM	ABNORMAL	SINUS BRADYCARDIA
				TERMINATION	70	NORMAL	NORMAL	
	906	34	Female	SCREENING	60	NORMAL	NORMAL	
				TERMINATION	76	NORMAL	NORMAL	
	910	21	Female	SCREENING	58	NORMAL	ABNORMAL	
				TERMINATION	59	ABNORM	ABNORMAL	SINUS BRADYCARDIA
	911	38	Female	SCREENING	61	NORMAL	ABNORMAL	
				TERMINATION	71	NORMAL	NORMAL	
	913	38	Female	SCREENING	80	NORMAL	NORMAL	
				TERMINATION	83	ABNORM	ABNORMAL	NORMAL SINUS RHYTHM WITH CCC S
	915	30	Female	SCREENING	63	NORMAL	NORMAL	
				TERMINATION	68	NORMAL	NORMAL	
10	1003	32	Male	SCREENING	58	NORMAL	ABNORMAL	

COP-1 9001 US DOUBLE-BLIND TRIAL (INCLUDING EXTENSION)
APPENDIX L11. ELECTROCARDIOGRAM DATA

TREATMENT=PLACEBO

CENTER NUMBER	PATIENT NUMBER	AGE	SEX	VISIT	HEART RATE	HEART RHYTHM	OVERALL EKG EVALUATION	RHYTHM SPECIFICATION
10	1003	32	Male	TERMINATION	57	NORMAL	ABNORMAL	
	1006	33	Female	SCREENING	85	NORMAL	NORMAL	
				TERMINATION	59	ABNORM	ABNORMAL	ECTOPIC ATRIAL RHYTHM, OTHERWI
	1009	31	Male	SCREENING	72	NORMAL	NORMAL	
				TERMINATION	65	NORMAL	ABNORMAL	
	1010	39	Female	SCREENING	79	NORMAL	NORMAL	
				TERMINATION	69	NORMAL	NORMAL	
	1014	33	Female	SCREENING	69	NORMAL	NORMAL	
				TERMINATION	90	NORMAL	NORMAL	
	1016	36	Female	SCREENING	72	NORMAL	NORMAL	
				TERMINATION	66	NORMAL	NORMAL	
	1019	34	Female	SCREENING	64	NORMAL	NORMAL	
				TERMINATION	72	NORMAL	ABNORMAL	
	1020	35	Male	SCREENING	67	NORMAL	NORMAL	
				TERMINATION	70	ABNORM	ABNORMAL	SINUS RHYTHM WITH SINUS ARRHYT
11	1101	45	Female	SCREENING	80	NORMAL	NORMAL	
				TERMINATION	70	NORMAL	NORMAL	
	1103	35	Male	SCREENING	70	NORMAL	NORMAL	
				TERMINATION				
	1106	34	Female	SCREENING	80	NORMAL	NORMAL	
				TERMINATION				
	1110	36	Female	SCREENING	79	NORMAL	NORMAL	
				TERMINATION	78	NORMAL	NORMAL	
	1112	26	Female	SCREENING	78	NORMAL	NORMAL	
				TERMINATION	54	NORMAL	NORMAL	
	1113	41	Female	SCREENING	77	NORMAL	ABNORMAL	
				TERMINATION	70	NORMAL	NORMAL	

APPENDIX K

Copolymer-1 Reactive Antibodies

Two of the clinical studies conducted with COPAXONE® in patients with relapsing multiple sclerosis included the collection of blood samples at various intervals during the active treatment period for analysis of serum copolymer-1 reactive antibodies. One of these studies was the double-blind, placebo-controlled Trial 01-9001/9001E in which antibody data were available from all 125 patients treated with copolymer-1 and a random sample of 20 % of placebo treated patients. The second study (1110-1) was an open-label investigation in which a subgroup of 43 of the 282 patients treated with copolymer-1 contributed data on copolymer-1 reactive antibodies. Results of both of these studies essentially revealed the same profile of clinical activity and antibody production. The clinical efficacy of copolymer-1 was apparent relatively early following treatment initiation and was maintained throughout the treatment period regardless of the changes in antibody titers. Copolymer-1 reactive antibodies were evident in virtually all patients tested, with maximum levels attained after an average treatment interval of 3 to 4 months. Thereafter, antibody levels slowly declined and stabilized at a level slightly higher than baseline. There was no indication in either study that either the serum concentration or the time-dependent profile of these antibodies was correlated with the clinical effectiveness or safety profile of copolymer-1. Specifically, no correlation was found between the profile of antibody production and the onset of relapses or systemic reactions or between the level of antibody production and the number of relapses or systemic reactions. While the exact character of these copolymer-1 reactive antibodies remains to be elucidated by ongoing investigations, the available clinical data strongly suggest that they are most probably non-neutralizing, non-IgE antibodies that appear to be directed against epitopes in copolymer-1 not involved in the drug's disease-protective properties. This is in contradiction to observations made in patients treated with interferon beta-1b, where the presence of neutralizing antibodies to IFN-β resulted in a significant attenuation in clinical efficacy.

To complement the clinical trial results, in studies conducted at the Weizmann Institute of Science, Rehovot, Israel, the ability of various copolymer-1 reactive antibodies to neutralize the biological activities of copolymer-1 (EAE inhibition, T cell proliferation and binding to MHC class II molecules) was tested in several *in vivo* and *in vitro* systems. Antibodies tested included polyclonal antibodies (rabbit and mouse anti-copolymer-1 antiserum), monoclonal antibodies reactive to copolymer-1, and sera from six patients who had been treated with copolymer-1 in Study 1110-1 and developed high titers of copolymer-1 reactive antibodies. The results of these *in vivo* and *in vitro* investigations demonstrated that a variety of monoclonal and polyclonal antibodies produced against copolymer-1, including those formed during long-term administration of copolymer-1 to patients with multiple sclerosis, did not interfere with the biological activities of this polypeptide. Thus, these results, like the clinical trial results, do not support the development of neutralizing antibodies with copolymer-1 administration.

It can be concluded that the formation of copolymer-1 reactive antibodies in patients with multiple sclerosis treated with daily subcutaneous injections of 20 mg COPAXONE® is likely a manifestation of the bioavailability and antigenicity of this

polypeptide This antibody formation is not associated with either short or long term safety issues and does not affect the clinical efficacy or safety of COPAXONE®

APPENDIX L

Kurtzke Expanded Disability Status Scale in Multiple Sclerosis

Note EDSS steps below 5 refer to patients who are fully ambulatory, and the precise step is defined by the Functional system (FS) score(s) EDSS steps from 5 up are defined by ability to ambulate, and usual equivalents in Functional Systems scores are provided A Mental function grade of 1 does not enter into FS scores for DDS steps

0 = Normal neurologic exam (all grade 0 in Functional Systems [FS], Cerebral grade 1 acceptable)

1 0 = No disability, minimal signs in one FS (i e , grade 1 excluding Cerebral grade 1)

1 5 = No disability minimal signs in more than on FS (more than one grade 1 excluding Cerebral grade 1)

2 0 = Minimal disability in one FS (one FS grade 2, others 0 or 1)

2 5 = Minimal disability in two FS (two FS grade 2, others 0 or 1)

3 0 = Mode e disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) through fully ambulatory

3 5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2, or two FS grade 3, or five FS grade 2 (others 0 or 1)

4 0 = Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations or lesser grades exceeding limits of previous steps Able to walk without aid or rest some 500 meters

4 5 = Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance, characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps Able to walk without aid or rest for some 300 meters

5 0 = Ambulatory without aid or rest for about 200 meters, disability severe enough to impair full daily activities (e g , to work full day without special provisions) (Usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding specifications for step 4 0)

5 5 = Ambulatory without aid or rest for about 100 meters, disability severe enough to preclude full daily activities (Usual FS equivalents are one grade 5 alone, others 0 or 1, or combinations of lesser grades usually exceeding those for step 4 0)

6 0 = Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters with or without resting (Usual FS equivalents are combinations with more than two FS grade 3+)

6 5 = Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting (Usual FS equivalents are combinations with more than two FS grade 3+)

7 0 = Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair, wheels self in standard wheelchair and transfers alone, up and about in w/c some 12 hours a day (Usual FS equivalents are combinations with more than one FS grade 4+, very rarely, pyramidal grade 5 alone)

7 5 = Unable to take more than a few steps, restricted to wheelchair, may need aid in transfer, wheels self but cannot carry on in standard wheelchair a full day, may require motorized wheelchair (Usual FS equivalents are combinations with more than on FS grade 4+)

8 0 = Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day, retains many self-care functions, generally has effective use of arms (Usual FS equivalents are combinations, generally grade 4+ in several systems)

8 5 = Essentially restricted to bed much of the day, has some effective use of arm(s), retains some self-care functions (Usual FS equivalents are combinations, generally 4+ in several systems)

9 0 = Helpless bed patient can communicate and eat (Usual FS equivalents are combinations, mostly grade 4+)

9 5 = Totally helpless bed patient, unable to communicate effectively or eat/swallow (Usual FS equivalents are combinations, almost all grade 4+)

10 = Death due to MS

Note EDSS should not change by 1 0 step unless there is a change in same direction of at least one step in at least one FS

Functional Neurological Status Evaluation

PYRAMIDAL FUNCTIONS

0 Normal

1 Abnormal signs without disability

2 Minimal disability

3 Mild or moderate paraparesis hemiparesis, or severe monoparesis

4 Marked paraparesis or hemiparesis or moderate quadraparesis or monoplegia

5 Paraplegia, hemiplegia, or marked quadraparesis

6 Quadriplegia

SENSORY FUNCTIONS

0 Normal

1 Vibration of figure writing decrease 1 or 2 limbs

2 Mild decrease in touch or pain or position and/or moderate decrease in vibration in 1 or 2 limbs, or vibratory decrease alone in 3 or 4 limbs

3 Moderate decrease in touch or pain or position sense and/or essentially lost vibration in 1 or 2 limbs, or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs

4 Marked decrease in touch or pain or proprioception alone or combined in 1 or 2 limbs, or moderate decrease in touch or pain and/or severe proprioceptive loss in more than 2 limbs

5 Loss of sensation in 1 or 2 limbs, or moderate decrease in touch or pain and/or loss of proprioception below the head

6 Sensation lost below the head

CEREBELLAR FUNCTIONS

0 Normal

1 Abnormal signs without disability

2 Mild ataxia

3 Moderate limb or truncal ataxia

4 Severe ataxia in all limbs

5 Unable to perform coordinated movements

BOWEL AND BLADDER FUNCTIONS

0 Normal

1 Mild urinary hesitancy, urgency, or retention

2 Moderate hesitancy, urgency, retention of bowel or bladder or rare urinary incontinence

3 Frequent urinary incontinence

4 In need of almost constant catheterization but without adequate bowel function

5 Loss of bladder function

6 Loss of bowel and bladder function

BRAIN STEM FUNCTIONS

0 Normal

1 Signs only

2 Moderate nystagmus or other mold disability

3 Severe nystagmus, marked extraocular weakness, or moderate disability of other cranial nerves

4 Marked dysarthria or other marked disability

5 Inability to swallow or speak

MENTAL FUNCTIONS

0 Normal

1 Mood alteration only

2 Mild decrease in mentation

3 Moderate decrease in mentation

4 Marked decrease in mentation

5 Dementia and/or chronic depressed alertness

VISUAL FUNCTIONS

0 Normal

1 Acuity better than 20/30 in the worse eye

2 Acuity between 20/30 and 20/59 in worse eye

3 Acuity between 20/60 and 20/99 in worse eye

4 Acuity between 20/100 and 20/200 worse eye or Grade 3 plus better eye 20/60 or less

5 Acuity 20/200 or less in worse eye or Grade 4 plus better eye 20/60 or less

6 Grade 5 plus better eye 20/60 or less

OTHER

0 None

1 Any other findings (Specify _____)

Ambulation Index

0 = Asymptomatic, fully active

1 = Walks normally but reports fatigue which interferes with athletic or other demanding activities

2 = Abnormal gait or episodic imbalance, gait disorder is noticeable to family and friends Able to walk 25 feet in 10 seconds or less

3 = Walks independently, able to walk 25 feet in 20 seconds or less

4 = Requires unilateral support (cane, single crutch) to walk, uses support more than 80% of the time Walks 25 feet in 20 seconds or less

5 = Requires bilateral support (cane, crutches, walker) and walks 25 feet in 20 seconds or less, or, requires unilateral support but walks 25 feet in greater than 20 seconds

6 = Requires bilateral support and walks 25 feet in greater than 20 seconds May use wheelchair on occasion *

7 = Walking limited to several steps with bilateral support, unable to walk 25 feet May use wheelchair for most activities

8 = Restricted to wheelchair, able to transfer independently

9 = Restricted to wheelchair, unable to transfer independently

* The use of a wheelchair may be determined by a patient's lifestyle and motivation It is expected that patients in grade 7 will use a wheelchair more frequently than patients in grades 5 or 6 Assignment of a grade, however, in the 5-7 range is determined by the ability of a patient to walk a given distance and not by the extent to which a patient uses a wheelchair

APPENDIX M

Table 1 ANOVA/ANCOVA Results from Analysis of the Observed Number of Relapses Over 24 Months. Trial 01-9001/9001E
All Patients Cohort

Model	Comments from Analysis	Treatment P-Value
Drug, Center, DxC		0.056
Drug, Center, DxC, BL EDSS, Sex, Prior 2-Yr Relapse Rate, Duration of Disease	BL EDSS (p= 004) and Prior 2-Yr Relapse Rate (p= 006) were significant	0 020
Drug, Center, DxC, BL EDSS, BL EDSS x D, Prior 2-Yr Relapse Rate, Prior 2-Yr Relapse Rate x D	BL EDSS x D and Prior 2-Yr Relapse Rate x D were NS; no baseline x drug interaction	N/A
Drug, Center, DxC, BL EDSS, Prior 2-Yr Relapse Rate	BL EDSS (p=0 003) and Prior 2-Yr Relapse Rate (p=0 006) were significant	0 018
Drug, Center	NS interaction term dropped from model	0.025
Drug, Center, BL EDSS, Sex, Prior 2-Yr Relapse Rate, Duration of Disease	BL EDSS (p= 011) and Prior 2-Yr Relapse Rate (p= 008) were significant	0 009
Drug, Center, BL EDSS, Prior 2-Yr Relapse Rate	BL EDSS (p= 008) and Prior 2-Yr Relapse Rate(p= 008) were significant	0 007

The p-values, as seen in Table 1, range from 0 007 using the covariates (baseline EDSS + prior two-year relapse rate) and main-effects-only (D and C) model to 0 056 using the main effects and interaction-only model (D, C, D x

Table 2: Trial 01-9001/9001E - P-Values for Drug Effect - Analysis at 24 Months

	STATISTICAL MODEL		
	Drug, Center, DxC	Drug, Center	Drug, Center, Baseline EDSS, Prior 2-year Relapse Rate
Primary Cohort All Patients (ITT)	0 056	0 025	0 007
Secondary Cohort			
Patients Treated at Least 730 Days (Completers)	0 066	0 040	0 015
All Patients with Imputation of Relapses	0 095	0 074	0 021
Retrieved Dropouts All Patients	0 072	0 035	0 011

The P-values as seen in Table 2 demonstrate a statistically significant difference between treatment groups, which is essentially consistent among the various cohorts for the primary efficacy endpoint, i e , the mean number of relapses.

END

BT

J H.M Research & Development, Inc , 5776 Second Street, N E , Washington, D C 20011

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM
DRUGS ADVISORY COMMITTEE

MEETING NUMBER 44

September 19, 1996

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CASET Associates, Ltd.
10201 Lee Highway, Suite 160
Fairfax, Virginia 22030
(703) 352-0091

PARTICIPANTS:

PRESENT FROM THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE:

Sid Gilman, M.D., Professor and Chair, Department of Neurology, University of Michigan Medical Center
Ermona McGoodwin, Advisors and Consultants Staff, Center for Drug Evaluation and Research, Food and Drug Administration
Orlando Carter Snead, III, M.D., Head, Division of Neurology, the Hospital for Sick Children
Patricia K. Coyle, M.D., Professor of Neurology, Department of Neurology, Health Science Center, State University of New York at Stony Brook
Chris Gennings, Ph.D., Assistant Professor, Department of Biostatistics, Medical College of Virginia, Virginia Commonwealth University
Ellyn C. Phillips, B.A., M.S., President Amyotrophic Lateral Sclerosis Association, Philadelphia Chapter
David A. Drachman, M.D., Professor and Chair, Department of Neurology, University of Massachusetts Medical School
Claudia H. Kawas, M.D., Associate Professor of Neurology Department of Geriatric Neurology, Johns Hopkins University School of Medicine
Zaven S. Khachaturian, Ph.D., Care Services, Chairman, Khachaturian, Radebaugh and Associates, Inc.

FDA:
Dr. Paul Leber
Dr. Russell Katz
Dr. Robert Temple

PARTICIPANTS:

Dr. Frances Meilach
Dr. Ruth Arnon
Dr. Aaron Miller
Dr. David Hoberman

PRESENT FROM THE NATIONAL MULTIPLE SCLEROSIS SOCIETY:

Donna DiCarlo, Patient
Brian Bowersox, Patient

PATIENT PARTICIPANTS:

Elizabeth Dumbell
Maria Hardin
Anita Gowen
Kathleen Andes
Jan Sedlak

PRESENT FROM TEVA PHARMACEUTICALS, USA:

Carole S. Ben-Maimon, M.D., Senior Vice President
Kenneth P. Johnson, M.D., Professor and Chair, Department of Neurology, University of Maryland, School of Medicine
Jerry Wolinsky, M.D., Professor of Neurology, Director, Multiple Sclerosis Research Group, University of Texas Health Sciences Center

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P R O C E E D I N G S [8:30 a.m.]

Agenda Item: Call to Order: Welcome and Information

DR. GILMAN: Good morning. It is a privilege to welcome all of you here. My name is Sid Gilman. I am a neurologist, Chairman of the Department of Neurology at the University of Michigan Medical Center, and Chair of this committee.

I would like to begin by having the members of the Advisory Panel introduce themselves. We will run around the table from my right. Dr. Leber, please introduce yourself and give your job description.

DR. LEBER: I am not a member of the Committee. I am the Director of the Division of Neuropharmacological Drug Products.

DR. KATZ: Russ Katz, Deputy Director of the Division of Neuropharmacological Drug Products, FDA.

DR. DRACHMAN: I am David Drachman, Chairman of Neurology at UMS Medical Center.

DR. GENNINGS: Chris Gennings, Department of Biostatistics, Medical College of Virginia.

DR. PHILLIPS: I am Ellen Phillips. I am the Consumer Representative to the Panel.

DR. McGOODWIN: I am Ermona McGoodwin, the Executive Secretary.

DR. SNEAD: Carter Snead, Department of Pediatrics and Neurology, University of Toronto.

DR. COYLE: Pat Coyle, Department of Neurology at SUNY, Stonybrook, New York.

DR. KAWAS: Claudia Kawas, Department of Neurology at Johns Hopkins.

DR. KHACHATURIAN: I am Zaven Khachaturian, with the Ronald and Nancy Reagan Research Institute of the Alzheimer's Association.

DR. GILMAN: Thank you all. I would like to give some general instructions to the Panel and also to the presenters today. I would like to run an orderly meeting and keep ourselves focused on the questions that the Panel is being asked to consider. For the presenters, from the sponsor, please tell us all that you need to tell us. We want to hear from you. Please do not leave anything back. Do not worry about the time. We want to have a full and open hearing. This is an open hearing. However, we would like to interrupt you as questions arise. I will ask the Panel members to indicate they wish to speak by raising their hands so that I could acknowledge your question. If the light should be out and I cannot see you, then please just speak into the microphone, identify yourself, and ask your question. I would appreciate having the sponsor answer the questions as they are posed, even if you are about to

show data in a couple of slides away from the place where you have been interrupted. Please just give us a brief answer and then let us know that you will answer this in greater detail later. Do not put off questions. These questions are going to be important. We have read the material. We have our questions, many of us, already prepared so we know what you have said in the document. Please tell us that and tell us anything further that you would wish to tell us. But we would like to have you address our questions. I can ask the same of the FDA members. If you will also answer our questions when they are asked of you, I would appreciate it.

This is an open hearing, as I have indicated. I would very much like to have the individuals who have requested to be heard make their presentations. I do ask that you keep them brief. We will have an opportunity to hear from you prior to our vote. You are scheduled to speak with us as soon as the Committee has concluded its discussion but before the vote so that we can hear what you have to say.

I will introduce those of you who have asked to speak. If anybody else in the audience who has not indicated that he or she wishes to speak, please let us know. You will have an opportunity to do so. Again, I ask that you keep your remarks brief for us.

With that I will turn to Ermona McGoodwin for the statement on the conflict of interest.

Agenda Item: Conflict of Interest Statement

DR. McGOODWIN: Thank you, Dr. Gilman. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the Agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting. We would, however, like to disclose for the record that Dr. Patricia Coyle, and her employer, the State University of New York, at Stonybrook, have interests which do not constitute a financial interest within the meaning of 18 USC 208(a), but which could create the appearance of a conflict of interest. The Agency has determined, notwithstanding these involvements, that the interest of the government and Dr. Coyle's participation outweighs the concern that the integrity of the Agency's programs and operations may be questions. Therefore, Dr. Coyle may participate in today's discussions without voting privileges.

In the event that the discussions involve any

other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

DR. GILMAN: Thank you. We are now going to enter our open session.

[Whereupon, the Committee proceeded in open session.]

Agenda Item: Open Session

DR. GILMAN: Panel members, let me just remind you that we have been asked two questions. TEVA Pharmaceuticals has provided results of two controlled clinical investigations of Copolymer-1 to look at its effectiveness in exacerbating remitting multiple sclerosis. We are asked: Are these studies adequate and well-controlled clinical investigations and does each provide evidence that would allow an expert knowledgeable and experienced in the management of patients with MS to concluded that Copolymer-1 is an effective treatment for MS? Second question: Has the sponsor provided evidence that Copolymer-1 is safe when used

in the treatment of multiple sclerosis?

With that I would like to ask Dr. Paul Leber, Division Director of DNDP to make introductory remarks. Dr. Leber.

Agenda Item: FDA Introductory Remarks

DR. LEBER: These will be I hope brief. It is largely a welcome to the Committee. We very much appreciate having you here so that we will have an opportunity to learn what your views are on a question that we bring to you not because we bring all questions to the Committee, but because we believe that this particular one involves questions of judgment and sentiment that we would not want to make on our own. I emphasize this because many people attach a lot of significance to bringing something to the Advisory Committee. I want to emphasize that we do not bring every question to the Advisory Committee. We do not have time and either would you; but we anticipate that there were no questions or controversy. We bring this solely because some of the questions that we have to answer are difficult, not necessarily because we know what the answer is, but we believe, as is often the case, that when an issue involves judgment and sentiment, opinion about the matter can be reasonably divided. So we need to discuss in a public arena so people will understand what the decision making process is, why we reach decisions either yea or nay in a case.

That is really why we are asking for your judgment because, as I want to point out, I put up the definition of substantial evidence as described in the Act. This deals with effectiveness.

I want to emphasize a couple of points about why your role is so important. Notice the emphasis here is that when we make decisions about whether or not products work we rely upon information gained in adequate and well-controlled clinical trials. The question we ask is not some general abstraction about whether the drug is effective; but we are asking something that is more focused in a way. It says: Can experts qualified by experience, and training, and knowledgeable in the area where the drug is going to be used conclude from the evidence in control trials that the drug will have the effective its sponsors claims for it? Now, that is an important point because we are not making some strange omnibus conclusion. What we are trying to find out is what experts would conclude the evidence support, and what the nature of the claim ought to be. So although we ask you whether or not the drug is effective, one important part of your answer will include effective for what. How, if you conclude this drug is effective for MS, what kind of claim do you think it is entitled to?

The second point I want to make, and I am going to change slides, is that decisions on NDAs, the licensing

vehicle by which we decide whether or not a drug can be approved for marketing, turn not only on questions of evidence of effectiveness, but on issues some of which we will not even bring to you, for example, how well the drug is made and what its biopharmacokinetic performance is, if it has one, but on questions of safety. It is important to understand that safety is not really described anywhere in precise language. I point out that there are at least three areas of the law that speak to why the agency would turn down a drug. I just want to emphasize what they are.

If you look at number two, the results of tests known to assess safety show the drug is unsafe or fail to show it is safe. This has to do with the absence of evidence, not being evidence of absence, as the line goes.

The first I skipped over was inadequate tests. That means you just have not done enough tests.

Number four is an interesting one. When you take everything you know all together in aggregate, is there enough information to make your decision? I just emphasize that as sort of the general guidance. I am not offering an opinion on any specific detail, but that is the framework of what we mean by safety. Safety in this sense is the judgment of experts, given what you know about a drug and what it is going to be used for, the nature of the population being treated, is the drug safe within that

context. Those are just the general introductory thoughts that I have about framing the discussion for today, that it is a framework, not more than that. It is certainly not a charge in the sense of do this or do not.

Anyway, I look forward to today's discussion. With this, I would like to introduce my colleague, the Deputy Director of the Division, Dr. Katz, who will present the data as we have handled it. Russ.

Agenda Item: Russell Katz, M.D., DNDP

DR. KATZ: Thanks, Paul. I also would like to add my personal welcome to the members of the Committee. As you know we are here to discuss NDA-20-622 for the use of Copolymer-1 in the treatment of patients with relapsing remitting multiple sclerosis.

If I can just correct Paul a little bit. I am not going to present the data from the Agency's point of view. We have written about it. You have all of our reviews and our summaries. You will hear a detailed presentation of the data from the sponsor immediately following my remarks. We have largely come to an agreement on the major points at least with regard to what the data are with the company in previous discussions.

So I am not going to present the data really; but what I would like to do is just make a few brief remarks also about -- in an attempt to focus your thinking prior to

your discussions on your vote, and also to help you think about some of the issues we would like you to think about while the data are being presented by the company.

You know that the application contains the results of two placebo controlled trials which are capable by design of demonstrating the effectiveness of Cop-1 in this patient population. What we are here to ask you is whether or not you think that the sum total of the evidenced supports an approval action.

The first study was performed by Dr. Bornstein, and his team at the Albert Einstein College of Medicine in the early 1980s. It was designed explicitly as a pilot study, but was an adequate and well-controlled trial.

It first came to public attention in 1987 when the results were published in the New England Journal of Medicine. In that publication, the study was reported as being statistically significantly positive on its primary outcome variable which was the proportion of patients who were exacerbation-free during the course of the two-year trial. As well, other secondary measures were reported as being quite positive.

The current sponsor, TEVA, was not involved in the conduct of this trial, but they did subsequently take over the development of the drug. In an attempt to confirm the Bornstein Study, they initiated a much larger second trial

of similar design. On the basis of the published results in the New England Journal of the Bornstein Study, and on the fact that the second control trial was ongoing, they requested permission to initiate a treatment IND for wider distribution of the drug to these patients somewhere in the end of 1992. And shortly thereafter permission to proceed with the treatment IND was granted.

Now, because the sponsor that not been involved in the conduct of the trial, the complete documentation for the trial was not immediately available to them and they have and had undergone a tremendous effort to retrieve the document from that trial. They have largely been successful and really obtained all of the relevant information we would need including individual patient data, case report forms, and that sort of thing. However, the protocol, that is to say the detailed plan for this study written prospectively before the initiation of the trial really had not been available to them and only recently became known to us. And the combination of the sponsor's ability to retrieve the original data as well as the unearthing, if you will, of the document that we believe to be the protocol that Dr. Bornstein followed, have raised together several questions about the trial.

The first is that when the sponsor did an analysis of all patients who were randomized, the so-called intend to

treat population, which is an analysis that you know that we do not necessarily always rely on as primary, but we certainly want to see, that analysis yielded a P value for the primary variable that was clearly not statistically significant by the usual rules. I think it was somewhere around .18. It had originally reported to be .038 or something like that. The discrepancy is explained by the fact that two patients who were randomized placebo were excluded from the analysis that was presented in the New England Journal. You will hear, I would imagine, considerably more about why the sponsor feels it was appropriate or at least the authors of the article felt it was appropriate to exclude those patients.

It was also the case that even when the intent to treat population was included in subsequent analyses of all of the other secondary measures they seemed to clearly persist in being statistically significant.

The other potentially interesting -- I will call it that -- problem that arose from the identification of the document that we did believe to be the protocol that was followed was the fact that that document explicitly calls for the enrollment of 40 patients into the trial. This was a small trial in any event. The reason that is important is because ultimately the trial enrolled 50 patients. The reason that is important is the following. We are aware of

a document that was written about a year after the protocol was written, about a year after the study was initiated which reports the results actually of an interim analysis of the data, an interim analysis that was not described in the protocol. That interim analysis yielded nominally statistically-significant results on the primary outcome variable and perhaps several others, that is to say, a P value of below .05. And then a document a year later, written in 1982 for the first time includes sample size calculations justifying the use of 50 patients. Ultimately, that is how many patients were randomized.

So putting this all together, what we have is a document trail, if you will, which is the following. The protocol says 40 patients is an interim analysis. The next document says we are going to have 50 patients and that is how many were enrolled. So at least it allows the possibility that the sample size as increased based on the results of the interim analysis. That is a problem. We can talk more specifically later on about why that has a potential to confound or make the interpretation of the trial problematic.

There is also the question of having to correct the P value at the end of a trial on the basis of -- because you have taken multiple looks. We are not exactly sure how many looks were taken. We do not even know about the

results of one interim analysis. So that complicates the interpretation of the trial.

Then, of course, there is the question of the exquisite sensitivity of the P value to the inclusion of two more patients so that you go from -- with 48 patients you go from a P value of .038 to a P value that is clearly not significant, with just the addition of two patients. That raises the question of the reliability of between treatment differences that emerge out of very small trials and what those mean and how stable those are.

That is particularly important when the data are seen in the context of the second trial. The second trial was conducted by the sponsor. It was considerably larger, about 250 patients who were enrolled in this trial. It was largely of similar design. The primary outcome variable in that study was the mean exacerbation frequency over two years, which was the duration of the trial. It was positive on that outcome; but essentially all other secondary outcomes were negative, including many of the outcomes that had been positive in the Bornstein trial, including the outcome that was the primary measure in the Bornstein trial, which is the proportion of patients who were exacerbation free.

Further, if you look at the between treatment differences that were seen in the larger trial, you see that

they are consistently considerably lower than, smaller than those in the Bornstein trial. For example, the one outcome that is positive in both trials was the mean exacerbation frequency. The difference between drug and placebo in the Bornstein study was about 1.6 exacerbations over the two years of the trial; whereas, in the larger study it was somewhere around 0.3. A similar comparison of the other outcomes show consistently smaller treatment effects, if you will, in the larger study.

With regard to safety, there is not anything that appears to be an affirmative risk in the database that we have seen, although there are several questions that we would like the Committee to look at.

One is the issue of chest pain. There was about a 26 percent incidence of chest pain in the large control trial compared to somewhere around 10 percent in the placebo group. We know very little about this symptom. We believe that there were not any serious sequelae from it as far as we know, but there is very little documentation about what the chest pain is, what patients actually felt. There is no systematic, for example, EKG monitoring at the time of these events. So we are not exactly sure what these mean and we would like to focus on that at least briefly.

Another safety concern is this relatively stereotyped reaction that occurs in a number of patients,

not uncommonly that the sponsor has dubbed the systemic reaction. They have created a definition for what that is. We are not sure what that is. We are not sure if it really is a syndrome as the sponsor essentially implies it is, whether these are events that are occurring at the same time but not really related. We are not sure. We would like the committee to just address itself to that however briefly.

Another potential issue is the question of the absence at this time of the usually required two lifetime in vivo cost and authenticity studies. As you probably know we ordinarily require these studies be submitted at the time -- be present anyway at the time of approval of a drug or our action of a drug. Those studies are -- and that usually applies for treatments that are given chronically for not immediately life-threatening illnesses. Those studies are ongoing. The sponsor is performing those studies. They will not be done for quite a while. The sponsor has chosen not to submit those at this time.

Just in that regard, it is interesting to note that one of several screen assays looking at the genotoxic potential of the drug or another series of tests that we ordinarily require was positive with Cop-1. That is a finding with which the sponsor does agree.

So we would just like you to look at the question of whether or not the absence of that ordinarily required

information is of concern to you at this time in your decision.

So, basically, in summary, what we have are two adequate and well-controlled trials. One is fairly small. It is negative on its primary outcome, at least with regard to an analysis of the intent to treat population, but it is very positive on pretty much everything else that was looked at. We have a larger -- a much larger study which was designed to replicate that finding. It is positive on its primary outcome, but essentially negative on the other outcomes.

The magnitude of the finding and findings in the larger study are considerably smaller than those that emerged out of the smaller study. So, as Dr. Leber has posed it to you, we would like you to address the question of whether or not the data in toto support a recommendation for approval of the product, and specifically with regard to what claim you think the data support, if they support any claim at all.

That is really the background I wanted to give to the Committee. With that, I will turn the microphone back to Dr. Gilman.

DR. GILMAN: Thank you, Dr. Katz. Before we hear from the sponsor, Dr. Bob Temple has joined us. Would you introduce yourself to the group please.

DR. TEMPLE: Sure. I am Bob Temple. I am Director of the Office of Drug Evaluation I, which is the office within which neuropharm resides.

DR. GILMAN: Thank you.

DR. TEMPLE: Thanks.

DR. GILMAN: Well, we will now hear from TEVA Pharmaceuticals, Carole Ben-Maimon, M.D., Senior Vice President, TEVA Pharmaceuticals, USA will initiate the presentation.

Agenda Item: Sponsor Presentations - TEVA Pharmaceuticals, USA

DR. BEN-MAIMON: Good morning everybody. Thank you for coming today. As you were just told, I am Carole Ben-Maimon, Vice President of Research and Development for TEVA Pharmaceuticals, USA. Before I begin, I wanted to thank the FDA for their attention and time spent in the review of our NDA. I wanted to thank the Panel for taking time out of your busy schedules to prepare and read all of the documentation.

Last but not least, I would like to thank the investigators who participated in our clinical trials, and also the patients because, without their commitment, none of us would be here today.

Today I will present to you the data supporting our claim that Copaxone is safe and effective for the

treatment of patients with relapsing MS. Copaxone represents a new class of immunomodulators developed to target the specific autoimmune response pathogenesis of multiple sclerosis. Thus, Copaxone is a drug we believe that is a new and unique therapeutic option for patients with MS.

Our first presentation will be from Dr. Johnson, from the University of Maryland. Dr. Johnson will review very briefly the pathogenesis of MS and discuss some of the clinical outcome measures that were employed in the clinical trials that support the claim.

Following Dr. Johnson's presentation, I will provide an overview of the toxicology and the development program for Copaxone. Following that, I plan to provide you with the data on the two adequate and well-controlled trials, and I will discuss the safety assessment incorporating some of the open-labeled trials including the results of our treatment IND.

Following my presentation, Dr. Jerry Wolinsky will present to you a clinical assessment of the use of Copolymer-1 in patients with relapsing MS.

Finally, I will return to the podium and obviously answer any questions that still exist that we have not responded to throughout the presentation.

I would now like to turn the presentation over to

Dr. Johnson. Dr. Johnson is the Chairman of the Department of Neurology at the University of Maryland and is a leader in the field of clinical research in patients with MS. Dr. Johnson has participated in several clinical trials in patients with multiple sclerosis and was the Project Director for the Phase III Multicenter Trial conducted and sponsored by TEVA.

Agenda Item: Multiple Sclerosis

DR. JOHNSON: In the next few minutes, I would like to briefly describe the key elements of multiple sclerosis, review the primary scale used to classify disability, and indicate the cardinal issues that we face in caring for MS patients. Next slide.

[Slide.]

DR. JOHNSON: The epidemiology of MS indicates that there are approximately 350 patients in the United States at the present time. The age of onset is 18 to 45 years, with a peak age of onset of 30 years. Seventy percent of cases occur in women.

In broad terms, we recognize three stages of clinical disease: Relapsing, progressive, and benign. And there are approximately 65 or a majority of the patients start with relapsing/remitting disease; however, about 15 percent have a progressive course from onset.

Maybe 20 percent of patients have benign disease,

but this can only be recognized decades after diagnosis when they fail to have further relapses or progression. The prevalence is, at any given time, is about equal numbers, 40 percent of patients in the relapsing stage and the progressive stage, and then the 20 percent who are destined for benign disease. Fifty percent of patients will require walking aids or a wheelchair within 15 years of diagnosis.

There is a relationship between the number of relapses and later fixed disability. If a group of patients has more than five relapses in the first two years, then the risk is that half of them will require some type of walking aid within seven years. If, on the other hand, this group has two to four relapses in the first two years, then half of them will take 13 years before they need walking aids. Whereas, if they have less then two relapses in the first two years, then you can see that it will be 18 years before half of them have the risk of walking aids.

Now, the pathology is quite well known at the present time. It occurs only in the central nervous system, in the white matter primarily, in brain optic nerve and spinal cord. There are discrete plaques which consist of focal inflammation demyelination, gliosis, and to a certain extent axonal loss, which obviously is permanent.

Pathogenesis is also well-known, although the cause of the disease remains a mystery. There is a

clearly-recognized genetic predisposition to the disease. In these patients T-lymphocytes sensitize to one of several myelin antigens, including myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein, and perhaps other antigens are present and lymphocytes are sensitized to them.

At irregular periods of time these lymphocytes invade the CNS and create an inflammatory focus which then damages myelin. Several different mechanisms of damage are recognized, macrophages, antibodies, and complement, cytotoxic T-cells and coinflammatory cytokines, to name some.

The central issue or the central kind of mechanism by which this all occurs is so-called trimolecular complex in which an antigen-presenting cell with its class II MHC apparatus presents an antigen, the autoantigen to the T cell with its specialized receptor. Most of the therapies that we think of at the present time are active somewhere within this trimolecular complex.

In clinical trials, we usually measure two different aspects of disease, one is the relapse rate, and the other is the disability which relies on a standard which is usually the DSS or EDSS, which were derived by Dr. John Kurtzke some time ago. He originally devised a DSS scale, which is a 10-step scale going from normal neurologic

state to death, and that was used in the early Bornstein trial.

Later, Dr. Kurtzke expanded this to the EDSS, which is a 20-step half-step scale, and that is what is in current use at the present time. It is a nonlinear scale. I have just put a few steps for your information. For instance, the EDSS-4 requires that a patient be able to walk for 500 meters unaided. At EDSS-6, the patient needs a walking aid of some type. By EDSS-7.5, the patient is restricted to a wheelchair.

Now, the EDSS depends on two things: Walking ability and the ability to function in seven different functional systems which have five or six grades each. These include the peripheral system, sensory system, cerebellar, bowel, and bladder, brain stem, mental and visual systems. Each of these the neurologist will grade according to level of disability. This is added to the ability to walk, and that determines the specificities of the EDSS.

Now, those of us who care for MS patients frequently recognize there are at least three major management issues. The first is relapse control, the second are ways of perhaps delaying disability. Sometime in the future, we hope to be able to reverse disability by remyelination, but there are no drugs to do that so far.

Finally, there are ways of modifying symptoms with steroids and other symptomatic therapies. These therapies must be safe for use in young-adult life, and well-tolerated during chronic treatment which will be measured in many years.

Relapse control is a major therapeutic goal. Relapses cause loss of work days, inability to care for the self, the patient, their family, and home. Remember, 70 percent of the patients are women. There is increased transient disability, increased pathologic fatigue, increased anxiety, increased risk of hospitalization, and increase to active or reactive depression, to just name some of the things which happen to a patient who is undergoing a relapse.

Also, you will recognize that I mentioned earlier that there is a relationship between relapses and later fixed disability. Obviously, ability to delay or modify disability is also of major importance. If patients can have a delay in their onset of disability, they will be able to complete their education, maintain employment, or manage care for their family. There is a delay in the need for walking aids. One of the unfortunately late aspects of MS is cognitive decline. If we can delay this, that is clearly of importance. Finally, it will maintain quality of life.

As you know, I and our group at the University of

Maryland have been deeply involved in the study of the interferons as therapy over the last 15 years. Up to 1993, we had either conducted or participated in five different control trials testing the effects of all three human interferons, alpha, beta, and gamma. We are proud to have been part of the development of interferon, beta 1B, recognized as the first treatment ever to alter the course of relapsing MS.

With my own personal experience, and the broad experience of our center over the past three years, it is now very clear to us that, while valuable, the interferons cause several problems as therapies for MS. Substantial side effects include: Long-term use in some patients who cannot tolerate the flu-like syndrome, skin reactions, or laboratory deviations.

We have also participated in publication of data indicating that almost 40 percent of patients over time, over three years develop neutralizing antibodies, and these patients have a clinical and MRI profile which is identical to patients with placebo.

This is disappointing obviously. You can imagine that we are very much involved in the study of how to get around this antibody issue.

As an experienced MS clinician, however, faced with the current options, it is my view that there is a

major unmet need for effective therapies, when we have only the interferons at the present time.

Thank you very much.

DR. GILMAN: Thank you very much. Dr. Ben-Maimon.

Agenda Item: Safety and Efficacy

DR. BEN-MAIMON: Right now I would like to begin with the preclinical and early clinical program for Copaxone.

Copolymer-1 is an acetate sale of synthetic polypeptides composed of four amino acids. It is dispensed in single-dose vials that the patient mixes with one cc of water for injection, and then administers subcutaneously.

Copolymer-1 was discovered at the Weizmann Institute in Rehovot, Israel in labs of Dr. Michael Sela, and Dr. Ruth Arnon, who are here with us today. Dr. Sela and Dr. Arnon designed a series of synthetic polypeptides to simulate the action of myelin basic protein. As you know, myelin basic protein is thought to be the inciting antigen in multiple sclerosis or one of the inciting antigens.

While none of these peptides was found to be encephalitogenic, some were found to reverse or prevent the development of experimental allergic encephalomyelitis or EAE in animal models.

The most potent of the polypeptides tested was Copolymer-1. Thus, this copolymer was chosen for further

study and ultimately for clinical development.

As Dr. Johnson described, multiple sclerosis is thought to occur when the inciting antigens bind to the MHC2 locus. You can see here this is the antigen-presenting cell with the MHC2 locus. The antigen comes in and binds to the site and is able to fit into the T-cell receptor. The antigen binds to the APC and is then presented to the T-cell receptor. The trimolecular complex, the APC, the T-cell, and the antigen, activate the autoreactive T-cells within the CNS and initiate an inflammatory response targeted against the myelin sheath. This attack affects the brain's and the spinal cord's ability to conduct neurological impulses.

The exact mechanism of Copaxone is not understood. It is hypothesized that it acts by competing with and even displacing the myelin autoantigens from the MHC2 locus. You see, if it would bind here and then could not make contact with the T-cell, you would not be able to activate the inciting antigens. The T-cells then cannot bind to form the necessary trimolecular complex required, and the activation of the autoreactive T-cells is prevented.

On the other hand, this slide demonstrates that although Copolymer-1 may prevent the induction of the autoreactive T-cell, it may still be able to activate the T-suppressor cell. Thus when these T-suppressor cells cross

the blood-brain barrier and are reactivated by exposure to MBP, they interfere with the inflammatory attack on the myelin sheath.

Studies to support this hypothesis include in vivo studies in EAE, as well as in vitro studies in both murine and human systems. Clearly, the complete mechanism has not been worked out, but this is the theoretical hypothesis.

I would now like to move on to a brief summary of the regulatory history for Copaxone. Trial BR-1, the earliest of the two trials, was completed in 1985 by the late Dr. Murray Bornstein at Albert Einstein College of Medicine, under an investigator IND.

In 1987, the FDA awarded Copolymer-1 for injection orphan drug designation. As a part of this process, FDA audited Dr. Bornstein's clinical site. In 1993, based on the results from Dr. Bornstein's trial, FDA approved a treatment IND in order to make Copolymer-1 for injection available to a broader population of patients. Approximately 600 patients are currently participating in the treatment IND today. This trial has provided us with considerable safety data in support of the NDA.

In 1994, the second pivotal trial for Copolymer-1 was completed. In 1995, TEVA submitted the NDA.

Prior to the initiation of the double-blind trial, several safety studies were performed. As you can see from

the slide, a total of 49 patients were exposed to Copolymer-1 in these early trials. Several of these patients had acute encephalomyelitis, while others had chronic progressive, and relapsing MS. Doses ranging from two milligrams several times a week to 20 milligrams daily were administered. The preliminary safety data obtained from these trials, particularly the trial with 16 patients, which we call BROB, conducted by Dr. Bornstein, set the stage for the double-bland trials.

Dr. Bornstein started his patients at a dose of five milligrams daily, five times per week, and titrated the dose up or down depending upon the patient's clinical course and adverse event profile. The maximal dose used in these studies was 30 milligrams.

Three of the patients with chronic progressive disease stabilized, as did two patients with relapsing MS. Eleven patients showed no effects and four patients reported injection-site reactions, while 13 reported other various systemic reactions. None of these events was serious. None was life-threatening. Thus, Dr. Bornstein chose as his optimal dose, in patients with relapsing MS, 20 milligrams daily self-injected subcutaneously. This is the dose that was then tested for efficacy in Dr. Bornstein's subsequent double-blind trial, Trial BR-1, and ultimately in the TEVA-sponsored, multi-center, double-blind trial. Based on

the evidence that this dose was effective in the two control trials, TEVA proposes the dose to be 20 milligrams self-injected subcutaneously.

DR. GILMAN: May I interrupt here just to ask a question?

DR. BEN-MAIMON: Yes?

DR. GILMAN: Those 13 other adverse reactions, were any of them the so-called systemic reaction that has been described later?

DR. BEN-MAIMON: Dr. Bornstein did not describe at this point discretely. What he called it actually was the vasomotor event. That really appears initially in the publication where two patients clearly reported a similar event. If you would like, I do have a list of the adverse events from his early trials.

DR. GILMAN: Yes. I would like to see what they were.

DR. BEN-MAIMON: Okay. That is slide G-79. Again, you have to recognize that these four trials were mostly, with the exception of BR-OB, most of the data is obtained from publications. On BR-OB, we actually do have case report forms and source documents and have been able to confirm most of the data. But many of these adverse events were taken actually just out of the publications.

DR. GILMAN: I do understand that. But the

question about the systemic reaction is very unclear. It is not clear to me exactly what the patients were experiencing.

DR. BEN-MAIMON: Dr. Johnson, Dr. Wolinsky, would you want to speak to that? They have seen the patients and can probably speak better to characterize it.

DR. GILMAN: Would you focus the slide please?

[Slide.]

DR. JOHNSON: This slide really does not give any information about the systemic reaction. Dr. Bornstein called it a vasomotor reaction. We do not know that that is true so we have used a more generic term of systemic reaction. Immediately after the injection, patients have a cluster of symptoms which may be chest tightness or chest pain, some flushing in their face, a sense of anxiety and dyspnea. This lasts anywhere from 30 seconds to 30 minutes. The fact that we do not have better information about it is that rarely has this ever been seen by a health professional just because of its brief duration.

You have to understand that this is a very rare event. Eighty-five percent of patients in the large trial never had one of these, and the 15 percent who did usually only had one in approximately 720 injections, that is daily injections for two years. So it is a very rare event for immediately after the injection. It lasts a brief period of time and has not been associated with any type of sequelae

in any of our patients.

DR. GILMAN: Well, while you are there talking about this event, here is a report of the death of a 46-year-old person who was hospitalized, received injections continuously. It is very unclear what happened to that person. Apparently, according to the records we have, that person lapsed into coma and continued to receive the injections experiencing these events and died. In hospital, did anybody monitor blood pressure or EKG of that patient?

DR. JOHNSON: I think Dr. Ben-Maimon will give you details of that case in great detail actually.

DR. GILMAN: All right. That was not a case that you observed?

DR. JOHNSON: No. None of the -- in any of the control trials, either the Bornstein Trial or in the major, multi-center trial, were there any deaths or any serious sequelae.

DR. GILMAN: Going back to Dr. Bornstein's experience with these adverse effects. You had a slide there showing what appeared to be a series of minor and even questionable adverse events as I scan that. Is that your impression?

DR. BEN-MAIMON: I think, in the early trials, the events were really benign, with the exception of the injection site reactions which I also will discuss with you

and were very mild. There really was nothing of any concern that was identified. The first time a vasomotor event really came to light as an event that probably was related to Copaxone was in his trial BR-1, which was his first double-blind trial.

DR. GILMAN: Again, do you think that these so-called systemic reactions are dose-related then, in that he was using a series of different dose levels in these early trials?

DR. BEN-MAIMON: I do not think so. Again, the etiology is very difficult to address. What I think we can say comfortably is that an IGE-mediated response is unlikely simply because patients are re-exposed over and over again even after they have these events. The severity does not change. The frequency does not change, and they dissipate without any kind of treatment. So I think the likelihood of any kind of an IGE-mediated hypersensitivity is low.

What the actually etiology is I really cannot speak to. There is not a lot of data. We do know that Copolymer-1 in in vitro studies, when the human basophils are exposed to it it does not do histamine release.

We also know that if you give the injection intradermally, there is a wheel and flare developed, and you can prevent or at least reduce the size of the wheel and flare using antihistamines. They have looked at

Triphenodine. But to give you a conclusive answer as to what the etiology is, I cannot. What I will do later on in the presentation is discuss for you the outcome of some of these events, what has actually happened to some of these patients. I do discuss the patient that you raised. You will see that the deaths that have occurred have occurred in CP patients primarily. There are only two deaths in RR patients, and those were in the Israeli open-label study and I think have a much clearer causality. The only control trial where there were any deaths were actually in Dr. Bornstein chronic progressive trial where he used a higher dose; but, again, that patient died as a result of a glioblastoma, not as a result of something associated with Copaxone.

DR. GILMAN: For the record, CP is chronic/progressive; RR is relapsing/remitting.

DR. BEN-MAIMON: Sorry.

DR. GILMAN: Thank you. All right. Yes, Dr. Coyle?

DR. COYLE: In the early testing was a non-daily dose ever looked at?

DR. BEN-MAIMON: Yes. In the very early testing, he actually used two milligrams several times a week, anywhere from three times a week up to five times a week; but these were very short-term trials. You know, the

longest dosing periods were six months because they were primarily safety/tolerability studies. So whether there was really any affect to those doses, I cannot speak to.

DR. GILMAN: Dr. Snead.

DR. SNEAD: The patient you alluded to with glioblastoma, is that the only malignancy that occurred in the Bornstein Trial and in the control trial?

DR. BEN-MAIMON: No. There was a colon malignancy in a 55 year-old woman; there was the glioblastoma that I spoke to. There have been -- I can show you a list of the malignancies that have occurred in the other trials. There are only three. I can find them for you.

[Brief pause.]

DR. BEN-MAIMON: There it is. Slide C-31.

[Slide.]

DR. BEN-MAIMON: There it is. There was a benign hamartoma. This is the glioblastoma from the BR-2 study. And then there was a single breast cancer in the Israeli open-label study. Those were the only malignancies that have occurred in any of the control trials, and then there was this colon malignancy that occurred in the 55 year-old female in Dr. Bornstein's early trial.

I think that once I speak to some of the exposure it will also put into perspective how many patient years and what types of data -- you know, obviously, if there had been

only three patients treated you would be concerned, but there is obviously a lot more exposure data available. Okay?

DR. GILMAN: That is fine. Thank you very much. Let's proceed then.

DR. BEN-MAIMON: Okay. We are at slide 24.

[Slide.]

DR. BEN-MAIMON: The nonclinical toxicology program for Copolymer-1 included in vivo and in vitro studies. Single-dose studies in the rat and the dog showed no toxicity at subcutaneous doses as high as 400 and 100 milligrams per kilogram respectively.

Seven repeated-dose studies were performed using the subcutaneous route. The species studied were the mouse, the rat, the dog, and the monkey. The studies of longest duration are the rat, which was 26 weeks or six months, and the monkey study of 52 weeks, or one year. Both of these studies employ doses as high as 30 milligrams per kilogram, which is at least 75 times the proposed human dose.

Adverse effects in all of the repeated dose studies were limited to dose-related inflammation at the injection site which was thought to be related to Copolymer-1.

Rats treated for six months, and monkeys treated for one year developed non-neutralizing Copolymer-1 reactive

antibodies at all doses. Immunohistochemistry revealed minimal to slight staining for C3 and/or Copolymer-1 in the renal, gonorrheal or basement membrane of some high and mid-dose animals, and in two of eight high-dose monkeys.

There was no evidence of IGG in any of these samples. Furthermore, the results of clinical chemistry, urinalysis and histopathology did not show any functional changes in the renal tissue.

Reproduction studies, including fertility and reproduction in the rat, two teratogenicity studies in rats, and one in rabbits, and two peri and postnatal developmental studies in the rat have been negative. Copolymer-1 was administered subcutaneously in these studies at doses as high as 37.5 milligrams per kilogram per day. There were no adverse events with regard to either fertility or reproduction and there were no adverse events on the fetus or the dam in either the rat or the rabbit. There were no adverse effects on the perinatal and postnatal development of the rats as well.

DR. GILMAN: Can I stop you there for a moment?

DR. BEN-MAIMON: Yes, sure.

DR. GILMAN: Going back to the issue of immune complexes in the glomerial live, your experimental animals, it raised the question in my mind as to whether you carry out systematic BUN determinations or other tests of renal

function and urinalyses looking for protein in the patient population.

DR. BEN-MAIMON: Yes, we did.

DR. GILMAN: I did not see that in the material.

DR. BEN-MAIMON: Yes, we did.

DR. GILMAN: Is it there?

DR. BEN-MAIMON: It is. Every three months patients had hematologies and a complete set of renal function tests, including BUN, creatinine, and urinalyses.

DR. GILMAN: And urinalyses?

DR. BEN-MAIMON: And there was nothing found.

DR. GILMAN: Nothing found. Thank you.

DR. BEN-MAIMON: Of course, you know, there is transient proteinuria -- the type of proteinuria that dissipates and comes and goes, but there was never any 24-hour proteins required. There was never any significant proteinuria established in any of the patients.

DR. GILMAN: I did not see that in this material. Perhaps you could show me later where it is located.

DR. BEN-MAIMON: Yes. It is probably not actually in the material.

DR. GILMAN: Can you tell us more about the transient proteinuria? Did this happen in relation to the injections or other times?

DR. BEN-MAIMON: No, it did not. It was clearly

related -- you know how when sometimes if somebody does not drink they have a plus-1 or a plus-2 on their urinalysis, and then when you repeat it it is negative? It was similar between the placebo group and the active group, and there was nothing thought to be associated with Copaxone.

DR. GILMAN: Do you have data showing that?

DR. BEN-MAIMON: I think we have. We have the creatinines. On slides -- let me show you first the renal function tests. Can I have slide HO-8 please?

[Slide.]

DR. BEN-MAIMON: These are the creatinines. Can I actually have HO-7 I guess first so that you can see it?

DR. GILMAN: Before you leave that, can we get a look at that?

DR. BEN-MAIMON: Yes. I just wanted to give you the criteria.

DR. GILMAN: Okay.

DR. BEN-MAIMON: The criteria for calling it plus one was that it was greater than .5 or a change of greater than 10 to the UM, and greater than two -- greater than an increase of one, in that the creatinine was considered a plus-2.

Can you go back to the slide before that?

[Slide.]

DR. BEN-MAIMON: And you can see that here is the

Copaxone-treated group and the placebo-treated group. There were no grade changes observed for BUN at all.

DR. GILMAN: All right.

DR. BEN-MAIMON: Okay. I do not have the urinalysis data on a slide.

DR. GILMAN: Can you just tell us about it?

DR. BEN-MAIMON: Yes. They were essentially negative. There was no difference between the placebo group or the active group with regard to proteinuria. I can tell you that in the animals also renal function was measured looking at creatinine, BUN, and urinalysis. There was no increased incidence of proteinuria actually. There was no incidence of proteinuria. There was no evidence of increasing BUNs in those animals over the six-month time frame.

DR. GILMAN: So you are saying that in the humans there is an equal incidence of proteinuria in the patients receiving medication and the patients receiving placebo?

DR. BEN-MAIMON: And it was all transient. That is correct.

DR. GILMAN: That is correct.

DR. BEN-MAIMON: And it was all transient, and there was nothing thought to be of clinical significance requiring 24-hour urine assessments.

DR. GILMAN: Thank you.

DR. BEN-MAIMON: Dr. Leber?

DR. GILMAN: Yes, please.

DR. LEBER: I know where you are going with the question that is why I wanted to raise the second level. The assumption is that safe passage on these measures in fact can speak to whether or not there is deposition of immune complexes in the wall of the capillary. I do not think we know that. Very early on in immune complex disease it might be possible to get deposition, even get proteinuria, but proximal tubular reabsorption would not lead to any change, nor would there be a change in function. So I really would suggest that you are going to have to live with the uncertainty. I do not think that these tests answer it. What they do say is that to the extent that you know you have not got advanced renal disease, which would require a fair loss of renal mass or a fairly flagrant injury to the capillaries to see it. But you cannot speak to trivial effects. The only way you could find out maybe is renal biopsy; but in no way would I ask any patient to undergo it.

DR. GILMAN: Well, but that also raises the question about patients with compromised renal function for any reason. Should those patients be excluded? I do not think that we have an answer to that issue either here.

DR. BEN-MAIMON: I think, and, again, I tend to

agree that the types of changes you are going to see take long periods of time. Even in the placebo group, you have got probably more in the placebo group since they were control trials and you only have two years' worth of data.

You will see from the exposure data that we do have longer periods of time in some of the uncontrolled trials, but then you do not have a control, and you have a population with bladder dysfunction, and all of the other things that complicate the assessment of the renal function.

DR. GILMAN: Yes. Obviously, that is the other point in this. People with MS who have spinal cord involvement can have very compromised bladder function that can, in turn, compromise renal function if not carefully monitored. Then the question arises should those patients have more frequent evaluations BUN, urinalyses and the like? Are they going to be a special group that one needs to pay attention to?

DR. BEN-MAIMON: I would like to ask -- we have a toxicologist with us. If it is okay, I would like to have her at least to speak to -- because there are some issues even with what was found in the animals that raise questions about whether or not these really -- the findings are even real. Frances?

DR. GILMAN: Would you introduce her please?

DR. BEN-MAIMON: Yes. This is

Dr. Frances Mielach. She is a consultant for us and is a toxicologist, and previously worked at FDA in the viral area.

DR. MEILACH: Yes. I looked at the data in those studies. It was only at the very high doses which, as Carole said, was many, many times the human dose.

DR. GILMAN: You are talking about animal studies now?

DR. MEILACH: Yes, the two animal studies. Also, the reports show that it was very minimal what you saw, just a little bit or immunohistochemical staining, and there was no IGG present. Even the people who wrote up the report said that very little could be completed from this. I would be very, very cautious in concluding that there is a problem relative to humans at the doses that are being administered because this happened at the very high doses in the animals.

DR. GILMAN: Tell us again what those doses were?

DR. BEN-MAIMON: Yes. Can we have slide 25? Sorry, it is 24.

[Slide.]

DR. GILMAN: And, again, you evaluated the reports not the slides?

DR. MEILACH: I did not look at the slides. I looked at a description of the laboratory that evaluated that. This was a group that was immunotoxicology experts

who wrote the report.

DR. BEN-MAIMON: The studies we are talking about the 26-week rat study. You can see the doses are as high as 30 milligrams, per kilogram, per day; and the monkey, which is also 30 milligrams per kilogram per day. The evidence of deposition was only in the very high-dose animals and obviously not all of the high-dose animals.

DR. GILMAN: Dr. Leber?

DR. LEBER: I am just taking advantage of the fact that by accident I know a little bit more about renal disease than I ought to given my job description.

[Laughter.]

DR. LEBER: Can you tell us anything in this immunofluorescent and/or immunohistochemical staining what the pattern of deposition of whatever the antigen or material that was in the glomeruli was? Was it lumpy/bumpy? Was it smooth-staining? That has some -- I mean, again, you know, in diabetes you can see very intense IGG staining and a fairly linear anti-GBMY pattern that is probably not related to an antibody against it. It has to do with changes in the GBM.

In this particular case, do you think this is immune -- I mean, does the histology look like lumpy/bumpy? Did they do EM thin sections or something?

DR. BEN-MAIMON: They did not do EM.

DR. LEBER: So you probably do not know.

DR. BEN-MAIMON: I think that is the answer. All I think we can say is that there is no IGG. There is C-3 and there is Copolymer-1, and there is no IGG. It is at the very high doses.

DR. LEBER: Did you find the attack complex there if you saw C-3 or C-3, 4, 5?

DR. MEILACH: There was minimal C-3, also, Dr. Leber. Basically, it was very, very minimal at the high dose and not all of the animals -- there were few animals at the mid-dose, but it was very variable. In other words, not all of the high-dose animals showed it, and it was not found at the low-dose. That is the best I can speak to it.

DR. GILMAN: Can you be a little more specific? By high-dose do you mean 30 milligrams per kilo, not at 20? What are you saying?

DR. BEN-MAIMON: There were -- and I can give you the exact numbers. Just a moment. There were, in the rat, three animals at the high dose, and I think one animal at the 10 milligram. In the monkey, there were two out of eight at the 30 milligram, and no other animals, and they were all male.

DR. GILMAN: So it is clearly dose-related?

DR. BEN-MAIMON: Yes, I believe.

DR. LEBER: I have one last point. This is on the

other side of the argument. I spent several years of my life working with a model of immune complex deposition in rats that does not occur in humans. I think that one of the things we have got to realize is that there probably are species differences. The extrapolation is tenuous, very, very tenuous.

DR. GILMAN: Granted. But it is a question that one raises particularly if people have compromised renal function.

DR. LEBER: I am just trying to be fair about what the model shows, not what I think the truth is.

DR. GILMAN: Yes. Thank you.

DR. BEN-MAIMON: Oh, thank you. I am very much in complete agreement with Dr. Leber on that point.

DR. GILMAN: Yes. All right. Thank you. Let's proceed then.

DR. BEN-MAIMON: So we will flip to -- did you have any questions about this one?

DR. GILMAN: No. This one -- did anybody else?

[No response.]

DR. GILMAN: No. This one looked fine.

DR. BEN-MAIMON: In addition to the mutagenicity of Copolymer-1, Copolymer-1 was studied in three in vitro assays and in one in vivo assay. Copolymer-1 was negative in the Ames and in the mass lymphoma assay, and Copolymer-1

was negative in two in vitro human lymphocyte assays in the absence of metabolic activation. However, in the presence of the added rat liver microsomes, the Copolymer-1 was positive at in vitro concentrations of a half to one milligram per cc. By comparison, Copolymer-1 is administered clinically at 20 milligrams in a 50-kilogram patient. Copolymer-1 was negative in the in vivo mouse micronucleus assay.

Copolymer-1 is composed of four naturally-occurring amino acids. After administration, it is degraded rapidly to small polypeptide chains. The degradation occurs in the subcutaneous tissues at the site of injection. Carcinogenicity studies in mice and rats are ongoing; however, there was no evidence of preneoplastic lesions in a six-month rat or the 12-month monkey. You see the data we have from humans.

DR. GILMAN: Dr. Snead, and then Dr. Drachman.

DR. SNEAD: Is the degradation to polypeptides predictable in terms of you can predict which specific polypeptides are going to be formed each time? Is there one that is predominately formed over another?

DR. BEN-MAIMON: No. The degradation is done through subcutaneous tissue. The polypeptides are variable.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: In a similar vein, what is the

uniformity of the original Cop-1? That is listed as a molecular weight of 4,000 to 13,000 kd I believe. Is it one entity or many or from batch to batch? Is it the same?

DR. BEN-MAIMON: It is a series of polypeptides. It is not one entity. It is a range that is controlled very specifically based on molecular weights and ratios of amino acids within the assay. There are various tests that we perform for each batch, of course, at the time of release that have certain specifications to ensure that the proportion of amino acids, the molecular weight, and the range of those molecular weights is the same from batch to batch.

DR. DRACHMAN: Was that true when Murray Bornstein first used it? Was it made that same way? Was the same control used in that way?

DR. BEN-MAIMON: It was similar controls in the proportions of the amino acids and in the molecular weights. We have been able to test as well some of the batches that Dr. Bornstein used in the product that Dr. Bornstein used. It performs similarly in EAE and in other types of models, and has similar amino acid compositions and molecular weights.

DR. GILMAN: Dr. Snead?

DR. SNEAD: So are you saying that this preparation is a series of four amino acid compounds with

the same four amino acids in different sequences? Is that what you are saying?

DR. BEN-MAIMON: That is correct.

DR. SNEAD: Okay.

DR. BEN-MAIMON: And different length chains.

DR. GILMAN: In the preparatory material that we received there is a comment that routinely sponsors are required to carry out life-time studies of carcinogenicity and we understand -- and it is repeated in this slide that there are two life-span studies ongoing. Can you tell us the duration of that set of studies currently and when they will be terminated?

DR. BEN-MAIMON: Dosing will be completed in the beginning of 1997. Of course, the histopath, and reports, and all of that can take some time.

DR. GILMAN: Can you explain why we had this long delay in getting these studies started?

DR. BEN-MAIMON: TEVA was of the opinion that they did not need to be performed. We obviously misunderstood the Agency. When we recognized that we were going to be required, they were started immediately; but it took us some time to realize that.

DR. GILMAN: Does the Agency want to comment on that?

DR. KATZ: Only that -- I do not have the records

here, but I believe that our records do demonstrate that for the past number of years, many years, we had urged the sponsor to initiate the studies because, as I had said earlier, and as you just mentioned, these studies are ordinarily required to be submitted at the time of submission of the NDA. We ordinarily like to have that information before we make a decision about the NDA. So I believe that the record shows that we have quite clearly had to ask the sponsor to do this in what should have been sufficient time to have them completed by the time of submission of the NDA.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: Just to follow up a little bit more on the heterogeneity, just could you say a word about the probability that a heterogeneous array of amino acids would achieve the appropriate confirmation to block myelin basic protein the way you described in the trimolecular complex? Is this a random event or is this -- I am not quite sure I follow.

DR. BEN-MAIMON: There are in vitro studies that show competitive binding with myelin basic protein. Maybe Dr. Arnon, from Weizmann, who has performed many of these studies can speak in more detail to actually how the studies are conducted. But in vitro there have been studies that have looked at the binding and competitive binding not only

to myelin basic protein, but to the other antigens that are thought to be active in MS. There is competitive binding as well with those.

DR. ARNON: We used Copolymer-1 in vitro studies of binding of Cop-1, Copolymer-1 to both a murine and a human cell-line. There are some very effective binding in a competitive activity towards all myelin proteins. So, at least in the in vitro studies we have shown that there is a capability of Copolymer-1 not only to inhibit the binding of myelin proteins, but also to displace myelin proteins from the human or murine studies.

Furthermore, the random or the diversity of molecular composition and sequence cause the Copolymer-1 molecules provides an advantage because it provides much more avid binding to the cells and, therefore, a better capability of entering and replacing the myelin contents. Does this answer your question?

DR. DRACHMAN: Yes. But what one would wonder is when you look at the heterogeneity, is there some single component or three, or five components out of the array that are really doing the work?

DR. ARNON: No. We have tried very, very carefully to fractionate the molecule in many, many ways, but we have never been able to come up with any particular fraction or particular sequence that have a better ability

than others.

DR. GILMAN: Thank you. Yes, Dr. Coyle?

DR. COYLE: How many different batches were used in the two control trials?

DR. BEN-MAIMON: Hundreds or multiples.

DR. GILMAN: All right. Please proceed.

DR. BEN-MAIMON: Okay. I just wanted to show one more of the carcinogenicity studies. I do not think that TEVA is in any way in disagreement with the Agency about this sequence of events. There was clearly a misunderstanding. The problem is that we are at this point and these trials take that long to perform. So I think that it is an issue of where do you go from here, and not a disagreement between us and the agency.

DR. GILMAN: We have a question from Dr. Snead.

DR. SNEAD: I have a question of the Agency, and that is say, for the sake of argument, if the NDA is approved and then these ongoing studies turn something up, what is the procedure?

DR. LEBER: We would obviously consider it in light of what the evidence was at the time and the significance. I mean, you cannot anticipate the scenario unless you know what the findings actually are. There could be a scattered number of tumors as there often are; but we would not think it is a strong signal. I suppose if it was

an overwhelming signal, you could do anything that considers the entire reversal of the risk-benefit judgment.

I think, in fairness to the firm, they were receiving part of it at the time we were telling them that we thought it was advisable to conduct such study, advise that may not be necessary. Also going on were other decisions made by the same Agency in a different area, in biologics, that did not require such testing arguably for other reasons. So it is a very mixed picture. I think they have our advice. They had other counsel. We are where we are. I think that I agree in that sense. That does not mean that I would not feel better having all of the information, but I think that is a fair statement of where we are. We did file the NDA despite the absence of it.

DR. GILMAN: All right. Please proceed now.

DR. BEN-MAIMON: Does that clarify it?

DR. LEBER: Probably.

[Laughter.]

DR. BEN-MAIMON: Okay. Before presenting the clinical data from the two control trials, I would like to provide you with a brief overview of the entire development program. A total of 906 patients with multiple sclerosis were exposed to Copaxone during a development program. Forty-nine of these patients were exposed in the previously-described safety and tolerability studies. An

additional 857 patients were exposed during the clinical program. Of these 857 patients, 779 had relapsing MS. This is the intended population for Copolymer-1 for injection. Seventy-three had chronic progressive MS and were enrolled either in Dr. Bornstein's compassionate use or in his control trial, as you can see by the placebo group over there. Of the placebo-treated patients, 151 had relapsing MS and 55 had CP to give you a total of the 206.

A total of 779 patients with relapsing MS have been exposed to Copaxone. Here you see it. Of these 779, 290 have actually been exposed for greater than two years, and there are actually 15 patients with relapsing MS that are out greater than five years. There are a few additional patients who actually have more than five years of exposure and have CPMS and have been exposed through Dr. Bornstein's compassionate use and are included in the safety data.

Two double-blind trials have been conducted in patients with relapsing MS. Trial BR-1 was the first study to be conducted and, as stated earlier, was performed by the late Dr. Murray Bornstein under an investigator IND. Twenty-five patients were enrolled in each of the arms of that study.

The more recent study, trial 01-9001/9001E, which I will try not to say too many times, was a TEVA-sponsored trial conducted at 11 U.S. centers. One hundred and

twenty-five patients were enrolled in the Copaxone arm, and 126 in the placebo arm.

A third double-blind study, as I alluded to earlier, was conducted by Dr. Bornstein in chronic/progressive patients and employed a higher dose of 15 milligrams injected twice daily.

In addition to these three blinded trials, there were several open-label trials, including the U.S. Treatment IND, in patients with relapsing multiple sclerosis.

[Slide.]

DR. BEN-MAIMON: I would now like to present the study design and the results of trial BR-1, the first of the controlled studies. TEVA based its evaluation of this study on original case report forms, source documents, grant proposals, and information obtained from Dr. Bornstein prior to his death, and Dr. Aaron Miller, who is here with us today and is available to answer any questions with regard to the trial's conduct.

Questions have been raised about whether 50 patients were prospectively planned to be enrolled in this study. Based on our evaluation of numerous documents, including an 1980 IRB submission, as well as the recollection of Dr. Miller and Dr. Ruth Arnon, who participated in designing the study, it is clear that the trial design always intended to enroll 50 patients.

Dr. Miller is here with us today and so is Dr. Arnon. You may ask them questions and they can provide you with whatever answers you need.

Of note is that this trial was supported by two grants from the National Institute of Neurological and Communicative Disorders and Stroke.

The results of Trial BR-1 were published in the New England Journal of Medicine in 1987 by Dr. Bornstein and his colleagues. An external advisory committee acted to oversee this trial. The external advisory committee had some of the most prominent and knowledgeable experts in the field of MS. You can see that John Kurtzke participated, as did Bill Weiss, who was an active statistician at the NINCDS.

Trial BR-1 employed a double-blind, placebo-controlled, randomized design and was performed in a single center. Dr. Bornstein was the primary investigator, and he acted as the coordinator for the trial, but he was not involved in patient care or evaluation.

Dr. Miller was a coinvestigator and acted as the examining neurologist for the trial. The examining neurologist was responsible for the management of the patients and for performing the neurological assessments of the patients, including the assessment of relapses and DSS.

This is the design of Trial BR-1. Patients were

initially screened. If they met entry criteria, they were then randomized either to receive Copaxone, at 20 milligrams subcutaneous daily, or placebo by the same route and timing of administration.

Patients were seen at one month, and then at three months, and then every six months thereafter throughout the trial.

DR. MILLER: Every three months.

DR. BEN-MAIMON: I am sorry. It is every three months throughout the trial.

If the patient had a relapse, they were asked to come in for an objective confirmation by the neurologist. Patients were treated for a total of 24 months, and then some of those patients were actually enrolled into an open-label study.

Patients included both males and females, 20 to 35 years of age with clinically-definite MS. Patients had to have been diagnosed at least one year prior to screening and had to have had at least two relapses in the two years prior to screening. In addition, patients had to be ambulatory with Kurtzke DSS scores between zero and six, and they had to be emotionally stable.

The demographic data show that the groups were well-matched with regard to sex, race, and age. As expected, the patients with multiple sclerosis, the majority

of patients were female, most were white, and the age was approximately 30 years.

Baseline disease characteristics were similar between the two groups. Duration of disease prior to your relapse rate and baseline Kurtzke DSS were all reviewed and found to be similar between the two groups.

The vast majority of the patients remained in the trial for the full 24 months. The top line represents Copaxone and the bottom placebo. You can see that dropouts occurred evenly throughout the course of the trial and were not predominately in one group or the other.

Dr. Bornstein's New England Journal of Medicine publication contains data on a cohort of 48 patients, as stated by Dr. Katz. Two patients were considered by the investigator to be unevaluable. One of the two was discontinued for ethical reasons after two months of participation. The other patient was found not to have multiple sclerosis. This patient had reported three other relapses by the time she discontinued. In the all-patient cohort, this patient is considered relapse-free, thus the analysis of this cohort employs the most conservative approach and includes the patient in the ITT but does not include the data collected over the seven months.

TEVA has reviewed all of Dr. Bornstein's data and has confirmed the results and the analysis in the

publication.

In addition, an analysis of the all-patients cohort or intend to treat cohort was conducted and the results of both will be presented throughout the presentation.

DR. GILMAN: I wonder if we could interrupt at this point and ask about a few of the details concerning the material you have just covered?

DR. BEN-MAIMON: Okay.

DR. GILMAN: The first question is we understand that the medication produces some reactions. They are primarily reactions at the site of injection, and there are the systemic reactions. What happened with the placebo administration? We there any local reaction in the skin?

DR. BEN-MAIMON: In these patients? I am going to ask Dr. Miller because he was there and evaluating these patients in the distant past for us.

DR. GILMAN: Please use the microphone.

DR. MILLER: First of all, almost from the beginning of the trial, adverse experiences were queried not by the examining physician.

Secondly, the skin reactions with Cop-1, for the most part, are extremely mild. Patients do not complain about them, for the most part, and there is very little to be seen. I do not have any recollection of being able to

ever tell a skin reaction that was due to medication.

After the trial was completed, we were queried as to whether we thought patients were receiving Cop-1 or placebo. I based my guess basically solely on how the patients were performing clinically.

DR. GILMAN: So you were the blinded neurologist examining these patients. You did not speak with them as I understand the situation.

DR. MILLER: I did speak with them about their neurological status.

DR. GILMAN: And you did not examine the skin where they had self-injected?

DR. MILLER: Correct.

DR. GILMAN: Where did they inject, the abdomen? What was the site?

DR. MILLER: Well, the sites were rotated. It was I think mostly thighs, but probably abdomen in some patients.

DR. GILMAN: Well, I guess I am a little confused, because in the documents it states that there is in fact a wheel and a flare, and some continued irritation at the site. But that is not the case from what you have just said.

DR. MILLER: Well, I think that Dr. Ben-Maimon, in referring to the wheel and flare was referring to

intradermal injections. These are subcutaneous injections.

DR. GILMAN: Which do not produce a local reaction, redness?

DR. MILLER: Generally not something that is visible. Again, I was not examining thighs and abdomens in these patients.

DR. GILMAN: So, the placebo did not produce such -- any kind of skin reaction at all; is that correct?

DR. MILLER: As far as I know.

DR. GILMAN: And yet the drug did in some patients? Yes?

DR. MILLER: Reportedly.

DR. GILMAN: All right. Yes, Dr. Drachman?

DR. DRACHMAN: You did not really go into it, but could you say a word about why nearly a thousand patients needed to be reviewed to find 50? What was going on?

DR. MILLER: Yes. In contrast I think to the subsequent trial in which I guess I was not a participant in that trial, but I presume many of those patients were patients being followed in MS centers. The patients who came and entered the first Bornstein trial were recruited mainly through a public relations effort. In fact, I think that Dr. Bornstein had been interviewed on a television news program which attracted a large response. So when those large numbers of screened patients are listed, most of those

were screened by a bank of trained people to speak on the telephone to patients. Most of them were obviously not candidates either. Their age was inappropriate, or their disease was obviously inappropriate.

DR. BEN-MAIMON: There are two issues I would like to clarify. First of all, of the 900 patients, or 900 and some patients who were screened, 140 passed questionnaires. So I think you are talking about, just as Dr. Miller said, people calling in and saying I have MS and then finding out they did not meet any of the criteria.

Of the 140 who were actually seen and examined and have psychological testing, 23 of those were not eligible because of age; 21 were not eligible because of the number of the relapses, and the documentation of relapses; and then there were 19 patients who lived far away, an things like that that got rid of approximately 90 patients or so. But I think when you talk about screening you really have to look at 140 patients, whereas the other was just a questionnaire.

The other issue, with regard to the injection site reactions, I think that what you will see as we go along is that most of these reactions that do occur are mild. Because of the severity, it may be very clear. There are quite a few reactions reported in the 9001 trial in the placebo group.

Now, the product that is used in the 9001 trial

has Mannitol in it, as did the placebo, and that was not present in trial BR-1. So it is possible that there may have been even more mild local reactions in that trial that do not impact.

DR. DRACHMAN: Yes. One other point really is the number of exacerbations during the previous two years. I gather, as I remember, that change -- some started out being two every year for two years, and eventually was one each year or two in two years. How did that work? Is that right? Did I say that correctly?

DR. BEN-MAIMON: I think that Dr. Bornstein originally was looking for patients with very active disease. Because of the issue of recruitment and the difficulty, I mean it took over three years to enroll patients in this trial. The difficulty with recruitment and getting people to comply and all of that, he actually began to accept patients with fewer exacerbations, clearly with multiple sclerosis, but not having as high a relapse rate in the prior to years as originally as planned. Do you have a recollection?

DR. MILLER: I do not have any recollection of a change in that entrance requirement.

DR. GILMAN: It is documented. Dr. Katz?

DR. KATZ: Yes. I wonder if you could say a little bit more about the two patients who you felt ought to

have been excluded. I am not sure what those ethical reasons were. The protocol actually is fairly detailed about the sort of psychosocial evaluations that patients were to have and they had to pass a fairly rigorous psychiatric, if you will, screening prior to entrance. And then one of them drops out because of what you call psychogenic reasons. I wonder if we could hear a little bit more about that?

DR. MILLER: In fact, these were two patients who were asked to leave the trial. Neither one -- in fact, both went kicking and screaming out of the trial. You have to remember, in part, that we were in a different time and a different place. This was pre-MRI -- a pre-MRI era in the diagnosis of MS.

The patient whom Carole referred to who was asked to withdraw because of ethical issues was a young woman who we firmly believed had multiple sclerosis but had extremely mild disease. She was a Kurtzke-0 or 1. I do not remember precisely.

A couple of months into the trial I think she dropped -- two months -- it became very apparent that this woman was disabled by the concept that she had multiple sclerosis. She was totally nonfunctioning. She had stopped work. She had stopped many of her social interactions. She was in either psychiatric or

psychological care. In discussions with her therapist we both felt that it was not in her best interest to reinforce her notion of her multiple sclerosis by her continued participation in the clinical trial so we asked her to leave. That was the first case.

DR. KATZ: Did she, based on let's say, for example, her relatively mild disease at entrance, did she violate the protocol? Did her inclusion violate the protocol in any way?

DR. MILLER: No. As far as I know, she met all of the criteria for entry.

The second patient was a woman -- and this is a somewhat embarrassing confession to make -- but, basically, after several months during the trial in which she was scored actually as having several relapses, I became convinced that all of her findings were psychogenic. I was convinced that she, in fact, did not have multiple sclerosis. Again, it would have been nice to have had an MRI in our hands perhaps before we included her. So we asked her to leave because we did not feel that she had the disease.

DR. GILMAN: That is a little confusing. Didn't you require hard neurological signs for entrance?

DR. MILLER: We required neurological signs, but I am sure, unless you are a lot better neurologist than I, you

too have probably been fooled in the past about neurological findings that were not physiological in origin or neuroanatomic in basis.

DR. GILMAN: Less as I have gotten older.

[Laughter.]

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Were the determinations that they should be dropped made before or after their group assignment was known?

DR. MILLER: Their group assignment was not known at the time they were asked to drop.

DR. TEMPLE: So they were dropped blindly?

DR. MILLER: Right.

DR. TEMPLE: Okay. And the reason they are important is that at least one or two of them -- they were both considered exacerbation-free. So, if you count them in the placebo group, the placebo group was looking better. That is why the statistical impact is so great. Is that true?

DR. MILLER: I will let Carole adjust that.

DR. BEN-MAIMON: The answer to that question is yes, as it relates to the proportion of relapse-free. I think you have to keep in mind there are other end points that were evaluated such as relapses which have symptoms.

DR. TEMPLE: No. This clearly has to do with what

was, for better or worse, designated as the primary end point.

DR. GILMAN: Yes. That bears upon the issue of the big change in P-value when those two are included or not included. The first one was dropped after two months. How about the second one?

DR. BEN-MAIMON: Seven months.

DR. GILMAN: Seven months.

DR. TEMPLE: It is just 14-8 versus 14-6. That makes a big difference when you have small numbers.

DR. GILMAN: Yes, exactly.

DR. TEMPLE: That is why things come out that way.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: Dr. Miller, you said that, based on your clinical judgment, you guessed at the end of the trial who was and who was not on Cop-1. How did you do?

DR. MILLER: I do not remember the precise numbers, but I think I was accurate at something like between 60 and 70 percent. Again, I do not remember precisely the procedure we followed; but, I believe, at the time that I was asked, I had information available to me about the relapses, plus I was seeing these patients very frequently and tended to remember who was having relapses and who was not. So I based my guess basically on who was relapsing and who was not. As it turned out, with the large

discrepancy in the relapse rates between the treatment and the placebo group, I tended to guess right more often than not.

DR. GILMAN: Did you guess based upon adverse reactions also?

DR. MILLER: No. I did not know the adverse reactions.

DR. GILMAN: Dr. Leber?

DR. LEBER: I have a question actually of Dr. Drachman. You asked about the number screened to generate the number sampled obviously because, I think, you are worried about external validity. Is that your point?

DR. DRACHMAN: Yes.

DR. LEBER: I just wanted to raise the point that we usually do not address that because our samples are often samples of what I guess people call convenience. We have to, by regulation, have a patient population in the trial who are reasonably sure to have the disease being study than who experts would agree has the disease. I do not think we have ever said that that is a representative sample of the patient population on whom the drug will be used in the statistical sense that your question allows me to infer you were getting at. Did we enrich them by our outcome with entry and selection criteria?

DR. DRACHMAN: The other issue being why the two

studies look different.

DR. LEBER: Certainly. Actually, I had a second question which I have been fascinated with for years. When you are doing an experiment that requires pairing, and assignment in pairs, you have to recruit, especially if you have a stream of patients showing up at the clinic, you have to decide how long you are going to wait to declare you have a match that constitutes the pair for which you are doing the randomization. If you had a whole pool of patients and centers, I could see you doing the match pretty easily because you have all of the data before you. But, if you are getting a stream flowing in and you do not know what the next -- how long did you wait and how do you know that you have a sufficiently close match to determine that a particular group constitutes a pair to whom you can randomize?

DR. MILLER: Unfortunately, I cannot really answer that question because I was not involved at all in determinations about whether a pairing existed or not. I think that Dr. Ben-Maimon might want to address further the issues of how these matched pairs were determined and when they were met. I had no knowledge of whether or not a matched pair existed at any point during the trial.

DR. BEN-MAIMON: I cannot say that we actually went back and looked at each pair, and the demographics and

the criteria that were used pair by pair. The enrollment was over a long period of time, well, a relatively long period of time. It took approximately three years. There were patients who were enrolled six months apart some of them in those pairs; but I cannot speak to the actual individual pairs. There were 24 matched pairs at the end. Two patients were unmatched in the ITT in the complete cohort of 50 patients. We never really looked at it on a pair-by-pair basis.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: Yes. I may have missed this. But the matching turned out not to be consequential in the analyses you did. You just analyzed them by groups. So the only function of the matching is sort of like stratification to try to get groups that are reasonably comparable. That is not always true. Sometimes people do analyses within pairs and in special ways. But, if I understood what went on, that really did not happen here. They just looked at the two groups.

DR. GILMAN: Dr. Hoberman?

DR. HOBERMAN: I did go back and look at the matched pairs. I believe that I found one putative matched pair that was not actually matched. I actually did do the grunt work to see whether or not these people were matched. I was really quite satisfied that they were matched.

As for the enrollment times, I also went back and I looked at when each pair was enrolled. I think that Dr. Ben-Maimon is probably about right that probably the maximum time between patients who were assigned to a pair was approximately six months. There was not anything that I saw that was really bizarre, like somebody being enrolled in 1979 in the pair, or whenever it was, 1971, and somebody else in 1973. It was not anything like that. So I did not have any problem with the enrollment or the matching.

Now, as for Dr. Temple's question, Dr. Temple is correct in that the outcome, whether you analyze the data by matched pairs which involves looking at the discrepancy in the number of placebo patients -- you take a pair and you ask the question, well, did the placebo patient have an exacerbation? Did the drug patient have an exacerbation? A discordant pair would be a pair in which the placebo patient did and the drug patient did not; and then visa-versa, the other kind of discordant pair would be if the placebo patient did -- I think -- I am not sure which one I said -- whatever -- but the opposite kind of discordance. The discrepancy between those two gives you the information about whether you could attribute the effect to the drug.

Now, in fact, in the publication, they did not account for that design so I just did it myself and I got exactly the same result. So the answer to Dr. Temple's

question and everybody else's is that it does not matter how you analyze the data, whether you take into account the matching or you ignore the matching and do a simpler test; you get the same P-value and the same conclusion.

DR. GILMAN: In fact, the matching slowed things down. As I understood the protocol, you matched -- you went serially. You determined whether the patient will receive placebo or drug based upon the previously enrolled subject. So you had to wait until you had a match for the last enrolled case if I understand it. Is that right?

DR. BEN-MAIMON: The first one was randomly assigned to the group, and then there was another match that was assigned to the opposite.

DR. GILMAN: Right.

DR. BEN-MAIMON: Like I said, the first 24 pairs are matched, and they did have two at the end.

DR. GILMAN: That were unmatched.

DR. BEN-MAIMON: Yes, because --

DR. GILMAN: That were both placebo?

DR. BEN-MAIMON: No. They were one in each group.

DR. GILMAN: Oh, they were?

DR. BEN-MAIMON: Yes.

DR. GILMAN: Oh, oh.

DR. BEN-MAIMON: At the very end of enrollment because of what you are saying rather than let things go for

a longer period of time, we did end up with one group of patients who were unmatched.

DR. GILMAN: Yes, Dr. Temple?

DR. TEMPLE: As David indicated, that only -- in a certain sense, if you are not going to analyze in some pair way, that is, you know, drug better in this number of pairs, drug worse in this number of pairs, it actually does not matter if they are matched at all. It is just a randomized trial.

DR. GILMAN: Yes.

DR. TEMPLE: It apparently comes out the same way however you do it.

DR. GILMAN: Yes. Dr. Leber?

DR. LEBER: Well, that is actually what I was trying to get at. I really wanted Dave to answer it. It may be then that this particular set of data we do get no difference between a matched pair analysis and a simple group comparison. However, there is a design reason for using matched pairs, and that is, if you think the sample of patients you are going to recruit is very heterogenous, you try to match them to reduce that source of variance. Then you are constrained to do one analysis rather than the other. Here it does not make any difference after the fact because the data came out the same way.

I wonder -- and that is what I was trying to ask

of Dave -- because I think that at the time we did the treatment, I think we made a big deal about this also because of the way the pairs were assigned, because you rally fixed the second member of you do the randomization based on the first. I seem to recall that it came out all right as a match pair. But is that a result of this dataset or is it generally true that a pair -- between groups analysis gives you the same thing as a matched pair analysis?

DR. HOBERMAN: It is not necessarily so. But you are using a different statistical test. You are using a different probability model. But you should not be surprised if it comes out similar. If it comes out appreciably different, then you start wondering and you look at the data.

DR. LEBER: That could happen. We just do not know.

DR. GILMAN: Dr. Drachman?

DR. DRACHMAN: Do we know whether, in the course of randomization, many more started as placebo at the beginning than started on drug? The reason I ask that is that, as you look at the outcome results, the large majority of the changes in score were within the first six months, three to six months. I mean, beyond that, the two groups look virtually unchanged. So that one wonders whether for

any visible reason there was a different degree of scrutiny or observation? Did you find any difference there or not?

DR. HOBERMAN: The only thing I can say is I share your interest in that result. You are talking about the Kurtzke scores?

DR. DRACHMAN: Yes, right.

DR. HOBERMAN: I do not know, but I am sure that the company knows more than I do about why that might have happened.

DR. BEN-MAIMON: The patients were randomly assigned to placebo or were active in the first. So there was no selection where placebos were assigned in the first six months and afterwards.

DR. DRACHMAN: Do you know? People win the megabucks every now and again. Did it turn out that a lot more ended up in the placebo group in the beginning?

DR. BEN-MAIMON: It was relatively even.

DR. GILMAN: Are you referring to the lottery?

DR. DRACHMAN: Yes, exactly.

DR. GILMAN: Okay. I see. I do not think that is relevant to this hearing, but okay.

[Laughter.]

DR. GILMAN: All right. It is a little after 10:15. Let's continue until 10:30 and then we can have a break. Please go on.

DR. BEN-MAIMON: I am going to just go back to the definition of relapse in the trial. Relapses were defined according to specific criteria. Patients had to exhibit either new neurological symptoms or worsening of existing neurological deficits. These findings had to persist for at least 48 hours and objective neurological findings were required. With an increase of at least one score and at least one functional system, sensory symptoms alone were not adequate without objective findings and would not have allowed the relapse to meet criteria and then be called a relapse.

The primary efficacy end point was the proportion of relapse-free patients. As you can see from the slide, the results were numerically in favor of Copaxone for both cohorts. The two patients who were considered unevaluable were both on the placebo group. I think we have sort of beat this to death so I will not repeat myself.

And what you see, again, though does speak to that. The 56 percent remains the same in the Copaxone group; the 26 percent increases to 32 percent when the two patients are included in the ITT cohort; and then you see the P-values that we have already discussed I think at length.

Relapse rate was evaluated and, again, was not the primary efficacy end point but was prospectively defined

using a categorical approach. Patients were grouped either as zero, one to two relapses, or greater than or equal to three relapses. The results of this analysis were statistically significant for both cohorts. You can see the P-values at .002 and .004.

The mean relapse rate was .6 in the Copolymer-1 group and 2.6 in the placebo group. Again, you see the effect of those other two patient. You see that the .6 remains the same. The 2.6 goes down slightly to 2.4 when you include two patients who had no relapses in the ITT group.

As can be seen from the Kaplan-Meier curve, the time to progression was longer for the Copaxone-treated group than for the placebo-treated group. The dark line on the top represents Copaxone; the bottom line the placebo group.

The result -- and here we only present the ITT -- they were both highly significant at .008.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: I am sorry. I have just one question. The two people who were excluded, you counted them as having no relapses, but one of them had three nominal relapses, right? You just decided to count them as zero because you did not think that the person had MS?

DR. BEN-MAIMON: That is exactly right. So,

again, I tried to point out that we were very conservative in the way -- you know, we include the patient, but we do not include the data.

DR. TEMPLE: Yes. That is very conservative. Okay. Thanks.

DR. BEN-MAIMON: But, again, I think that it is important. I appreciate you bringing that up. It is going to be right in the middle. So, again, I think what we are dealing with is a small trial. What is important is that the effect is in favor of Copaxone. Again, speaking a little bit to what Dr. Leber stated earlier about the claim, the claim is really reduction of relapses. So, although the primary efficacy endpoint is proportion of relapse-free, we are not making a claim that we prevent relapses. I think that is just something to keep in mind.

I think I did this one.

The disability of patients was assessed using the DSS score.

Change in disability was assessed by both an analysis of time to progression and using a categorical approach.

For the categorical analysis, patients were considered improved if their DSS score at the last visit decreased by at least one point. They were considered worsened if it had increased by at least one point.

Dr. Bornstein combined the unchanged and the improved group and performed a categorical analysis of the results, and the results were not significant for either cohort but were numerically in favor of Copaxone. Again, the two patients who withdrew were progression-free. So you see the change in the proportion in the placebo group.

Progression was defined as an increase in DSS score of at least one point that was maintained for at least three months. Time to progression in the Kaplan-Meier curve is presented here. You can see again the Copaxone line on the top, the placebo line on the bottom; time to progression being statistically significant in both cohorts.

The proportion of progression-free patients was numerically in favor of Copaxone, but, again, was not statistically significant for the all-patient cohort. Again, this speaks to the two patients who joined the group over here. You can see again that the numbers are clearly in favor of Copaxone. But when those two patients joined the group, you end up with a different P-value.

I am going to start the multi-center trial. It might be a good --

DR. GILMAN: I just wanted to ask a question about the 40 versus the 50. Again, the narrative that we were provided from the Agency suggests that Dr. Bornstein, in 1987, indicated that he had selected 40 cases in the 1980

trial and now we are hearing from the sponsor that, in fact, the original designation was 50 cases. So I find myself confused about that. Can you go over that in just a little more detail?

DR. BEN-MAIMON: I think that it is a confusing picture to some extent. The documentation that we are relying on we have obtained through the FOIA, the Freedom of Information Act through the grants. We have what regulatory documentation we have from Dr. Bornstein cited itself. Again, with Dr. Bornstein being deceased, it is difficult. We rely on Dr. Miller quite a bit for his memory and his recollections.

DR. GILMAN: But he was blinded.

DR. BEN-MAIMON: But he was blinded. But he did know -- I have to say that even though he was blinded though he would have known how many patients he was intending to enroll in the trial. That is part of this design.

Basically, the story is this. There was a grant submitted in 1982, if I remember correctly, that has this interim analysis in the power statement. It also references in that document a disapproved grant. Now, because it was disapproved we could not get it. I think it may actually have been the substance where the protocol that we are calling the protocol that was submitted in 1987 was obtained. But when he talks in 1982 grant about the interim

analysis and the power statement, he actually says that, in an effort to fix whatever was wrong with our disapproved grant that these things were done. So I think that what was happening was he was obtaining funding in 1978 and 1979 for the trial. When he submitted his grant request in 1980 it was disapproved. He then went back in 1981 and 1982 to try and fix that, performed the power statement, and looked at the data in order to obtain funding from the NIH.

We do have an IRB submission that is signed in 1980 that says 50 patients. That was before the initiation of the trial.

So I think that the answer is that, yes, this is a confusing picture. What we did to try and fix that was go back and look at the first 40 patients to see whether, based on the primary efficacy end point the proportion of relapse free, whether or not, if he had just enrolled 50 patients what would have happened. The P-value is .058. So I am not sure that it matters necessarily. I just wanted to let you know.

DR. GILMAN: Dr. Katz, and then Dr. Khachaturian.

DR. KATZ: Yes. I will just give you my understanding at least of the documentation that we have. The sponsor submitted as the protocol for the Bornstein study, a portion of a grant request that was actually written in 1982. This was ostensibly the prospective

protocol, or as close to it as they could come up with. When we read that protocol it had statements in it that suggested that this was not a prospective document. Like in the body of this 1982 document were statements like 16 patients have already completed the trial. So we knew right away that that was not a prospective protocol. We called the company. They provided us with a 1981 grant proposal which had the results of an interim analysis in it. So that clearly also was not a prospective protocol.

So we went through our files and we came up with a document submitted to the FDA by Dr. Bornstein in 1987 on the heals of the publication of the article in the New England Journal. That included a document dated February 1980 which Dr. Bornstein, in his cover letter to us said this is the protocol that I used. That document was dated a month before the study was initiated. That document explicitly says 40 patients. There are no sample size calculations. There were no plans for an interim analysis. It says 40. And then we know it is not a typo because he then talks about 20 matched pairs. It is quite clear that that document which we believed to have been the document that was the protocol that was followed at least for a while said 40 patients.

We have no other independent documentation that the sample size was to be 50 prior to the results of the

1981 interim analysis, except for the sponsor's statement that there is this IRB document which says 40 or 50 patients.

DR. BEN-MAIMON: No, it says 50.

DR. KATZ: It says 50? We have not seen that document. Okay. I understood that it said 40 or 50.

DR. BEN-MAIMON: No, it says 50.

DR. KATZ: All right.

DR. BEN-MAIMON: The earlier grants actually say the 20 to 30 matched pairs.

DR. KATZ: Okay.

DR. BEN-MAIMON: This document explicitly does document it.

DR. KATZ: Okay. So there are conflicting documents that presumably were prospective. As far as I know, there was no document which suggests that there was to be a correction at the end based on the fact that they had taken interim looks. Nor am I aware of any document that talks prospectively about any interim analyses. So I do not really know how many were done.

We know that the external advisory committee had the authority to stop the trial not only because of potential safety problems, but if there was overwhelming benefit. So there could have been an action taken on the basis of an interim analysis to terminate the trial because

of effectiveness so that that leans more towards making the case that the ultimate P-value might have to be corrected for multiple loads. That is what we know.

DR. BEN-MAIMON: We agree. There is clearly conflicting documentation. Dr. Miller can attest, and Dr. Ruth Arnon, who worked with Dr. Bornstein in the design of the trial, they recall 50 patients. Again, documentation is loose.

I think what we need to also keep in mind though is that the analysis of the 40 patients for the primary efficacy end point does give you a .058 P-value. I think that Dr. Hoberman may have even looked at 32 at some point.

DR. HOBERMAN: I looked at 32, and the P-value was .027. But I was wondering, Russ, wasn't there a quote by Dr. Bornstein in a document attesting that the trial should not be stopped? Now, did that refer to the stopping on the way to 40 patients or to 50 patients?

DR. KATZ: Well, I do not know. I believe the statement from Dr. Bornstein occurs in the 1981 document which reported the results of the interim analysis. He says, given the importance of the trial, the blind must be strictly maintained. I do not know that it says -- I may have the document, so I can look at the break. Right, in fact, it is in my review as to exactly what it said, assuming I have quoted him accurately. We can look that up.

But it does not say anything about 40 or 50 patients. There quite clearly is a statement in that document or in the 1982 document where it says that the committee could stop the trial for overwhelming benefit.

I think that given the fact that these are patients with multiple sclerosis, and there were no therapeutic agents out there in 1980, ethically, that caveat has to be in there. But there are no criteria for the stopping to find. It just says overwhelming evidence.

DR. KATZ: Right. There are no statements prospectively, again, about the interim analyses or what -- right, what criteria would be used to stop it if any criteria in fact --

DR. BEN-MAIMON: If any at all.

DR. KATZ: -- were contemplated being used.

I can just read you the statement, at least a portion of it that I have excerpted in my review which says: "In this regard, I must call attention to the conditions imposed by its being a blinded study. It is obviously necessary to disclose the data to the site visit team in the committee in order to permit a proper consideration of this proposal. So, clearly, the results in the analysis were known to his external committee. The details of this report must, however, be treated in strict confidence to avoid jeopardizing the blind nature of this study itself."

So, at least as far as what I have extracted, it does not --

DR. BEN-MAIMON: Dr. Miller, if you want to just -- I can tell you that Dr. Miller did not know about anything until I told him so.

DR. MILLER: Yes. As the blinded investigator, I had no knowledge of an interim analysis having been either planned or performed. In fact, I did not even realize that one had been done until I had a conversation with Dr. Ben-Maimon a few weeks ago.

DR. GILMAN: Dr. Khachaturian and then Dr. Temple. Please use that microphone.

DR. KHACHATURIAN: Concerning the matter of documentation, did you try to explore through the university about the unapproved grants? Because grants are submitted not by the individual, but the institution. So the research-sponsored office should have copies of the unapproved or approved grants. That should be your source of information on what was submitted.

DR. BEN-MAIMON: We went back to Albert Einstein not only for those types of documents but also we went back to the IRB to try to see whether they had any documentation other than the submission that we were able to obtain from Dr. Bornstein's files. The records are in some basement somewhere years later, and they were not terribly helpful in

providing them to us.

We have gone through piles of information to try and get what we have gotten. As Dr. Katz states, we knowingly put into the NDA what we had, what we could best use to reconstruct.

When you go over the -- and I want to make very clear that this is in direct contrast to the actual clinical data where the documentation is somewhat confusing and lacking with regard to the grants and some of these other documents. The clinical data, the case report forms, we have the case report forms -- we have all of the source documents on every patient including laboratory studies and original documentation. It is clear from those documents that there was never a change at least in the information being collected throughout the course of the trial. It is actually quite an impressive series of case report forms for an investigator-run trial.

So I think the documentation is clearly different. We have very good documentation on the data, and not such great documentation on exactly the conduct.

DR. GILMAN: Dr. Temple?

DR. TEMPLE: As Dr. Katz was indicating, the question of 40 or 50 is really primarily a question about whether there was an interim analysis and what the statistical consequences of that are. It has never been

clear to me what the consequences of increasing the sample size without having intended to stop are. I gathered that there is a fair debate among statisticians about what that should be, especially when 40 -- when 80 percent of the patients are already locked in. It is hard to influence the overall result that much.

It is worth mentioning -- I am sure that everybody has been assuming this -- that this applies only to the official primary endpoint, that interim looks will not affect the exacerbation rate in any major way because any correction you could imagine would not be enough to change that very much.

DR. GILMAN: Dr. Gennings?

DR. GENNINGS: I have two questions. When was the NIH funding actually.

DR. BEN-MAIMON: I do not think that your mike is on.

DR. GENNINGS: When did the NIH funding actually begin?

DR. BEN-MAIMON: In 1978-1979.

DR. GENNINGS: So when you were talking about a disallowed protocol?

DR. BEN-MAIMON: He submitted grants every year. 1979 was -- 8 (sic) was actually first. In 1979, there was a grant. There was something in 1980 which we did not have

until the FDA provided it to us. Then, in 1981, there is this reference to this disapproved grant. Okay? So every year he was extending his funding.

DR. GENNINGS: They were just annual reports?

DR. BEN-MAIMON: Yes, they were just annual reports.

DR. GENNINGS: My other question is I guess toward the FDA, and that is how unusual is this to have one of the studies just based on documents, and memories, and things, and not on a prospective deterrent?

DR. KATZ: Well, I can only speak from my relatively limited personal experience. In my experience, it is unusual. We should not think this was not a prospective trial. This was clearly a prospective trial. It was well-done, and the documentation, as you point out, of the patient experience in the trial is very good. It is just a question of what were the plans? What were the people going to do? From my experience it is quite unusual. Ordinarily, the applications we get have been from the outset performed by sponsors, you know, commercial sponsors who know what the rules are and usually conform to them.

DR. GENNINGS: But my concern is like a file drawer effect. That is, if it was a negative study, it would never have been reported in the New England Journal. So is it unprecedented that a company would choose a study

out of the literature and then try to reproduce it in a new study?

DR. KATZ: No, no. I think that, if we think it is a valid study, if they can use it, it is not uncommon -- well, it certainly has happened where the studies are taken from the literature and presented as pivotal trials and NDAs.

DR. TEMPLE: What is unusual here is that it arose from a noncommercial source. That is relatively unusual and getting less so for noncommercial sources to do randomized trials. It is very hard to find. So whenever that happens it is not too surprising to me that some of the rigor that drug companies bring to designing protocols, writing it all down and running it through their system is not found. I think that that is what you observed.

DR. BEN-MAIMON: But, as Dr. Katz said, this was prospectively defined and it was a control trial. I think we have made an effort, and I hope that Dr. Katz agrees, to provide you with all of the data on Copaxone, including, in the safety database, giving you the safety in the CP trial. I think that you can rest assured that the data you are seeing, there are not other patients who have been exposed to Copaxone that we have not told you about. We have been complete. I think that the safety database is as complete as it can be.

DR. GILMAN: Well, thank you, Dr. Ben-Maimon. Let's take a 15-minute break. We will resume our meeting at five minutes of 11:00.

[Brief recess.]

DR. GILMAN: All right. Let us resume. Dr. Ben-Maimon is going to continue now.

DR. BEN-MAIMON: Well, now I guess we will turn to the multicenter trial performed to assess the efficacy and safety of Copaxone in relapsing patients that was sponsored by TEVA..

The trial was supported by a grant from the Orphan Drug Division of FDA, as well as a grant from the National MS Society. The results of this study were initially presented in the annual meeting of the ANA in 1994 and were published in 1995 in Neurology by Dr. Johnson and the other participating investigators.

There were 11 clinical sites participating in the trial. The sites were dispersed throughout the U.S. in order to ensure a representative sample of the patient population with relapsing MS.

Leading neurologists with expertise in the area of MS participated. The sites were coordinated by the Project Director, Dr. Johnson, who was also responsible for making the medical decisions as the trial was ongoing.

There was a steering committee that was charged

with managing the conduct of the trial and making conduct-related decisions. The committee was made up of Dr. Johnson, two company representatives, and a representative from the contract research organization responsible for the monitoring, drug packaging, and shipments, and the day-to-day coordination of the clinical sites.

A safety committee was charged with the review of safety data in a blinded fashion. This committee was completely independent of the conduct of the trial, the company, and the investigators. It met quarterly and reviewed adverse events, and laboratory data, and then made recommendations based on their review.

The committee was chaired by Dr. Van Den Noort, a leading neurologist at the University of California, and also participating were Dr. Miller, Dr. Gomolin, the late Dr. Melix, and Dr. Steven Reingold.

The trial was a multicenter, double-blind, randomized, placebo-controlled phase III trial. This is the design. Patients were screened. After meeting entry criteria, they were randomized to receive Copaxone 20 mg subcutaneous daily or placebo.

Patients actually visited the center on a monthly basis where they received randomized treatment and were assessed for concomitant medication used, as well as adverse

events.

Neurological exams were performed at zero, one, three, and then every three months thereafter for a period of two years. The neurological exam and EDSS assessment was performed by the examining neurologist. The examining neurologist was responsible for the quarterly assessments of neurologic function and the evaluation of potential relapses. A second neurologist functioned as the treating neurologist and was responsible for the treatment of relapses, adverse events, and other issues that came up in the course of the trial with regard to patient care. This ensured an independent assessment of neurologic function by the examining neurologist that was not influenced by adverse events or clinical course.

You can also see from this slide that once patients completed the core 24 months of dosing, they were enrolled into a double-blind extension. I will go into a little more detail now on what that means.

The trial, as I stated, was originally designed as a 24-month study. Approximately three-quarters of the way through the trial, prior to the completion of patient dosing, the protocol was amended to include a double-blind extension. This was done so that each patient would be switched to open-labeled therapy around the same time after all of the patients had completed the 24 months of the core

trial.

There was an initial period of seven months during which patients were enrolled. Patients then went into the 24 months of dosing and then into the extension.

Those who enrolled into the core study early, as you can see here, completed the 24 months early and spent longer periods of time in the extension. Those who enrolled later in the trial completed the 24-months of dosing, and then spent less time in the extension.

Following the double-blind extension, patients were switched into an open-label study for which data were not available at the time of submission to the NDA.

The initial 24 months of dosing was referred to as trial 01-9001, and the extension was referred to as trial 01-9001E. Results from both are presented for all endpoints.

It is important to remember that there as no interruption in double-blind therapy. During the extension, patients remained on the same treatment to which they were originally randomized. All sites participated in the extension. All patients who completed the core 24 months were eligible for participation in the extension.

Patients did have to sign a second informed consent at the completion of the first 24 months of dosing to enroll into the extension, but investigators and patients

were all blinded throughout the conduct of the extension.

DR. GILMAN: But then, at the time that the open label occurred, the patients knew that they were getting -- what they had gotten previously?

DR. BEN-MAIMON: Actually, not. We waited until the data was locked for the extension before we released any of the randomization codes. So they did not know until all of the database was locked and neither did the investigators.

Males or females were eligible for participation. They had to be between 18 and 45 years of age, and had to have clinically-definite MS by Poser's criteria. They had to have been diagnosed at least one year prior to screening and had to have at least two relapses in the two years prior to screening.

In addition, they had to be ambulatory with the Kurtzke EDSS score between zero and five, and had to be clinically stable for at least 30 days prior to enrollment.

A total of 251 patients entered the trial; 125 into the Copaxone arm, and 126 into the placebo arm. The groups were well matched with regard to sex, race, and age. Approximately 75 percent of the patients were female, most were white, and the average age was 34 years of age. Thus, the population studied was representative of the general population of patients with relapsing MS based on

demographic characteristics.

Baseline disease characteristics, including duration of disease, prior two-year relapse rate, and Kurtzke EDSS score were also evaluated. These parameters also showed that the groups were matched and were representative of the population with this form of the disease. Patients with MS had approximately a six to seven-year history of the disease, a prior two-year relapse rate of three, and a baseline Kurtzke EDSS between two and three.

The exposure was similar for both Copaxone and the placebo group. You can see that the placebo group is on the top here, and the Copaxone group is on the bottom. The rate and timing of drop-outs was similar between the two groups. This was the case for both the core and the extension.

Now, please, note that the drop-off here is not a result of patients discontinuing therapy, but are results from these patients being switched into the open label study and thus continuing treatment. So this actually represents the timing for which there is available data submitted.

There were 284 patients screened for this study. As you can see, the vast majority of patients completed both the core, as well as the extension. It is important to note that nine patients elected not to participate in the extension. Thus, as long as the design and conduct of 9001E

are kept in mind, the data collected during the extended double-blind dosing period provides valuable information for the assessment of safety and efficacy.

DR. GILMAN: So what was the duration of those nine patients dropping out of the extension period?

DR. BEN-MAIMON: Well, the nine patients actually completed 24 months, but chose not even to enter the extension.

DR. GILMAN: I see.

DR. BEN-MAIMON: Okay?

DR. GILMAN: Yes.

DR. BEN-MAIMON: A revised statistical plan was submitted prior to the completion of the dosing portion of the core protocol. Oops, I went to the wrong slide. I am sorry. This is the criteria for relapses. I am sorry.

The patients who thought they might be having a relapse were asked to inform the site and visit the center within seven days of the onset of symptoms for neurological exam. This exam was performed by the examining neurologist. If the signs and symptoms met the predetermined criteria, a relapse was reported on the case report form. Treatment of the relapse was delegated to the treating neurologist and not the examining neurologist.

Criteria, as shown on this slide, required the appearance or reappearance of neurological symptoms that

lasted at least 48 hours. An increase of at least a half a point in EDSS or an increase of at least one in each of at least two functional systems, or an increase in at least two points in one functional system.

In addition, objective confirmation by the neurologist, and a period of 30 days' stability prior to the onset of symptoms with no other attributable causes were required.

Now, a revised statistical plan was submitted prior to the completion of the dosing portion of the core protocol. Please note that although several cohorts were prospectively defined and analyzed, the all-patient cohort, or ITT cohort, was considered as the basis for statistical inference. The results obtained from each of the cohorts were consistent with those obtained from the ITT cohort.

The prospectively-defined primary endpoint for this trial was the mean number of observed relapses during the course of the trial. Multiple models were fit to this data including an ANOVA that included drug, and center, and drug by center as interaction terms, and an ANOVA which included drug and center only as main effects, and an ANCOVA which included prior two-year relapse rate and baseline Kurtzke EDSS score as covariates.

In addition, FDA performed a T-test and a Mantel-Haenszel analysis of the entire distribution of

relapses. The results for those two are presented here as well.

The results of the model at 24 months yielded P-values between 0.007 and 0.055. These results were considered statistically significant. Clearly, all of the models provided internal consistency.

Of note is that these mean relapse rates are over two years. At 24 months, the annualized rates were .65 for the Copaxone group and .84 for the placebo-treated group.

Several other end points were analyzed in support of the primary efficacy end point. All of these end points were prospectively defined with the exception of a categorical analysis which was defined after the database was locked.

What is clear from the results I am about to present is that, although not all end points achieve statistical significance, all of the endpoints are numerically in favor of Copaxone and support the effect on relapse rate and the internal consistency of the data collected and the effect.

The data presented here is the median time to first relapse in patients treated with Copaxone, which you can see as 2-8 -- 187 days, versus 198 days for the 24-month time point. This did not achieve statistical significance at 24 months, but is numerically in favor of Copaxone. The

difference is maintained when the extension data is included.

The proportion of relapse-free patients was also numerically greater in the Copaxone-treated group. Three patients treated with placebo, who had been relapse-free during the 24 months of dosing experienced a relapse during the extension. None of the Copaxone-treated patients who were relapse-free during the core 24 months experienced a relapse during the extension. What you see here is that the 33.6 remains the same, whereas, the placebo group, those three patients account for three patients in the placebo group becoming non-relapse-free, having relapses.

Several endpoints relating to disability were evaluated. This slide shows the mean change in EDSS score from baseline for each of the visits in the treatment groups. What you see here is the placebo group on the top. Each of these represents the change from baseline, the mean change in baseline for each time point. The Copaxone group is on the bottom.

DR. GILMAN: Are the bars to show range or what are you showing there?

DR. BEN-MAIMON: Those are the error bars.

DR. GILMAN: They are error bars?

DR. BEN-MAIMON: Yes. They are error bars.

Patients treated with Copaxone on average remain

stable or experienced slight improvement, as evidenced by the slight decrease in the mean EDSS scores. As you remember, increasing EDSS scores is associated worsening while decreasing is associated with improvement.

Patients treated with placebo on average tended towards a slight increase in their EDSS scores. A repeated measures analysis yielded a statistically-significant result with a P-value of .023. When data from the extension is included in the analysis, you can see that the magnitude of the difference increases.

DR. DRACHMAN: Would you be able to comment, turning back to that slide, why during the initial double-blind phase most of the change was within the first three months?

DR. BEN-MAIMON: I do not have an answer for your question. Obviously, we have noticed it as well. You see that the Copaxone group -- I am going to need another pointer. I think that the batteries are running out.

As you can see, the Copaxone group pretty much remains flat. There is this increase that is clearly maintained over the course of the 24 months. I do not have an answer to why that occurs. There are several hypotheses, but I do not have an answer.

The error bars though do not cross, and the change is maintained across the 24 months. As you would expect, as

you get out over two years, you would start to see changes in EDSS as evidenced by the data obtained in the extension. Exactly why there is a change early on, I do not have an answer for. There is nothing unique about that group. We have looked at the demographics. We have looked at those changes. We have looked at it center by center to see whether there was something going on and we cannot come up with a reason.

Dr. Wolinsky, would you like to comment?

DR. WOLINSKY: I think, while we do not have an explanation for that, the important thing, at least as I see this as a clinician looking at the data, is the fact that the curve stays flat for those patients who are on Copolymer-1 and the overall trend on the curve for those patients who are on placebo is showing an increase. Now, there is some other data that Dr. Ben-Maimon will turn to in a moment that, instead of looking at this group data and perhaps not the most appropriate way to use an EDSS score, which is, in fact, ordinal, and not linear. When you look at this in a categorical sense, as you will see in a moment, this kind of trend is also supported.

DR. BEN-MAIMON: So I think -- okay?

A categorical analysis, which I think is what Dr. Wolinsky just referred to, of those patients who either improved, worsened, or did not change throughout the trial

was also performed. For this analysis, patients were grouped into three categories. Patients were considered improved if their EDSS score decreased by at least one point when the termination visit was compared to baseline. They were considered to have worsened if their EDSS score increased by at least one point when their baseline was compared to termination. They were considered unchanged if they did not meet either of the criteria.

The first column here shows those patients that improved, the second those that were unchanged, and the third those that worsened. The distribution of the patients between these three categories were analyzed using a categorical approach and a repeated measures analysis which took into account all of the visits throughout the trial and the date of which it -- this is the data presented from the termination visit compared to the baseline visit. The analysis is actually repeated measures and takes into account all of the data throughout the course of the trial.

We are often asked about whether there were patients experiencing relapses at the time points analyzed that could have contributed to the evaluation of this data. It is of note that there were no patients in the midst of a relapse at the termination visit. Thus, the results for baseline to termination visit does not include any data from relapsing patients that may have complicated the

interpretation of the results. So what you see here is that there are more patients who improved, pretty much the same, unchanged, and fewer patients who worsened. The repeated measures analysis gives you the .037 while the baseline to last visit gives you .024, which is also statistically significant and would not include patients who have had relapses.

Similarly, this slide shows the results of the categorization of the study population at the time of the core plus extension. Again, internal consistency is demonstrated as these findings reflect a similar distribution such that more patients improved on Copaxone and fewer worsened. Again, this is really just to show you the internal consistency between this and the 24-month data.

Progression was defined as an increase of at least one point in EDSS score that was maintained for three months. This was the prospective definition. Proportion of progression-free patients and time to progression based on the same definition were analyzed. Very few patients in either group showed evidence of progression. Approximately 75 percent in both groups remained progression-free. So there was no statistical significance obtained because clearly the placebo group did not differentiate itself in the Copaxone. They all stayed pretty much in the same grouping.

These are the data as analyzed from the control trials, providing the evidence of effectiveness for Copaxone in patients with relapsing MS.

I would like to show one more slide before we go on to safety. This is the level of Copolymer-1 reactive antibodies. Copolymer-1 reactive antibodies were actually measured throughout the 9001 trials in all patients.

A sample curve demonstrates that patients treats with Copaxone show evidence of an increase in Copolymer-1 reactive antibodies over the first three to four months. This is then followed by a decline of protein baseline by about nine months. Almost all treated patients developed some level of Copolymer-1 reactive antibodies. Antibody levels were not correlated with relapse and were not unique in patients who were relapse-free when compared to those patients who had had at least one relapse.

Several in vitro studies have been performed to assess whether these antibodies are neutralizing. These studies using human sera and looking at Copolymer-1 reactive antibodies and their ability to block Copolymer-1's affect on EAE, its protective affect have not provided any evidence that these antibodies are neutralizing.

DR. GILMAN: Before you go on, there are some questions. Dr. Drachman first.

DR. DRACHMAN: I know that somewhere along the way

I must have seen data on the reproducibility of the Kurtzke scale test retest interexaminer reliability, but I do not remember them. What are the data on that?

DR. BEN-MAIMON: Why don't I hand that off to one of the clinicians who can speak better to the Kurtzke itself.

DR. JOHNSON: Well, Dr. Drachman, the Kurtzke scale is not the ultimate precise scale that we would all wish for. So a number of things are done to try to overcome whatever deficiencies it has. First of all, in this trial, there was a training program which all centers participated in prior to the conduct of the trial.

Secondly, the trial used the same examining physician throughout the course of the trial for each patient. Now, there were times when people went to the ANA or on vacation and someone else had to perform the EDSS, but by and large a single set of examining and treating neurologists were assigned to an individual patient and conducted all of the examinations throughout the course of the trial.

So even though there is some -- you are right that there can be some variability between examiners. In this trial, in the case of the experience of each individual patient, the same examining neurologist made the determination at each time. That plus the training program

at the beginning I think lessened greatly the risk that there would be variability in the data per patient.

DR. DRACHMAN: Yes, but we are looking at an order of magnitude of plus .2 versus minus .05. So what I am really asking is what is your interpretation of the meaning of that given that we know that this is a nonlinear scale with a certain degree of variability? I realize that you have done whatever one can do to make it as reliable as it could be. But what is your view of the meaning of that order of magnitude and the reliability? If you see, let's say, you, Ken Johnson, having seen thousands of MS patients, see someone today and then see him again without looking at his face, what would be the probability of a slight difference, how much?

DR. JOHNSON: Well, this trial was not designed primarily, and the patients were not recruited primarily to look at differences in disability. We were looking at relapse rate.

I think that this is a substantial difference when you look at the size of the population that was involved and if you look at the categorical differences which are also statistically significant. I do not know if you looked at the difference between the 24 months and the 24 months plus the extension, but the trend continues to get much more impressive over the course of time. My own

interpretation is, one, it is statistically significant, and two, that, in my mind, it has substantial clinical usefulness.

DR. GILMAN: Dr. Katz?

DR. BEN-MAIMON: Dr. Katz, is this relating to this issue?

DR. KATZ: No, not specifically.

DR. BEN-MAIMON: I just wanted --

DR. KATZ: It is related to the EDSS. No, go ahead.

DR. BEN-MAIMON: Okay. Also, I think when you are talking about means, if you look at that -- and I will go back. Oops, I am going forward.

[Slide.]

DR. BEN-MAIMON: It is slide 67. You are looking here at means. So inter-rater variability and give persistent throughout the time points. And the error bars clearly should account for some of the variability in the assessments that are being made as well. So, again, I think there is a difference in meaning and the clinical relevance. Dr. Wolinsky, do you have a comment on it?

DR. WOLINSKY: I think you are pointing out the important issue here is that we can, for example, look at Nosworthy's data, where he has looked at groups of examiners on patients who supposedly are fresh, and it is shown that

about a half-point change in the EDSS is noise in the system even for good examiners. That is why in the categorical end points, a change of one or greater than one point was taken. This data though because of the error bars, is accounting for that inherent noise in this particular test measure. I think that is the important issue for this data.

DR. GILMAN: Well, except that in those first three months the placebo group rose and then stayed more or less stable. I think that is part of the concern that Dr. Drachman is expressing.

Dr. Leber.

DR. LEBER: This may not be the right time to introduce it, but I think that because the inference here is getting to the size of the measured estimate of treatment effect, that we ought to try to put on the table some of the problems that I think you have in a chronic illness. We face this with dementia. You follow somebody who is deteriorating at an irregular or regular rate over a period of time. The size of the treatment effect, even if the drug totally stopped the progression of the illness is a function of the patient sample randomized and the duration at which you track the patient, assuming that the placebo group deteriorates rapidly, and this is with an effective drug, it is not the null, you get a big treatment effect estimate. If the placebo group hardly deteriorates at all, you get a

small treatment effect. That is one of the reasons I am so suspicious about using a numerical value here as an index of how big the effect actually is. That does not mean that this means this is good evidence of the treatment effect. It simply means that you may have an experiment that does not have sick enough patients in it to detect the effect you have just been looking at. I think that is more the thrust than these arguments about the size of the realized effect which worried me. Because we went through this with Pacmed. If you look at six weeks, you get a very different estimate than when you look at six months, and probably very different than if you looked at several years, and it is all hostage to the control group, not to the active group under this set that the drug stopped at. I do not think it stopped it. That was just one philosophical point that I think would be useful to get on the table before we get too much into the side effect issue.

DR. GILMAN: Well, of course, we are looking at EDSS here and, in fact, relapse rate is another matter.

DR. LEBER: Yes. But what this might not be a good sample is my point to look at EDSS it might be fine to do some other --

DR. GILMAN: Yes.

DR. LEBER: -- to decide what you think the assay sensitivity is of -- it is like the calibration here may not

be good enough to pick up this effect because of the sample you have.

DR. GILMAN: Right. Dr. Katz.

DR. KATZ: If I could refer you to I think the next slide. Yes, that is the one. You get statistically-significant results regardless of which analysis you do here. I just wanted to make a couple of points. As far as I know, this one was not the protocol-specified analysis or the breakdown of the data.

DR. BEN-MAIMON: Yes.

DR. KATZ: You presented a somewhat similar slide for the Bornstein Trial. We looked at this outcome in a binary way, where we just looked at percentage unchanged or improved as one group. I do not know if that was a protocol-specified analysis as well. Those results were really not significant. We looked at an analogous binary distribution of the data on this outcome, analogous to the one you did for Bornstein. That is also clearly not significant. It is also not a product or specified outcome. We get a P-value of somewhere around .2.

DR. BEN-MAIMON: We actually looked at -- F-70 please. We actually looked at Dr. Bornstein's data broken down into three categories. I will show it, but it is not terribly enlightening. It basically confirms what he saw before. There are trends. There are numerical trends. Why

don't we put it up? But the statistics remain above .05. I will show you that.

I think, again, I think Dr. Leber's point is an important one -- that the rate at which the placebo group progresses is really, and the length of time you watch people for, because we know it is a slow disease, is of importance. You can see that this just confirms. This is the same analysis we performed, and it gives similar results to Dr. Bornstein's improved no change versus the worsened group.

Back to slide 60 -- do you want to still see 67?

[Slide.]

DR. BEN-MAIMON: Sorry.

DR. DRACHMAN: One other point was that MRIs were done on some 15 or so patients. What did you find on those? What did that show?

DR. BEN-MAIMON: Did you want me to leave that or did you want to make a comment before I go onto MRI, Dr. Leber?

DR. LEBER: I wanted to follow up. I wanted to make sure that my point is not misunderstood. I am simply saying that you cannot make much of the treatment effect. That means that I cannot interpret your study the way you want to interpret it. It does not mean that I agree that you have shown a point because you failed for a reason that

we can --

DR. BEN-MAIMON: I understand.

DR. LEBER: -- find comfortable to explain why we do not see the effect size you would like to see. I mean, a lot of it is the spin on what I am saying. I am saying is that you may not have the study to test the question of progression that you think you have. It might very well be a test for the frequency of exacerbation. I think that the distinction between the two is critical.

I also had one other question, but I can wait until after the question that you had.

DR. GILMAN: Let's go to the MR scan data then.

DR. BEN-MAIMON: G1 please.

[Slide.]

DR. BEN-MAIMON: I would just like to sort of qualify what we have with regard to MRI. At the time that the trial was initiated in 1991 the MS Society was doing some work at looking at surrogate markers in the relevance of MRI and its use, and how it should be used with regard to MS. We had a grant from the National MS Society to perform MRI at a single center and there were actually 27 patients whom you will see who were enrolled at that center. This was purely a pilot study. It was small numbers of patients. I just want to put the caveat that the data I am presenting is data. I do not think that really any conclusions can be

drawn from it.

Next.

[Slide.]

DR. BEN-MAIMON: With a single Center at the University of Pennsylvania, there were 14 patients who were treated with Copaxone and 13 who were treated with placebo, and the MRIs were performed frequently at zero, one, three, and then pretty much every three months thereafter.

The patients were randomized either to 14 patients on Copaxone, 13 on placebo. Fourteen of those patients completed the trial, versus nine in the placebo group, and there was a single patient who had a baseline visit and a 24-month only, but did not contribute in the interim, and did not have any MRI studies in the interim.

The database that we are presenting to you represents all 14 on Copaxone and only 12 on placebo because a single patient only had a baseline MRI with no comparison throughout the course of the trial.

The end points that planned to be looked at were the presence or absence of gadolinium enhancement, the number of foci of gadolinium-enhancing foci, and the volume of gadolinium enhancement. Again, we also looked at the T2 volumes.

Of note is that we were unable to evaluate the endpoint for volume of gadolinium enhancement because of a

problem in the way the early MRIs were performed and an inability to come up with accurate volumes for that parameter.

What you see here when you look at the proportion of gadolinium-enhancement-free patients at any time point -- at zero, as expected, 50 percent of the patients in each group have lesions and 50 percent do not. What you see is in the placebo group you have a range of approximately 60 on average, 60 to 70 with a slight increase in the Copaxone-treated group as you get out to more patients being lesion-free, enhancement lesion-free. But, again, it is a pilot study, and the numbers are very, very small.

From the standpoint of lesion burden, we basically showed what everybody else has been reporting, and that is a lot of variability in T2 volume, making it almost uninterpretable. The error bars are so big that any trends that you might see probably are not meaningful. This data I think is very difficult to interpret.

Dr. Wolinsky has been intimately involved in the MRI issue. Do you want to make some comments?

DR. GILMAN: Yes. Can you tell us a little more about the methodology? How many slices were examined?

DR. BEN-MAIMON: Do you want to put that slide up?

DR. GILMAN: Do you use uniform MRI machines?

DR. WOLINSKY: These were done at the University

of Pennsylvania. They were using, I believe, five-millimeter, ungapped cerebral slices, conventional T1 and the T2-weighted conventional dosing with gadolinium with usual delay.

Their methodology for scoring the enhancements was basically an investigator, operator-driven, counting lesions, as well as just clicking them off.

DR. GILMAN: Not size of lesion?

DR. WOLINSKY: Size of lesions could not be done in this study for technical reasons having to deal with some of the perhaps mistakes made as patients were enrolled into this study. If you think back to when these were done, gadolinium was just being introduced as an adjunct tool in imaging at all, let alone in clinical trials.

There was a software program which has been developed by the investigators at the University of Pennsylvania which is an automated program for image analysis which was used to quantitate the T2 volumes. It has, according to the investigators, an extremely high reliability. That was what was used to calculate the T2 volumes. So that was actually rather independent of the reader and more dependent upon the so-called fuzzy logic connectors of their artificial intelligence system.

DR. GILMAN: The readers were radiologists?

DR. WOLINSKY: The readers were radiologists. I

think there was one neurologist as well. Jeff Cohen was involved in this study at that site and was quite involved with Dr. Grossman and his team in the neuroradiologic center there.

DR. GILMAN: Clearly, they were blinded.

DR. WOLINSKY: They were blinded.

I would state that because of our interest the investigators, as a whole, and fortunately TEVA as well, we are embarking shortly on a 30-center study across Europe and some Canadian centers to address specifically the question of whether or not Copolymer-1 has an affect on enhancements; to what extent that affect on enhancements is; how quickly that occurs in monthly scanned patients and whether or not that persists. But this is really a project to look more into the level and mechanisms of action of the drug than it is to look at further measures of clinical efficacy. We think that we have that already.

DR. GILMAN: Yes?

DR. DRACHMAN: The lesion volumes are, of course, very variable. What about change in lesion volume? Did you look at the difference beginning to end?

DR. WOLINSKY: Well, if you look -- if we go back to the slide which shows -- this is actually just the number of enhancements. But, if you look here at -- what we are looking at now is mean T2 weighted lesion volume. So you

can see that the lesion volumes are rather similar between the two groups allowing for this difference, of course, in terms of the variation in volume.

Now, if you look at, if you will, a delta lesion volume without trying to mislead anyone, the lesion volume is flat or drops slightly in the group of patients treated with Copolymer-1. It is somewhat larger on those with placebo. The difference will favor the drug. But this is not a large enough group to make any meaningful conclusions on.

DR. DRACHMAN: Was it done as a paired initial versus later study difference rather than as a group? I mean, that is going to be very, very difficult to know. But if in one individual treated it drops and in those who were on placebo it increases, I wonder whether that sort of a paired analysis --

DR. WOLINSKY: I do not believe that a paired analysis is available for us to show to you. Dr. Leber?

DR. GILMAN: Dr. Leber?

DR. LEBER: I just have a related technical question with the last error bar histogram. I know that you did not get follow-up on every -- not all 13 and 14 of those randomized were rated each time for you, are they?

DR. WOLINSKY: Right.

DR. LEBER: What is the difference between the

numbers contributing to the zero and 24-month score? Are they different patients that lead to those or is this a coherent set?

DR. BEN-MAIMON: A coherent set, with the exception of the one patient.

DR. LEBER: Okay.

PARTICIPANT: Would you repeat that?

DR. GILMAN: It is a coherent set.

DR. WOLINSKY: Same patient.

DR. BEN-MAIMON: It was the same patients. Okay. Shall we keep going?

DR. GILMAN: Dr. Leber?

DR. LEBER: In honoring this order that as you present the information I will ask you questions about it, you had a slide just a little bit earlier about the appearance and then some depth of essence in the antibody level.

DR. BEN-MAIMON: Yes.

DR. LEBER: That is fine. Then you reach a conclusion based on something related to the activity of whatever you find in EAE about whether or not it is neutralized. That is what I wanted to get to. You are the ones who have introduced the idea that this is an important point. So I wanted to examine what is the validity of the test to say that you know the antibodies are not

neutralized? I would not have asked the question because I am not sure how to interpret it. How do you know they are not neutralized?

DR. BEN-MAIMON: I do not think that we do know for sure. I do not think there is anything conclusive. There is data clearly -- there is no data to show that they are, but it is not conclusive data to show that they are not.

DR. LEBER: So what did you mean when you said that they were not neutralized?

DR. BEN-MAIMON: I said -- no, I did not. I think I said that these studies using human sera and Copolymer-1, and their ability to block the protective effects of Copaxone on the development of EAE have not provided any evidence that they are neutralizing.

DR. GILMAN: All right. Ms. Phillips?

MS. PHILLIPS: You mentioned the extension study and you said that nine patients did not choose to participate. Could you just briefly say why?

DR. JOHNSON: This period of time when we were going from the 24-month trial into the extension was precisely the time when Betaseron came on the market. A certain number of patients decided they would rather take a drug for sure rather than maintain their participation in a blinded trial where they could be on the placebo. So the

main reason for patients not continuing was to switch to Betaseron at that time.

DR. BEN-MAIMON: I think it is important to remember that nine out of the population was actually a relatively small percentage. But it was not related to the therapy. It was primarily related to, as Dr. Johnson said, the advent of something that they knew they could get.

DR. GILMAN: Dr. Snead has a question.

DR. SNEAD: When one looks at these data and compares them to the other trial, I noticed that in the New England Journal paper there is really an extensive description of the preparation of the compound that was given. In this paper, it simply said that it was prepared under an FDA-approved manufacturing process. Are you satisfied that basically the same formulation was used in both studies, given the heterogeneity that we have heard about today?

DR. BEN-MAIMON: Well, I can tell you that the formulation, not the drug product, but the formulation was slightly different. There was Mannitol in the lab formulation that was used in the 9001 trial, and there was no Mannitol in the Bornstein Study. But the drug substance is the same. I am comfortable with that. We have looked at it both in molecular weight, amino acid ratios, most of our release testing parameters. We have looked at its activity

in EAE. There is just nothing to suggest that there is a difference.

DR. SNEAD: All of those things are the same batch to batch?

DR. BEN-MAIMON: Yes.

DR. SNEAD: Okay.

DR. BEN-MAIMON: And are tested.

DR. GILMAN: Let's proceed on to safety then.

[Slide.]

DR. BEN-MAIMON: Just to give you the database. 906 patients have been exposed to Copaxone. Thirteen of the patients only had baseline visits and, therefore, could not be assessed for changes with regard to safety. An additional 49 patients participated in the early safety tolerability studies and are not included in the database. Thus, there is a total of 844 patients who have been treated with Copaxone that provide the safety database, and 206 for placebo.

There were seven deaths in the entire clinical program. None of the deaths are believed to be related to Copolymer-1 for injection. Out of 779 patients with relapsing MS, two patients died in open-label studies, these two. The other patients all had chronic progressive MS and all of the deaths have occurred in uncontrolled trials.

One patient died, which is this patient, of a

respiratory arrest after repeated visits to the emergency room for abdominal pain. This patient was a 40 year-old female with a 15-year history of multiple sclerosis and an EDSS score of 5.5. No adverse experiences were reported throughout the course of the trial by the patient. Just prior to her death, about two weeks before, she began complaining of some leg pain and weakness. She visited the emergency room just prior to her death complaining of abdominal pain. They did an obstruction series which was negative and discharged her.

She then, two days later, while transferring into bed, became acutely short of breath and died. The paramedics were called. They were unable to resuscitate her and the family refused a postmortem.

DR. GILMAN: Was it assumed that she had a pulmonary embolism?

DR. BEN-MAIMON: That is not documented anywhere; but, clearly, clinically, I would be suspicious. But there are no scans, there are no pulmonary tests that were performed, and we do not have a post.

I think that what is important to know though is that she did not get Copaxone on the day of her death. So it really does not fit the description of a systemic reaction which occurs immediately after the injection.

DR. GILMAN: Was she paraplegic or paraporetic?

DR. BEN-MAIMON: She was.

DR. GENNINGS: Paraplegic?

DR. BEN-MAIMON: Paraplegic, yes. She was wheelchair-bound. She was unable to walk. She was transferring from bed.

The second patient who died in this trial, this patient, was a 43 year-old female with a nine-year history of MS and an EDSS score of 4.5. The patient died due to respiratory insufficiency while in the intensive care unit and being treated for septic shock and multiple organ failure. The patient had developed a urinary tract infection which was complicated by urosepsis. Then autopsy confirmed that the patient suffered from multiple sclerosis but had died secondary to generalized sepsis. She had been treated for approximately three months prior to her death.

DR. GILMAN: What was the site of the infection in that patient?

DR. BEN-MAIMON: She actually had E. Coli growing out of almost all of her blood samples. She had pseudomonas and candida out of a CV site intravascular line. They found just multiple organ failure. She had renal failure. She had hepatic failure secondary to the infection.

DR. GILMAN: But was the initiating event renal or urosepsis?

DR. BEN-MAIMON: Urinary tract infection.

DR. GILMAN: Yes. All right.

DR. BEN-MAIMON: Actually, the last patient whom I will discuss in any kind of detail is this patient. I will discuss it because you raised it earlier. That was the patient who had been in the intensive care unit and who had been in coma. Again, I have to speak to the fact that this was a patient who participated in Dr. Bornstein's compassionate use program, so was not actually being followed by Dr. Bornstein, but was being followed by a private neurologist. The patients had received Copaxone for 22 months. Shortly thereafter, approximately a year after initiating therapy, deteriorated and went into coma.

The reports that Dr. Katz describes of chest pain and anxiety started actually at the same time he supposedly went into coma and are reported by his family members. There is basically handwritten documentation that he is feeling anxious. I do not have an answer to the question. We have not been successful in obtaining any other documents from the hospital, although we have tried. The patient's family cannot be contacted anymore. So I cannot answer the question. The patient had a trach and died when the trach was being changed. They could not reinsert the tracheostomy.

DR. GILMAN: Well, there are several puzzling features about this. One was, if he was in coma, how could

he complain about systemic reactions?

DR. BEN-MAIMON: I agree. I do not know the answer to that.

DR. GILMAN: Why was he given a tracheotomy initially?

DR. BEN-MAIMON: Because he was unable to be weaned from the ventilator.

DR. GILMAN: Why was he put on the ventilator?

DR. BEN-MAIMON: What is indicated there was from his secondary progressive MS. It was MS-related.

DR. GILMAN: Was he quadriplegic?

DR. BEN-MAIMON: Yes.

DR. GILMAN: Plegic?

DR. BEN-MAIMON: And with an EDSS score of eight.

DR. GILMAN: He was treated with drug though even up to the day of death?

DR. BEN-MAIMON: Yes.

DR. GILMAN: And he did have these "systemic reactions" I understand.

DR. BEN-MAIMON: He has reported on his case report forms reports of chest pain, anxiety, and shortness of breath at varying times throughout the course of his treatment. Therefore, they qualified it as a systemic reaction. Can I say that they were classically immediately related to the injection? They were -- the collection of

symptoms that we have described I do not know.

DR. GILMAN: Do we know whether he had renal failure?

DR. BEN-MAIMON: No, he did not.

DR. GILMAN: He did not have it?

DR. BEN-MAIMON: He did not have renal failure.

DR. GILMAN: Did he have an EKG at any point during this course in hospital?

DR. BEN-MAIMON: Not that I have access to. I assume he has, but I do not have access to it.

Let me tell you about the other five patients.

DR. GILMAN: Yes please.

DR. BEN-MAIMON: So the five other patients all had CPMS and all were participants in Dr. Bornstein's study. One patient, while participating in Trial BR-2, the control trial in patients with CPMS, died from a glioblastoma.

The last four patients were all in BR-3, the compassionate use program. One of the patients died from a florid pneumonia. One patient died from a colon malignancy, and actually had discontinued Copaxone prior to her death. The third was the patient we just discussed. The fourth patient died as a result of pulmonary failure thought secondary to a progressive MS.

DR. GILMAN: Can you tell us about the patient with pneumonia, 2049, patient number 2049?

DR. BEN-MAIMON: That patient did have an autopsy and had a florid pneumonia diagnosed at the time.

DR. GILMAN: Was MS in fact verified?

DR. BEN-MAIMON: Yes.

DR. GILMAN: In the patient with glioblastoma, was an autopsy performed?

DR. BEN-MAIMON: Yes.

DR. GILMAN: Did the patient have both glioblastoma and multiple sclerosis?

DR. BEN-MAIMON: Yes, on the autopsy report.

DR. GILMAN: Thank you.

DR. BEN-MAIMON: Okay. I think, in conclusion, with regard to the deaths, none of the deaths have occurred in the control trials. Two of the deaths have occurred in patients with relapsing MS in TEVA-sponsored trials. The other deaths have all occurred in patients with more progressed disease and in trials primarily in the compassionate use program.

Let's now turn to adverse events. Eight and a half percent of patients with relapsing MS who were treated with Copaxone withdrew from clinical trials due to adverse events. This is compared to 2.7 percent of placebo patients. Of these withdrawals, 19 patients withdrew from the control trials versus four percent withdrew from the control trials who were treated with placebo.

Of the 19 patients in the pivotal trial who discontinued due to adverse events, four patients in the Copaxone-treated group discontinued due to local injection site reactions, while one patient in the placebo-treated group withdrew for this reason.

Four patients in the Copaxone-treated group withdrew due to unspecified adverse events, and two of these were in Dr. Bornstein's study.

The second most common event which was reported in three patients in the Copaxone-treated group and no patients in the placebo-treated group was unintended pregnancy. Dyspnea, infection, urticaria, and vasodilatation were reported in two Copaxone-treated patients each and led to the discontinuation of these patients.

DR. GILMAN: Before you go on, could you go back to that slide?

DR. BEN-MAIMON: Yes.

DR. GILMAN: I am a little puzzled now because four patients withdrew because of local injection site reactions, yes? Dr. Miller had earlier said that the injection site reactions were trivial or could not be seen. Can you reconcile those comments?

DR. BEN-MAIMON: Well, I think that you will see, as we go on, that the severity of these events are mild primarily. But, obviously, certain events are more

bothersome to certain patients than other events. We all know that side effects are patient-dependent as to how much they will tolerate.

There were four patients who did withdraw because they considered these events to be significant enough and bothersome enough that they could not tolerate it. There was also one patient in the placebo group who withdrew. So, taking an injection everyday I think you cannot minimize the fact that patients do not like it and often withdraw.

You should also note that, I think, if you add this up, you will see that it is not 19. That is because some patients actually report more than one event at the same time. One of the patients who had a local injection site reaction also had a systemic reaction. So which was actually the cause and effect relationship I cannot answer. But these were the events that were ongoing at the time of discontinuation.

This slide shows the 11 most commonly-reported adverse events. They were also more frequent in the Copaxone-treated group. Local injection site reactions, chest pain, and vasodilatation were thought to be related to Copaxone treatment. I am going to go into more detail with regard to those.

DR. GILMAN: What do you mean by hypertonia?

DR. BEN-MAIMON: These are costart terms.

DR. GILMAN: They are what?

DR. BEN-MAIMON: These are costart terms.

DR. GILMAN: Oh.

DR. BEN-MAIMON: So what the verbatim was for that term I cannot tell you off-hand.

DR. GILMAN: All right.

PARTICIPANT: There are a lot of them though.

DR. GILMAN: Yes.

DR. BEN-MAIMON: It may have been a spasm which you would see or muscle stiffness in this population.

First local injection site reactions. These reactions seem to have several components. Well, induration, mass, inflammation, pruritus, erythema, and pain have all been reported. As you can see, these same events are also reported in the placebo group, but clearly at a lower incidence.

This slide shows the complaints for the local injection site reactions were almost always mild. This is the proportion of the patients and this is the end with reporting mild events. Infrequently they were moderate, and there was only a single event that was a severe event that was related to pain. There has not been any skin necrosis reported. As I said earlier, only four patients withdrew out of the 126 treated, 125 treated.

With regard to systemic reactions, Dr. Bornstein,

in his original publication, reported an event that he referred to as a vasomotor event. The event was associated with chest pain and shortness of breath and occurred sporadically in two patients in his trial.

In trial 9001/9001E, a similar event was described by the two patients, and by patients and investigators. The event was unpredictable with regard to its initiation of therapy, and it occurred within seconds to minutes of the injection and lasted usually from a minute, to 15 to 30 minutes. It was associated with vasodilatation which was usually reported as flushing or chest pain in combination with palpitations, anxiety, and/or dyspnea.

In an effort to assess the incidence of these events, a definition was created before opening the code based on investigator and patient description. This definition required the simultaneous report of either chest pain or vasodilatation associated with at least one of the secondary symptoms, palpitations, dyspnea, or anxiety.

Based on this definition, 19 patients in the multicenter trial, or 15.2 percent of patients treated with Copaxone reported this event as compared to four patients or 3.2 percent of placebo-treated patients. Ten of these 19 patients experienced a single episode during the dosing period. It is of note that all but five of the 19 patients completed the full two years of dosing and 14 enrolled in

the extension of the trial. Of the five patients who discontinued prematurely, all but one patient were exposed to Copolymer-1 for injection following the systemic reaction. Of course, all of the patients who continued were exposed on an ongoing basis to copolymer one for injection, following the report of the systemic reaction.

The one patient who experienced seven episodes continued in the trial and completed the study. Prophylaxis of this patient with Benadryl and other antihistamines did not impact their occurrence or their severity. The reactions were all similar in nature and included chest pain, shortness of breath, and flushing. There were no sequelae and all events resolved within 20 minutes in this patient. This patient did enroll in the extension and has also continued in the open-label study. One of the four placebo patients also discontinued due to this adverse event.

The reporting of the primary components, either vasodilatation, chest pain, or both by the patients who had a systemic reaction, revealed that both of these events were commonly recorded as primary symptoms. What we tried to do was look at whether this was a useful definition. Here you see vasodilatation, chest pain, vasodilatation and chest pain. You can see that the primary symptom in those 19 patients was pretty much evenly distributed as the report.

Palpitations and dyspnea are clearly related. Anxiety probably had nothing to do with this at all.

DR. GILMAN: How long do these symptoms last usually?

DR. BEN-MAIMON: Anywhere from 15 to 20-30 minutes.

DR. GILMAN: How soon after injection do they come on?

DR. BEN-MAIMON: Almost immediately, some within minutes, but almost always within five minutes. Okay?

The incidence rates for the components of the systemic reactions for all patients participating in the multicenter trial are presented on this slide regardless of whether the patients experienced predefined systemic reactions.

What we did was we took the components and we went back to the overall database and looked at the incidence rates. Again, you see that the -- with the exception of anxiety, they are more common in the Copaxone-treated group.

There were a total of 87 patients with relapsing MS in the clinical programs. This includes all of the exposed patients now, not just the multicenter trial, who experienced at least one systemic reaction.

A total of 152 events were reported by these 87 patients over the dosing interval. None of these events

were life-threatening. Some were treated with antihistamines. But even those who were not treated, all were resolved without sequelae. A review of the demographics of the patients who reported systemic events, their medical histories, available ECG data, which is limited, data regarding vital signs, and other adverse events reported by these patients, did not identify anything unique about this population when compared to those patients who did not experience a systemic reaction. Some have hypothesized an intravascular injection may be the cause, but, again, there is no data to support that.

DR. GILMAN: Dr. Coyle?

DR. COYLE: Was there any relationship to where the injection was being given or to body mass, or perhaps to people who had more problems with skin reactions, and not just the systemic, but also the chest pain, which really you question if that is a subcomponent?

DR. BEN-MAIMON: We looked at the local injection site reactions as compared to the systemic reactions and there is no correlation. There are patients who have both, but it is a relatively common finding in the injection site reaction so you would expect that. But there really does not appear to be a correlation. We also looked at the severity of the injection site reactions for in patients who were more severe. There was nothing that we could find.

We also looked at the antibody profiles in the patients who were having systemic reactions versus those who had not. The antibody profiles do not differ. I can show you -- we have looked at conmeds that were taken by the patients with systemic reactions as compared to those who had not, and it is the same listing of most concomitant medications. We have looked at the demographics. So the answer to your question is no. We have not been able to find anything that is predictive of the population who would experience those.

DR. GILMAN: Dr. Katz, and then Dr. Drachman.

DR. KATZ: Yes. Could you talk a little bit about what the patients mean as far as you can tell by chest pain? That could cover a lot of ground. Just to play devil's advocate, how do you know that these events are not cardiac in origin, even the systemic reactions?

DR. BEN-MAIMON: Okay. Let me talk first -- some of the chest pain -- obviously, 26 percent of the patients reported chest pain in the Copaxone-treated group, but 10 percent of the patients on placebo also reported chest pain. So I think that needs to be taken into account.

Clearly, the verbatims include the real chest pain, but they also include some reports of costochondritis, and pain that went -- you know, sharp pain that clearly is not cardiac in nature.

DR. KATZ: So when you say reports of costochondritis, that is something that somebody diagnosed after a patient had a complaint of something.

DR. BEN-MAIMON: Right.

DR. KATZ: But what are those patients complaining of?

DR. BEN-MAIMON: Pain when you push on my chest, or when I take a deep breath it hurts me over here. Just things that are not typical of chest pain.

I think it is worthwhile to hear from Dr. Wolinsky if he can characterize the patients who have actually reported it. You may get a better feel for what the physicians are hearing as compared to what I am telling you.

DR. GILMAN: But a costochondritis that occurs with the injection?

DR. BEN-MAIMON: No, no, no, no. Again, I was speaking to the 26 percent overall incidence in the trial, not the 19 patients.

DR. GILMAN: Oh.

DR. BEN-MAIMON: The 19 patients clearly have something linking to this.

DR. WOLINSKY: I think that Dr. Johnson probably will want to describe this as well. But, in the patients who were in the trial at our center who reported chest pain that fit this, or discomfort that fit this syndrome, it

really was quite variable. Sometimes the patients would say I have injected myself. I felt anxious, I felt short of breath, I felt a constriction in my ability to breathe, had a hard time taking a deep breath. My spouse noticed that my face was flushed. In some cases, I felt like my heart was beating fast, but it then passed within 15 minutes or so.

I remember specifically one young man, I guess I am getting older, who called about five or six days after he had had this episode because his wife demanded that he talk to me about this. He said he had injected himself. He felt tightness in his chest. It just increased in intensity for about five or six minutes and then it went away. He did not recall having any of the other components of the reaction even though I questioned him for that. Because he was a male, and because he was young, even though this was five days before hand, I said, look, take yourself to your clinician and ask that he go over you for a cardiac examination, EKG, et cetera. He passed all of that with flying colors. Unfortunately, he has no further experiences like this.

One of my patients, who was on a different drug and then shifted to Copolymer under a treatment IND that I do not manage in Houston, called me after one of her injections. She was so frightened as to call 911 and get the ambulance emergency medical services out. She described

feeling, again, tightness, difficulty breathing, considerable anxiety, but then had to, as she said, almost battle the EMS personnel because by the time they got there it was over and she did not want to go into the emergency room.

DR. GILMAN: Dr. Katz?

DR. KATZ: Maybe you said this and I missed it. Of the chest pains that were not associated with this so-called systemic reaction, how many of those were seen immediately after the injection or were they sort of spontaneous, unrelated reports?

DR. BEN-MAIMON: They were spontaneous, unrelated reports.

DR. KATZ: Almost all of the ones that were not related to the systemic reaction?

DR. BEN-MAIMON: Yes. Almost all of these events.

DR. WOLINSKY: I think that one of the things that is perhaps worth mentioning is originally in the protocol we had the intention because we expected this reaction, given the experience with the previous work with Copolymer to have patients not injection themselves with the drug again until they have scheduled to come to each of the centers so that they could inject themselves with the drug under observation. Because patients did not do that, we

eventually amended the protocol so that we would, amongst other things, not have patients under-reporting for fear that they would have been scolded for doing what they were supposed to do.

DR. GILMAN: May I ask, how many of these patients had a subsequent similar event -- injected themselves once, had chest pain, shortness of breath, intense anxiety, and then experienced the same event?

DR. BEN-MAIMON: As you can see, of the 19 patients, 10 had only one event, four had two, three had three, and two had four. I can provide you with more information on actually what happened to those patients, how long they continued in the trials. I can tell you that only two patients discontinued at the time of the -- well, actually, one discontinued at the time of the first event, and one discontinued at the time of the second event. All other patients were reexposed.

DR. GILMAN: Dr. Leber.

DR. LEBER: This may speak somewhat to the etiology or mechanism. If you were to look at this in terms of the time to first onset after initiation of treatment, do you know the distribution of time? Is there a period in which there is no risk?

DR. BEN-MAIMON: No.

DR. LEBER: Can you get this on the first day of

treatment?

DR. BEN-MAIMON: I do not think we have had anybody yon the first day. Fortunately, those patients are monitored. So it would be nice. We could have gotten vital signs.

DR. LEBER: Is there a way to know what the shortest latency for the first event of this kind was? If it were very delayed, it would certainly pose that you would have to do some kind of preparation to reverse those effects, raising the antibody question.

DR. BEN-MAIMON: Okay. I want to answer Dr. Katz's question because I do have a little bit of information on some of the chest pains. I have a slide on time to systemic reactions in these patients.

DR. KATZ: I am less interested in the chest pains that we are seeing in association with the systemic --

DR. BEN-MAIMON: It is general.

DR. KATZ: Oh.

DR. BEN-MAIMON: Okay.

[Slide.]

DR. BEN-MAIMON: Try G54. This is the number.

[Slide.]

DR. BEN-MAIMON: Do you remember? G60. Sorry.

[Slide.]

DR. BEN-MAIMON: Here this may speak to it. Three

patients experienced the first event within the first three month, one greater than, and then you can see this speaks to the fact that it is pretty well dispersed throughout out.

DR. KATZ: This is the chest pain?

DR. BEN-MAIMON: No. These are patients with systemic reactions. I wanted to finish the systemic reactions, and then I thought we would move on to the chest pain.

DR. GILMAN: But those are only withdrawals.

DR. KATZ: Yes. What does that mean, this time interval to withdrawal?

DR. BEN-MAIMON: This is the duration of treatment for patients compared to the all --

DR. KATZ: I see.

DR. BEN-MAIMON: This is the time to -- there were four patients who withdrew due to systemic reactions -- sorry -- withdrew who had had systemic reactions. This is the time to which they withdrew. We also have the time to the event.

DR. GILMAN: But what about the ones who did not withdraw?

DR. BEN-MAIMON: They continued in the trial.

DR. GILMAN: Do you have similar data to the time to onset?

DR. BEN-MAIMON: Do you remember which one it is?

DR. LEBER: This is kind of coarse. If you have an interval of from zero to three months, it could all happen on the last day of the third month.

DR. BEN-MAIMON: G50.

[Slide.]

DR. LEBER: Do you know where they really are.

DR. BEN-MAIMON: G50.

[Slide.]

DR. GILMAN: This is also a very small subset.

DR. BEN-MAIMON: Yes. This tells you the time to the first episode, the days on therapy, the time of the first reaction, and then the days that these patients withdrew. Does that help you? Again, that may be more than what you wanted.

DR. GILMAN: Again --

DR. LEBER: That is a subset of everyone who has had a reaction. I was asking for everyone who has had a systemic reaction. What is the distribution of onset times for the first event?

DR. BEN-MAIMON: Okay. I do not think we have it on a slide.

DR. GILMAN: Do you have the information if not on a slide?

DR. BEN-MAIMON: Yes. We have looked at the distribution and it is pretty much evenly distributed. I

think that the doctors can speak to the fact that it is relatively unpredictable. We actually did an analysis to see whether we could do halter monitoring or at-home ECG monitoring. Based on the occurrence of these symptoms, and the sporadic nature of them, you needed a power, and you needed to monitor patients on a daily basis for every injection for something like six months.

DR. GILMAN: Yes. I understand the problem with predicting who is going to have an event, but let's get it straight. You have looked at all of the patients who had a so-called systemic event?

DR. BEN-MAIMON: The 87, correct.

DR. GILMAN: Okay. And those patients you said were more or less evenly distributed. Do you mean by that that most of them did not have their event until 30 or 40 days out from their beginning, which is what those patients you just showed seemed to have? Is that what you are saying?

DR. BEN-MAIMON: That is correct.

DR. LEBER: This is not a critical question. It may be that you do not have the information, so be it. It would seem that for every patient who had a systemic reaction, they had it on a given date, and they started treatment on a given date, so really you would just have to display those times.

DR. BEN-MAIMON: No, I do not have that. I have it for the patients who discontinued only.

DR. LEBER: A little history.

DR. GILMAN: Are the data available so that you might come up with them over the next hour or two? If you could do that, we would appreciate having that information.

DR. BEN-MAIMON: Okay.

DR. GILMAN: Okay, Dr. Drachman.

DR. DRACHMAN: There are two things. First of all, the notion that these might be panic episodes I am sure is one that you have thought of. Did you have any of the individuals breathe in a baggy, for example, the way one does with hyperventilation? Was that one of the modes that you used or candy? No?

DR. JOHNSON: No, Dr. Drachman. We did not try doing anything like that. There was obviously a substantial experience in rare patients with this reaction from previous trials. We had felt that it was benign right from the beginning. As the trial continued it became more obvious that it was benign. It was so rare and so unpredictable that it was very difficult for us to determine how we would even study it. But we did not actually ask patients to see if they were having an anxiety or try to reproduce an anxiety reaction.

DR. DRACHMAN: The other question. I believe you

said that following the injection the Copolymer disintegrates locally rather quickly. Do you know from your animal studies whether it always disintegrates this same way or whether it may give you a different subset of polypeptides one time or another? Do you know that from the --

DR. BEN-MAIMON: I do not think I have that answer.

DR. DRACHMAN: -- from the animal data?

DR. BEN-MAIMON: I do not think that we have an answer for that, whether they are the same series of polypeptides at every injection. Most of the data on the degradation comes from tissue monogenates. So I do not think we have the answer to that question.

DR. GILMAN: All right. Then let us proceed please.

DR. BEN-MAIMON: I actually did not answer Dr. Katz's question on chest pain.

DR. GILMAN: Yes.

DR. BEN-MAIMON: Again, it should be noted that ECGs were done at entry and at exit, and there were no changes over the long-term in EKGs. I acknowledge Dr. Katz's clear concern that chest pain may be cardiac and not evidence of a long-term change in EKG.

There were also no changes in vital signs noted.

Vital signs were obtained at every visit and, again, were compared and looked at for changes. The chest pain is G80.

DR. GILMAN: Well, of course, but you never captured an event to see whether blood pressure rose in fact or fell?

DR. BEN-MAIMON: That is correct. There was one patient who was seen by 911 and they did take vital signs, and the vital signs were stable.

DR. GILMAN: This was the woman that Dr. Wolinsky described? She was already well by the time --

DR. BEN-MAIMON: That is a problem. In a lot of these patients, the event is already resolved by the time 911 has gotten there. So it is shortly after the event, but it is not actually in the throes of the event.

We do have one more recent patient who was in the treatment IND who also called 911 and actually was transported to the hospital and had an EKG and a chest x-ray that were normal. But, again, it was 20 minutes after the onset, and I cannot speak to whether she was actually having chest pain at that time or it had resolved.

These are the patients, 33 patients on Copaxone versus 13 who had chest pain. Of those patients, 19 of those patients actually reported a systemic reaction. So it is interesting to note that those 19 do appear in the 33. Patients reporting chest pain as a component of a systemic

reaction were 14. Patients reporting chest pain who withdrew for any reason were six. So these patients dropped out and also reported chest pain; but three of the placebo patients who reported chest pain also dropped out. I am not really sure how enlightening this data is. It is what we have got basically. Okay?

DR. GILMAN: Okay.

DR. KATZ: Okay.

DR. GILMAN: Please proceed then.

[Slide.]

DR. BEN-MAIMON: There are two control trials supporting the effectiveness of Copaxone in patients with relapsing MS. In order to summarize, I would like to show the two studies side-by-side with regard to efficacy to better point out the similarities and the differences.

With regard to the frequency of relapses, this was the primary efficacy endpoint in the multicenter trial. As you can see the mean number of the phase III trial achieved after two years of dosing statistical significance based on various models shows a statistically-significant reduction in relapse rate.

In trial BR-1, a significant reduction was also obtained as is expressed here by the categorical analysis.

Other endpoints relating to relapse rate provide supportive evidence of the effectiveness of Copaxone in

reducing the frequency of relapses. This was the primary efficacy endpoint, as we discussed for the Bornstein study and achieved statistical significance in the publication cohort but not in the all-patient cohort. And, again, achieved trend showed just trend or numerical trends in favor of Copaxone, as did the median time to first relapse without statistical significance.

Changes in disability were assessed in several ways. Mean change in EDSS was evaluated in the multicenter trial, but not in trial BR1. You can see a statistical significance was achieved with regard to the repeated measures analysis.

A categorical analysis of change in EDSS and DSS was also performed. The distribution of patients between the three categories is statistically significant for those patients treated with Copaxone when compared to those treated with placebo, as evidenced here. This was supported by the results of Dr. Bornstein's study, which did not show statistical significance, but did demonstrate numerically similar trends.

Time to progression was statistically significant in trial BR1, however, only 25 percent of patients in either group met the criteria for progression in trial 9001. Therefore, we believe that Copaxone is effective in treating patients with relapsing MS, as demonstrated in two

well-controlled trials.

Copaxone has been tested in 857 patients with MS, 779 of whom had relapsing MS, and has been found to be safe and well-tolerated.

What I would like to do now is turn the floor over to Dr. Wolinsky for a clinical perspective on the use of Copaxone. As an investigator in the trial in the multicenter trial, and a participant in the ongoing open-label study, Dr. Wolinsky has extensive clinical experience with Copaxone in this population.

DR. GILMAN: Just before you do that can I just go back for a moment? I see in looking at my notes that there are a couple of questions that I had which were not answered.

DR. BEN-MAIMON: Okay.

DR. GILMAN: One was in both trials steroids were permitted. Can you tell us the frequency with which steroids were used, placebo, compared to treated patients who received drug, doses of steroids, methods of administration of steroids?

DR. BEN-MAIMON: If I can. May I have slide G52 please?

[Slide.]

DR. BEN-MAIMON: In Dr. Bornstein's study, in Trial BR1, you can see that the number of patients treated

with placebo was 10 versus 25 for Copaxone and 14 versus 25 in placebo. It is slightly different, but probably not that different.

This difference here probably relates to the higher number of relapses that these patients experienced, so, therefore, they had more treated relapses. Next.

[Slide.]

DR. BEN-MAIMON: Oops. Not that one, sorry. What is it? G68?

[Slide.]

DR. BEN-MAIMON: This shows that there were pretty much similar numbers of patients treated with steroids in the multicenter trial. We broke it down into oral and IV. You can see that there is a slightly lower dose for both -- lower number of days of treatment for the oral and the IV in the Copaxone group as compared to the placebo group, but it is not --

DR. GILMAN: Do we know the types of steroids used?

DR. BEN-MAIMON: Primarily methylprednisolone and prednisone, but for more than that I do not have my chart.

DR. GILMAN: Oral and IV?

DR. BEN-MAIMON: Yes.

DR. GILMAN: And duration? Did you talk about duration?

DR. BEN-MAIMON: No. The duration is pretty much similar between the two groups.

DR. GILMAN: You mentioned also that you used anti-inflammatory agents or combination steroids and anti-inflammatory agents, but I did not see very much in the way of a description of which agents you used and in which cohorts.

DR. BEN-MAIMON: Dr. Johnson?

DR. JOHNSON: The second trial, the 9001, in fact, we did not use anti-inflammatory agents. They were restricted, or they were not to be used.

DR. GILMAN: I see.

DR. JOHNSON: But it was almost impossible out of 251 patients were patients not to take Advil or Ibuprofen. Probably the most specific mistake or the most specific incident of breaking the protocol was using anti-inflammatory agents in the course of the 9002 trial. We repeatedly cautioned the investigators and the patients, but still found that they were using concomitant medications.

DR. GILMAN: So they at least did report these uses?

DR. JOHNSON: Yes.

DR. GILMAN: All right. We will go on to Dr. Wolinsky then.

Agenda Item: Medical Perspective

DR. WOLINSKY: Thank you. Before I highlight some of the medical management issues raised by the results of the Copolymer-1 trials that were just so ably demonstrated by Dr. Ben-Maimon, allow me to repaint the nature of the disease that I and my colleagues must battle.

Earlier, Dr. Johnson described, in general terms, the consequences of MS on disability and its impact upon the patients who must live with that disease. Sometimes it is easier to understand this in numbers.

Can I have the first slide?

[Slide.]

DR. WOLINSKY: First, in hard dollars, there are the tangible costs, which include personal services, home alterations, special equipment, and transportation, lost earnings, and disease-specific medical costs. These total just under $10 billion per year for all patients with MS in the United States. That breaks down to about $35,000 annually per patient. For those patients who have progressed and have the more severe forms of the disease, it is $50,000 per annum. It is a little bit less for those with relapsing disease.

Next slide.

[Slide.]

DR. WOLINSKY: If one thinks about days lost, 39

percent of all MS patients will have at least one day of restricted activity in the last two weeks. Sixteen percent of MS patients' activities were restricted for eight or more of the last 14 days. Twenty-seven percent of all MS patients spent at least one day bed-confined in the last two weeks. Ten percent spent most or all of the last year bed-confined.

The good news is that patients with MS who are still in the workplace do not lose anymore days than their healthy colleagues. Our role is to keep them there.

Next slide.

[Slide.]

DR. WOLINSKY: In terms of hospitalizations, nearly a quarter of all MS patients are hospitalized at least once a year. At the time that these data were prepared, about one in every 500 hospital stays was due to a patient admitted for MS.

Fifty percent of MS admissions are acute or urgent, that means that most are precipitated by relapses. The care, however, extends beyond hospitalization. About nine percent of patients when discharged from the hospital will still require home health care in order to function. Eight percent will go on to some form of intermediate care facility, and fully 10 percent are discharged to skilled nursing facilities where many of them will remain for the

rest of their lives. Thus, we certainly have a need for drugs that impact this disorder.

Next slide.

[Slide.]

DR. WOLINSKY: In two independent but mutually-supportive trials, Copolymer-1 has been shown to reduce the frequency of relapses and arguably slows the progression of disability.

The relapse finding is maintained across all levels of disability and, in fact, appeared perhaps to be more pronounced in those patients who were leased disabled at the time that they entered the trial.

The changes in the EDSS score from entry to exit suggest strongly that patients on Copolymer remain stable and, in fact, twice as many patients were measurably improved at the end of the study who were randomized to Copolymer than those who remained on placebo.

Next slide.

[Slide.]

DR. WOLINSKY: Neutralizing the antibodies. There is no evidence to date that daily treatment with Copaxone induces antibodies which inhibit its activity.

The clinical efficacy is maintained throughout the dosing period even though essentially all patients on Copolymer-1 within three months develop antibodies to this

compound.

Next slide.

[Slide.]

DR. WOLINSKY: In more than a thousand patient years of exposure, some cases lasting up to 10 years, this drug seems to be well-tolerated. There were fewer MS-related hospitalizations both in the larger pivotal trial and for those patients in Copaxone under all of the treatment programs.

There have been no known product-related laboratory abnormalities seen in over 800 patients studied across all studies.

The animal studies have shown no effect on phytotoxicity or teratogenicity.

Next slide.

[Slide.]

DR. WOLINSKY: More to the point, for a disease that disproportionately affects young women, it is of note that five women conceived during prolonged Copaxone treatment, despite our admonishments otherwise. Three of these elected to continue their pregnancies and all three delivered healthy babies who are still developing normally. There have been no abnormal electrocardiographic changes seen in the patients studied nor significant overall changes in vital signs.

Next slide.

[Slide.]

DR. WOLINSKY: The drug does not appear to be associated with depression, suicide, or with any flu-like symptoms, nor were there any drug-related seizures.

Next slide.

[Slide.]

DR. WOLINSKY: There are local site reactions. These are more commonly observed in the trials in patients on Copaxone. They include erythema, pain, inflammation, pruritus, and mass. But I can tell you, as an investigator participating in the trial, that these reactions are mild particularly in comparison to any other injectable medication.

Next slide.

[Slide.]

DR. WOLINSKY: Systemic reactions have been seen. They appear to be self-limited, and they occur in relationship to the subcutaneous injection of the drug. These have been defined as chest pain and/or vasodilatation with or without one of the following: Palpitations, probably anxiety, dyspnea, and at times diaphoresis.

Next slide.

[Slide.]

DR. WOLINSKY: They occur unpredictably in terms

of the duration of patients on therapy. The majority of patients who have reported one reaction have only experienced one. Resolution usually is within 15 minutes. The recognition of the timing, the pattern, and the duration of this syndrome should not lead to confusion with those more ominous processes that might independently occur in MS patients.

Next slide.

[Slide.]

DR. WOLINSKY: For those of us confronted everyday with patients with multiple sclerosis, Copolymer-1 represents a novel clinical option for our charge. This is a serious disorder with no prevention or cure, and for which alternative and multiple therapies are necessary. It is well-tolerated. This favors considerably compliance and the potential for maintaining long-term efficacy is clearly there. Thank you.

DR. GILMAN: Thank you, Dr. Wolinsky. Questions, Dr. Temple?

DR. TEMPLE: Dr. Wolinsky, you mentioned a whole bunch of serious consequences of having MS. You also intriguingly suggested that there were fewer hospitalizations for MS in these data. Were any of these other consequences measured? Time off work for disability, and all of the things that you talked about being bad could

have been measured in this trial. I just wondered if any were.

DR. WOLINSKY: I think I will turn this question back to Dr. Ben-Maimon. There were questionnaires which were collected regarding and essentially diaries for the patients that addressed issues of quality of life. I do not think that I can speak to the summation or the analysis of the data.

DR. TEMPLE: I meant things like hospitalization, need for long-term-care, the things you were talking about earlier.

DR. WOLINSKY: If you look at hospitalization, and if we look just in the larger of the two trials, and there is a slide specifically that speaks to this which is number 75 in the original set. It may have changed its number. Basically, it shows about a 40 percent reduction in hospitalizations specifically for MS in those patients on Copolymer versus those who were randomized to placebo. The proportions.

DR. BEN-MAIMON: G67.

DR. WOLINSKY: G67.

[Slide.]

DR. WOLINSKY: So that there were roughly equal, somewhat slightly lower proportion of patients on Copolymer who were admitted to hospital for any reason; very similar

proportions for those related for non-MS issues, and then a difference -- and I cannot calculate fast enough, but I think that is around 40 percent for those patients admitted to hospitals specifically for MS-related issues.

If one looks at the data, and this may be biased a little bit; but, if one looks at the data from all patients in the Copolymer program, compared to all patients who were followed as part of placebo groups across all trials, the reduction is about five-fold in favor of the drug.

DR. GILMAN: Dr. Drachman.

DR. DRACHMAN: I hope this is not an unfair question. But answer it as you choose. Given what is now available and given a patient with MS, where would this treatment fit in if it were approved? Would this be the first drug you would use? Would this be the second back-up drug, if someone had intolerable flu-like symptoms, and beta sera? What is your clinical judgement?

DR. WOLINSKY: Now, I am going to give you my personal judgment because I cannot speak for anyone on this issue except myself. For the patient who has been relatively recently diagnosed who has mild to modest disability, who will be concerned about side-effects, and who will be concerned about how long a drug that I start them on is likely to be effective, Copolymer is a very good first choice.

For a patient who is on one of the interferons and is having significant side-effects with one or another of the interferons, Copolymer becomes a reasonable drug to switch them to.

For a patient who has developed neutralizing antibodies at high titer and who I feel may have lost clinical efficacy being into their second or third year of treatment with one of the interferons, there is no choice available unless Copolymer is available.

DR. GILMAN: Dr. Leber?

DR. LEBER: I have a question and it relates to what he reduction in hospital rate means. What are the reasons for hospitalizing someone with MS that actually occurred in this database under both placebo and drug treatment? Was it exacerbation?

DR. WOLINSKY: I will turn to Dr. Ben-Maimon to speak to that directly. But, at our institution, hospitalizations were almost exclusively for attacks.

DR. LEBER: So it was basically a re-expression of the effect on frequency?

DR. WOLINSKY: In that sense, there is another way of showing a different form of the data.

DR. LEBER: It is just another way of expressing --

DR. WOLINSKY: Exactly.

DR. LEBER: -- what you would expect. So it is not something new. As a matter of fact, it does not really give you much more information about the importance except to the extent that this particular population that we have sampled happens to have a disease severe enough to cause them to be hospitalized with an exacerbation. That is all.

DR. WOLINSKY: It is a different way of measuring the other end point. Although it does take into account, given the changes that have been occurring in the medical industry over the course of which this study has been done, which attacks were most severe.

DR. LEBER: And maybe the duration of hospitalization. The reason I was getting at it was really a follow-up on what I think Dr. Temple was getting at, that, on the one hand, you lay out all of the truly terrible things that can befall someone with frequently exacerbating or remitting, or progressive MS. We set that out as the gain and then you have a treatment, which, on some measures, is "effective." Then you say, look, this is a treatment for that. The question really fairly answered, if you are setting out how terrible the disease is is how much of an impact you have really had on the disease. I think that that distinction is always critical because it is one thing to say we have an effect that we can measure and another thing to imply that you actually have an effect of such

magnitude and significance. I just want to know where we come out. I have a hard time knowing, even though all of the things you have iterated or enumerated are important, and everyone agrees, how big an impact this really has as distinct from whether or not you can show an effect. I think that is an important distinction for the committee.

DR. WOLINSKY: I think that is a very important distinction. Again, I am going to step out, if the committee allows me, from any role that I might be playing here to take it to a different level.

There are about 1,400 patients that I follow in my clinic in Houston, about 80 percent of them actively by our group. There has been not question that drugs which only affect the attack rate have made a tremendous difference in how often I am dealing with patients and how well they are faring. So just on that one issue, as a clinician, this is not a trivial endpoint.

DR. GILMAN: Well, I might comment though that when you do a multicenter trial, the frequency of hospitalization becomes a very difficult measure because various clinicians will hospitalize or not hospitalize depending upon their own individual judgment as to how severe an attack may be first. Second, there will be third-party carrier issues with respect to other hospitalization that will be paid or not be paid. That can

influence judgment of a clinician as well. I think it is not a wonderful marker. Of course, you do have a placebo group. Presumably you would have a placebo group in the same center with the same clinicians. All the same, there are major problems in that particular measure these days particularly.

Dr. Coyle?

DR. COYLE: The effect on the lapse rate was related to a certain extent on EDSS, in that the best effect was seen in the low EDSS, although it was covered across the board. I am wondering about other outcomes when you broke it down by entry EDSS, whether the benefit was maintained at the higher entry EDSS.

DR. BEN-MAIMON: So you want to see the outcomes by baseline EDSS?

DR. COYLE: Right.

DR. BEN-MAIMON: F19. Sorry, wait.

[Slide.]

PARTICIPANT: F52.

DR. BEN-MAIMON: Sorry, F52. Sorry.

[Slide.]

DR. BEN-MAIMON: Can you focus it? So here you see the baseline EDSS from zero to two, two to four, and greater than four. You can see that for Copaxone there still is a reduction in the number of relapses even at the

higher EDSS scores. Proportionally it is slightly higher at the lower EDSS scores. Does that answer your question?

DR. COYLE: Did you look at any of the other outcomes like the change in the EDSS, for example?

DR. BEN-MAIMON: The mean change?

DR. COYLE: Yes.

DR. BEN-MAIMON: No, we did not look at that by baseline EDSS. That is actually though adjusted for baseline EDSS as a covariate, so it should not be affected by baseline EDSS.

DR. GILMAN: Any other questions from the Committee?

[No response.]

DR. GILMAN: Then has the sponsor obtained data as yet with respect to time to onset of these serious reactions? Can we see those data? Systemic effect, sorry.

DR. BEN-MAIMON: What we are presenting is the mean and then you can see the ranges. You have to keep in mind that the trial is two years. This is time to the first event within the trial. You can see that they are pretty broad. Okay?

DR. GILMAN: Sorry. Wait a minute. This is 19 and four. That is the total in then?

DR. BEN-MAIMON: That is the total number of patients who had criteria based on our definition of

systemic reactions.

DR. GILMAN: I see. And this is only the first reaction?

DR. BEN-MAIMON: And it is only the first.

DR. GILMAN: You have not looked at the second, or third or fourth?

DR. BEN-MAIMON: That is correct. It is timed to the first reaction.

DR. LEBER: So there is no risk for three weeks?

DR. BEN-MAIMON: I am sorry. I cannot hear you.

DR. GILMAN: So it is broad?

DR. LEBER: No risk for three weeks.

DR. GILMAN: Yes. Right. So you are all right for three weeks. You cannot tell when it is going to happen though. All right. Thank you very much for doing that. I appreciate that. That is very clear. Are there any other questions from the committee?

DR. SNEAD: Yes.

DR. GILMAN: Yes, Dr. Snead?

DR. SNEAD: I have one question for the sponsor. In the neurology paper, there is mention of the potential benefit of using the interferons with Cop-1. Is there any animal data on that kind of combination?

DR. BEN-MAIMON: There is in vitro data, not animal data, suggesting that the mechanisms of action, since

they are different, or possibly different may actually be synergistic. But there is no animal data on safety that is available at this time.

DR. GILMAN: Dr. Arnon?

DR. ARNON: The interferon that is being used is human interferon. In any animal studies, we would have had to use the same species interferon and there it would not be the same interferon that is being used. So this actually prevented us from doing experiments that will really parallel the question that we are asking.

DR. GILMAN: Dr. Katz?

DR. KATZ: Yes. We have been talking about counts of relapses. Can you brief us on anything about the nature of the relapses that occur between treatment groups? Were they basically the same sorts?

DR. BEN-MAIMON: They were basically the same. We did look at severity, which clearly, even with regard to relapse speaks a little bit to what was already stated, the different centers and different physicians, and different patients qualify things as serious differently. But with the data that we had there was no difference between the groups.

DR. GILMAN: Ms. Phillips.

MS. PHILLIPS: Did you have an access program?

DR. BEN-MAIMON: What is an access program? A

compassion IND?

MS. PHILLIPS: Yes.

DR. BEN-MAIMON: Yes. We have one.

MS. PHILLIPS: Could you speak a little bit about that -- the number of people who are enrolled, how they were enrolled, if people withdrew and why?

DR. BEN-MAIMON: Yes. We have a treatment IND. It is run pretty much as an open-label study. We have approximately 80 centers currently open throughout the United States. There are to date about 600 patients in that trial. We, as an open-label study, we use the safety data but are really unable to obtain much in the way of efficacy data from it. But patients are screened every three months. They are seen every three months. They have vital signs obtained. They have neurologic exams, and they are evaluated for concomitant medications and adverse events. All of that data was included in the presentation that you saw.

MS. PHILLIPS: Was the 600 the maximum that you permitted?

DR. BEN-MAIMON: Actually no. There is no limited as to -- I think it is actually a thousand, or two thousand by the FDA regulation. But, again, patients have to sign an informed consent. Patients do have to return to the sites every three months. They have quite an extensive neurologic

exam and a battery of laboratories. That does often discourage patients from participating.

MS. PHILLIPS: So you feel that is why you did not reach your maximum?

DR. BEN-MAIMON: No. I think that we are still enrolling.

MS. PHILLIPS: Are you still enrolling?

DR. BEN-MAIMON: It is going up, and we may reach our maximum. It is just a matter of timing.

MS. PHILLIPS: Thank you.

DR. GILMAN: Well, it is 10 minutes of 1:00. I suggest an hour lunch break. We will see you back at 10 minutes of 2:00.

[Whereupon, at 12:53 p.m. the meeting was recessed for lunch, to reconvene at 1:53 p.m. this same day.]

A F T E R N O O N S E S S I O N [1:53 p.m.]

DR. GILMAN: Let us resume our discussions now. Let me start by complimenting the sponsor, and particularly Dr. Ben-Maimon. I thought that was a very clear, succinct presentation. I greatly appreciate having you answer the questions posed of your directly.

At this point, I would like to ask whether the sponsor has any other information that should be presented to us?

DR. BEN-MAIMON: Nothing more.

DR. GILMAN: Nothing further.

Now, does the FDA wish to make any commentary about the material we have heard thus far?

PARTICIPANT: None.

DR. GILMAN: All right. Then the Committee should open up its discussions then. Perhaps I should lead off and state --

PARTICIPANT: The FDA staff does not want to respond?

DR. GILMAN: The FDA staff does not wish to respond. The question was whether the FDA staff wishes to respond? The answer was no. They will answer questions, but they do not wish to make a statement at this point.

Agenda Item: Committee Discussion

DR. GILMAN: Let me try and provoke discussion

among the Committee by telling you my own personal reaction to this, and then we can have some discussion around the table with agreements or disagreements. From the material that I have personally reviewed and from the information provided us today, it strikes me that there have been two double-blind, placebo-control studies completed. Both of them showed that drug significantly reduces the frequency of relapses as compared with placebo. There are lots of concerns about the first trial because of the difficulty in identifying the total number of patients planned for originally, whether that was changed over time, difficulty of retrieving data. The second trial I think provides information that is much more clear. But it does appear that the two indicate that the number of relapses was reduced.

With respect to the question about slowing of disability, I personally had some problems with the conclusions there. My main problem was the demonstration that the placebo group showed in the first several months, three months I think it was, a worsening, whereas, the drug-treated group stayed essentially flat. Then we have heard some discussion about the quality of the EDSS. So I personally have some reservations about that secondary outcome measure. I am not entirely convinced myself that it showed effectiveness; but I am convinced by the data showing

a reduction in frequency of relapses.

With that then it seems to me the sponsor had demonstrated two well-performed trials, one very well-controlled, well-performed, and the second one moderately well-controlled and performed. The beneficial effect is significant according to the statistics. I would say that it is a mild effect, as I would view the results of this, but, nevertheless, an effect.

So that is pretty much a summary of how I see the data. I would like to see whether Committee members agree, disagree, want to debate these points or not.

Dr. Coyle?

DR. COYLE: Well, as the MS person on the Panel, I would totally agree.

DR. GILMAN: Good. Thank you. All right.

DR. COYLE: Any non-MS people on the Panel want to agree or disagree? Dr. Khachaturian, and Dr. Temple?

DR. KHACHATURIAN: Why were you more concerned with the worsening of the placebo at the beginning rather than the hump? Also, there was a hump at the end. If the disease has a certain cyclicity, it seems to me that there could be such oscillations in the system.

DR. GILMAN: That is certainly true. But why just for three months after the initiation of the trial? Obviously, that is happenstance or appears to be

happenstance. The sponsor did not have a good explanation for that. It just gives me concern because then the curves are essentially flat except at the very end, and then there was a difference. So I am not saying that it shows no effect with respect to progression of disability. But, if you coupled that with some concerns that Dr. Drachman expressed very nicely about the EDSS and how sensitive it is, then I guess that I am just not totally convinced.

Let's see. Dr. Temple, and then Dr. Kawas.

DR. TEMPLE: I just want to bring up one point to make sure that you consider it. The primary endpoint in the initial smaller study was complete absence of relapse. That is the one that is more statistically marginal, and that conceivably could be affected by what kind of adjustment you thought might be needed for the trip from 40 to 50. The relapse rate data is sufficiently robust that any adjustment you make would not matter.

One of the things we worry about sometimes is changes in the primary endpoint. I guess my own view in this case is that rate was unequivocally a secondary endpoint so that whatever adjustment you make probably would not make much difference about that. But I think that the Committee ought to pay attention to that. It was clearly the rate that was the thing the company set out to confirm in the larger study. I just want to flag that as something

that might be considered.

DR. GILMAN: Yes. I think that is good to point that out. I was taking that into account in my own comments about how I view these data.

Dr. Kawas?

DR. KAWAS: Primarily, Dr. Gilman, I agree completely with your comments at the beginning of this. I just wonder, if in terms of the initial jump that causes quite a bit of the effect, it looked to me like it happens again in the extension phase.

DR. GILMAN: Yes.

DR. KAWAS: To my mind, that lends a little more credibility to the data and reinforces the difference between the groups. It does not just happen in one stage and then completely stays flat. It looks like in the extension phase you get, once again, an increment.

DR. GILMAN: Well, that is true. I guess that one interpretation of that is that the drug-treated group may have shown that worsening, except that it received -- that group received drug, and perhaps drug prevented that from happening. That is one way to look at the data, but we do not know that.

Dr. Drachman?

DR. DRACHMAN: What we do not know about the second hump is what the end was. Remember there was a

decreasing end -- those who were -- that the end, the extension was zero to seven months. Is that right? Do I have it right? So that the end was decreasing. It is not the same population overall. It is those who entered later who were being observed. So I do not know what to make of that. But that is really more or less aside from the point.

I would agree with Dr. Gilman. We are always hoping that we are going to see a drug that is as good as penicillin was for pneumonia. That is not so much anymore, but was for pneumonia. It is always a little disappointing, in a way, when it turns out that we are dealing with small effects that may not be curative.

There are a number of remaining questions that I think are worthwhile underlying. One of them is -- and one of the ones that to my memory has sort of troubled Cop-1 from day one is the nature of the drug which, when we first heard about it many years ago, and you may remember that, Sid, as I do, is that no one could quite say what it was or what it turns out to be, and how it breaks down, or why it does what it does. The mechanism and theory of action make me a little more comfortable, but not totally because I do not know that that is fully shown or you know the precise nature of what it is that is doing the blocking. Nevertheless, that is where that started. There is a

holdover about a drug as heterogeneous treatment, which is as heterogeneous, and in which it does not fit the simple model of a single drug with a single action that we really understand. Nevertheless, that and the size of the benefit are two questions that remain. We are dealing with rather small benefits. We do not know, as you pointed out, whether the course is altered at all. It will be very valuable to know that, to know what the MRI changes are over time. So I think that that may modify the way in which we use the drug.

Now, that having been said, the drug is safe so that there is really no evidence at this point that it is something that we would worry a great deal about giving and where we might do more harm and violate our first principle of first, do no harm. So that is a very good feature.

Clearly, there is a need for a drug dealing with this disease. This drug seems to have, for all the weakness of the Kurtzke scale in picking up and identifying with a high reliability and precision, very small benefits. Yet, when you look at all of the data, they all point the same way. So fundamentally I agree with you. I wish I knew more about these other features.

DR. GILMAN: I did want to get to safety as a separate consideration here. Let's keep on. Dr. Leber and then Dr. Temple.

DR. LEBER: I was just going to ask Dave to

clarify how he concluded that the drug is safe. It is not that I am questioning your judgment. I wanted you to sort of explicate in more detail how you weighted the various phenomena that have been described and why you discounted them. I guess it is out of order now.

DR. GILMAN: Yes. Could we just hold that and let's just deal with efficacy at the moment? I would like to deal with safety as a separate discussion item, if you do not mind, Paul. Dr. Temple?

DR. TEMPLE: I just want to make sure I know what we are hearing. The bulk of the analyses that we did were focused on exacerbation rate, and that was the focus of the trials. There are little hints -- and there are analyses and measurements that relate to progression. That certainly has not been the primary focus. So you need to be quite clear on what you think has definitely been shown. The exacerbation rate data I think have been discussed sufficiently, and I think that we understand what we think about that.

The other -- if that is something that you think might have been shown here, that is very important because that would change what the labeling says. Are you suggesting that there is clear evidence, a little bit of evidence that needs to be confirmed or what on the effects on progression?

DR. GILMAN: Well, again, I am not compelled by the data I have seen to conclude that there is a significant, robust effect upon progression myself.

Dr. Kawas?

DR. KAWAS: Ditto.

DR. DRACHMAN: Same.

DR. GILMAN: Dr. Drachman also. But the effect on relapse is clearly significant and mild.

Yes, Dr. Gennings?

DR. GENNINGS: I guess what I would say on that is that I do not feel very comfortable about using the Bornstein study as showing a significant relapse proportion because I am sort of an intent-to-treat person, and I would tend to include those two patients that the original study excluded. Then that would not be significant. However, in the original study, the relapse rate was also significant, and that was reproduced in the 9001/9001E study.

So I would come down to say that the relapse rate seems to be an efficacious endpoint, but the proportion responding may not be different.

DR. GILMAN: Yes. I actually came to the meeting thinking pretty much the same because I also prefer to look at it in an intend-to-treat analysis.

When I heard Dr. Miller though comment about the rationale for excluding first one person after two months,

the second person I think after nine months I believe you said --

PARTICIPANT: Seven.

DR. GILMAN: Seven months -- thank you. I thought, well, that makes sense. I was a little more comfortable excluding those two patients. Again, this is a personal reaction to the data I heard.

Dr. Temple, and Dr. Khachaturian.

DR. TEMPLE: If you are going to leave the one who did not have the disease out, then you have got to count that person as having three episodes. I mean, it is really very conservative to both leave them out and count them as failure, and not count their putative episodes. That still will not get it to less than .05 even with the seven versus, but it is close.

DR. GILMAN: Well, I guess I am in the position of defending all of this. I do not know quite why. Yes, agreed. Yet there is a trend in favor of effectiveness for the drug with respect to relapse rate.

DR. TEMPLE: No, that is what I was saying.

DR. GILMAN: That is what you are saying?

DR. TEMPLE: I was saying that the intent-to-treat in the way it was described is over-conservative with respect to one of those because it both -- it says that a patient who had -- a placebo who had three nominal relapses,

should not be counted as having any relapses, should be counted as having a no-relapse person because we know the person did not have MS.

DR. GILMAN: Yes.

DR. TEMPLE: I guess I would say do not count them if you do not want to. Count the three relapses if you want to and then it is a placebo patient with relapses. But to do both is a bit much I would suggest.

DR. GILMAN: Okay. I agree with that.

Dr. Khachaturian?

DR. KHACHATURIAN: I would like to have the microscope turned around a little bit and look from the other end. We are talking quite a bit about the statistical significance and so on. I would like to hear from those who are treating MS patients to what extent this compound is going to have a significant effect on alleviating or making life better for these patient. Even if 10 percent of the patients of 300,000 are affected, that seems to me to be a beneficial effect given that nothing else is on the market. Shouldn't we be looking at it sort of from a wide-angle lens rather than narrowing on the small?

DR. GILMAN: Well, of course, there are two beta interferon agents.

DR. KHACHATURIAN: But we heard that this has some significant --

DR. GILMAN: They have side effects clearly.

DR. KHACHATURIAN: Could we have some discussion on the global merits of having something like this to the patient population?

DR. GILMAN: Well, does an MS person on the panel want to speak or shall we ask members from the sponsor's group? Dr. Coyle?

DR. COYLE: Well, I do not think that there is any doubt that cutting down clinical relapses which can be emotionally, socially, neurologically, medically debilitating to the patient, and you just do not have a patient, you have a whole structure, or a whole family of loved ones, et cetera, that that is a benefit. You really have not even addressed the other questions. We are seeing trends in the MRI data. My best bet would be that ultimately you will be able to show that if you cut the lapses you are affecting disability and you are really affecting the disease process. So it is clear in my mind that that is of benefit.

DR. GILMAN: Dr. Leber?

DR. LEBER: I examined -- in a way, I tried to make this point before. I think that it is the overall global question everyone wants to know is how much good I can do? The regulatory question may be somewhat narrower. Even though we appreciate the value of that question, the

issue before the Committee is is there more evidence from these trials that would allow you as experts to conclude that he drug will have the effect claimed for it? I think that is because that question is within reach. The other part of the question is very speculative. I mean, who is to know what value a drug will have before it is actually used? Then valuing the value is itself a very personal, private thing. I mean, one person's 10 percent difference is another person's trivial difference, but somebody else's very important difference. I think that is why we do not get into it.

The question that we want to learn from the Committee is, given what you know about the drug, given what you know about is panoply of risks, does this represent a treatment that can be represented as effective in use and safe for use? If you can tell us that, I think that is what we need to know. Sometimes we want you to flesh out why you decided that it is safe and effective. I think you have done that. I think that Dr. Temple has pointed out that, if you think this is frequency so far proven, case about progression in doubt, that is useful to us because it affects labeling. But you cannot get into these value questions.

DR. KHACHATURIAN: My question was really exactly in the context that you are putting it. I was saying is it

really worth quibbling about whether the significance is at the .18 or some other level?

DR. LEBER: That is a different question. It is a very different question.

DR. GILMAN: Yes. Very good. Dr. Temple?

DR. TEMPLE: We would say it is because significance levels are how you determine whether what you see is true, as opposed to sort of nice work if you can get it.

DR. GILMAN: Yes.

DR. TEMPLE: I guess that the only other thing I would say is that we do expect that, as you consider whether the benefits outweigh the risks, that you make some judgment that the benefit is tangible and not ridiculous. I am not suggesting that it is. I think that everybody would assume that an impact on exacerbation rate that is measurable is probably not ridiculous. But we are not -- I guess I do not feel completely indifferent to the value of what has been shown, although, it turns out, as Paul says, that it is so hard to get into those value judgments, and we do not really measure exactly the size of the effects either or the impact very well. But I guess I wanted to slightly say that we are not totally indifferent to that. I think that the whole discussion conveys what you think of the value of the benefits that have been assessed.

DR. GILMAN: Thank you. Dr. Drachman, you want to comment still?

DR. DRACHMAN: Well, I think you have largely made the point that not only do we decide whether there really is an effect, but whether it is clinically detectable by the patient that is of any use. The degree of use is what I think we do not really measure.

Were there some effect that was measured only by a blood test that had no concomitant, then we might say, well, you know, so what. Here is one that is clearly detectable, first of all, by virtue of the fact that, in order to know whether or not there was an exacerbation, this has to be brought to the attention of the examiner. So we already know that. So that would be the modification of your comment. Is that fair?

DR. LEBER: I am not sure that I -- I mean, part of this is very philosophical. But I think you are talking about the value of the outcome measure. Does it measure something real and valid? If you are talking about an exacerbation, everyone agrees that an exacerbation is a clinical event to be avoided. So, if you do one in a thousand that is good. That is not the question beyond that, but we would not go beyond that question. Someone might say, well, one per thousand for this cost is not worth it. We do not want that. We want to know whether the

outcome space you are looking at to measure the quality of the drug is a valid one. Once you have decided that, and once you have decided that it is not due to chance, fraud, or bias, that these are trials that support this can change the exacerbation rate, that is critical to us. If it can do it in one person, good. If it can do it in everyone, much, much better. We are in that, I sense, indifferent. It is not our job to call that. That is a social value judgment which I like to say my bartender and I have equal votes on.

[Laughter.]

DR. GILMAN: Other commentary about this point?

[No response.]

DR. GILMAN: Nevra Shinian, are you in the audience? Nevra Shinian? If you are, please go to the reception desk of the FDA. There is an important message for you.

Let's go next to the issue of safety. I am not entirely sanguine about what I have heard. It is true that a very large number of patients have been studied. We have a reaction in some of these patients, not well described largely because, even though it has been described very nicely verbally by patients and transmitted to us secondhand by the physicians, the nature of it is still not entirely clear. It is a pity that we do not have EKGs during event. I understand the problem in capturing those events clearly.

That is problematic. But I am mostly troubled by that one patient, the 46 year-old man who died in-hospital with the attendant events and uncertainty about what really happened to that individual. I appreciate that may have absolutely nothing to do with the drug. It sounds as if one of those patients, the paraplegic woman, had a pulmonary embolism. That can happen to anybody who is immobilized because of paraplegia. The same kind of comment pertains to the person with pneumonia. As we look through those data, both written and the presented material, I cannot see any particular sequence of events that sounds as if this is a dangerous agent. I guess that my difficulty stems from uncertainty about what these systemic reactions really consist of. I entirely agree that they sound benign, and they are pretty rare. Pathogenesis is uncertain. The causative factors, why some people had only one event, why they did not occur until three weeks out, and then occurred at almost any time random. It is unclear whether more than that will occur in a particular individual over five years or 10 years and what that significance will be. They are troubling -- not enormously troubling, but somewhat troubling as I heard this data presented.

The other concern was that raised by the FDA, and that has to do with long-term effects in experimental animals. While we do not have any positive information

indicating that there is something to be worried about, still, the regulatory request was not complied with, and so that gives me a little bit of pause only.

Then there is the question about immune complex deposition. It sounds as if that is not of major concern. Again, as I indicated earlier, I do have the problem of people with multiple sclerosis who may be paraplegic, who have neurogenic bladders that do not empty well, who are prey to infection that may involve kidney function, and then are going to further do injury to kidney function because of an agent that deposits immune complexes. Other information we heard assuages my concern a great deal.

So I just have those three minor problems, I guess, with the safety of this agent.

Let me hear if my colleagues feel similarly or feel that I am being overly conservative. What do you think. Dr. Coyle?

DR. COYLE: I do not know, as I hear it, I mean, this systemic reaction is very peculiar. We would like to know what is going on in the chest pain. It is a little bit bothersome in a much higher proportion. Yet there has not been a single case of morbidity that is really documented attributable despite almost a thousand patients having been tested. So that really reassures me somewhat that although these are puzzling reactions, and you would really like to

figure out what is going on and hopefully that will be discovered, it does not seem to be associated with any sort of significant morbidity risk.

The other thing is that really, it would seem to me that this agent is going to be touted primarily in ambulatory relapsing and particularly early on in the mildly disabled. Perhaps this is a real treatment for the so-called benign MS. I am not really sure if there is an advantage documented to using it in the very severe bed-ridden quadra/paraplegic MS patient. I do not know that that is a population that would really be used very widely in.

DR. GILMAN: Thank you. Dr. Drachman, you and Dr. Leber had some interaction about this issue. Dr. Leber was asking how you arrived at the notion that it is a safe agent. I wonder if you would mind going back to that issue.

DR. DRACHMAN: Really rather similarly to the way Dr. Coyle did. I am impressed no so much by the rarity of the event, but rather by its frequency. Now, that may seem a little paradoxical, but there were 38 or some odd events that did occur and, as you said, without either any measurably change in any of the usual things that we measure or without any directly-related untoward consequence, meaning that it is not as if the sword of Damocles is hanging waiting to fall. You have already seen that number

of attacks.

Yes, certainly not everyone gets the attack, but even when they do there do not seem to be any documented changes that are either measurable by the tests we do or that have subsequent effects.

DR. GILMAN: Dr. Leber.

DR. LEBER: I am just going to draw this point out because I think that it is useful when we make our final decision that we are very clear on what the limits of what we are talking about are.

First, the word rare conveys whatever anyone using it wants it to mean. But, if something occurs in 15 percent of the patient population, I would say, for public health purpose, it is not rare. I think that everyone now can debate that. That would be my judgement. I can imagine of it were 15 percent with something serious, the public health burden would be tremendous.

The second question I think is very much the point you made. You had a few realizations of this episode. But 39, or 20, or even 100 of an example of something does not really tell you with great reassurance from a public health perspective what the natural history of that phenomenon are.

Let's say for a moment that these episodes, whatever they may be -- and I have no idea even if they are coherently defined -- they have sort of said, well, this is

a syndrome. Maybe it is and maybe it is not. Whatever they are, having looked at a handful of them, it does not really tell you from the public health perspective how risky it is.

I just want to elevate this issue of doubt. It is not that you have not had safe passage so far. But the level of assurance that you can gain from safe passage in 39 is not ghat great. If you use the rule of three you could still take one-third of them or one-tenth -- ten percent of people with this reaction could still -- five percent of the time are saying very terrible happened to them and just throw that out. Because I think you should realize that we take reassurance from small sets of safe passage. There is doubt left.

DR. DRACHMAN: The way I would view it is that in the course of this study one of the investigators and one of the members of the advisory team died of unrelated events, as compared with none of the 38 -- none of the people with the 38 attacks.

[Laughter.]

DR. DRACHMAN: The risk level is therefore, as I can point out to you, less than one per thousand years of exposure.

DR. GILMAN: Well, the risk is not running the study.

[Laughter.]

DR. DRACHMAN: Right.

DR. TEMPLE: That is a completely unprecedented analysis. We have never heard that one.

[Laughter.]

DR. GILMAN: All right. Dr. Kawas?

DR. KAWAS: Just to add to both sides of the equation. I essentially feel that the drug looks safe from the standpoint of most of the things that matter most, and that includes at least with the relatively short interval of watching mortality does not appear to be in excess.

However, despite that I have some agreement -- I feel I agree with Dr. Leber in that these complaints are referable to the chest, I mean, to the heart, and they have pulmonary and cardiac components to them. The natural outcome of them in this limited sample was a benign one. I do have some concerns about the events and the potential in the long run for them making the drug a little less safe than we currently appreciate.

DR. GILMAN: Are there other comments from the committee about safety? Yes, Dr. Snead?

DR. SNEAD: Only that I share you concern about the absence of long-term carcinogenic studies available now.

DR. LEBER: Can we find out what that means? I mean, having a concern is one thing, acting on it is another. Do you think that that was enough to impact upon

the approvability of the drug?

DR. SNEAD: No, but it makes me less comfortable in voting for approvability than I otherwise would feel.

DR. GILMAN: Okay. All right. Any further discussion by the Panel?

[No response.]

DR. GILMAN: All right. Dr. Temple, yes?

DR. TEMPLE: Well, just as part of it, we had some discussion, as Russ said, about whether the application should be filed without those data. At least part of my reason for thinking that it could be and that this represented a judgment that we should ask the Committee to make is that you are talking about something that is basically amino acids once you get down to it. Not that you ever know things without studying, and we are all empiricists here; but, as a candidate for being a tumorgen, it is not as high as some other things. All of our empiricists will shake their heads and accuse me of not being empirical enough. But I still think that, as molecules go, you are somewhat less worried about amino acids than you are about other things.

DR. GILMAN: Dr. Leber.

DR. LEBER: Let me point out that this has got a window of internal flavor. If you are a theoretician and you want to make up stories, you could argue that this drug

really is not just amino acids. If it were, it would not be effective. It is doing something to immune tolerance and/or activation. We do not know what. What prevails against tumors? The immune system. Modify the immune system and I can come up with a long tale that would suggest this potential risk. That is the problem with this. Anybody who is marginal clever can make up anything they want.

DR. TEMPLE: That is why you need to do the studies eventually.

DR. GILMAN: Yes. But the key question is does this modify the Committee's view with respect to approvability? I think that the answer to that will have to lie with each Committee member.

DR. GENNINGS: But that is given with the qualification when the results come back and showing something bad that things could be change. We cannot approve things that --

DR. GILMAN: If we decide to determine today whether we wish to recommend approval, then that is our action today. If an adverse outcome from those animal studies occurs in the future, then the FDA will have to make its decision about how to interpret that and what to do about it.

DR. TEMPLE: Let's just be clear on the legal status. There is a specific provision in the law that says

that, if any of the things you have to decide that led you to grant approval no longer are true based on new information. You can reverse that rule. You can reverse that decision. There is no doubt about it.

DR. GILMAN: Depending on what it shows, how convincing it is, whether it is unconvincing.

DR. TEMPLE: If you get information that makes you think the drug is no longer safe, then you can act against the drug too --

DR. GILMAN: Yes.

DR. TEMPLE: -- and not approve it anymore.

DR. GILMAN: A question then. Would it come back to this Committee?

DR. TEMPLE: Sure, probably.

DR. LEBER: Unless it was so clear-cut that we felt it was a public health emergency and did not have time to come back to it. But short of that, sure.

DR. GILMAN: Yes.

All right. Any other concerns from the Committee or discussion points?

[No response.]

Agenda Item: Open Public Hearing

DR. GILMAN: All right. We have had some requests to hear from some seven people who wish to speak before us. This is an open hearing as you know. I urge you to be brief

please. Many of us are neurological clinicians who care for multiple sclerosis patients ourselves and are aware of the devastating consequences of the disease in some people. So please be brief. People whom I would like to welcome are Donna DiCarlo first. Please use the microphone. There is a microphone right here if you would like to go there. Either one is fine.

MS. DiCARLO: My name is Donna DiCarlo, and I live in Maryland. I am here as a representative of the National Multiple Sclerosis Society. A third of a million people with MS are benefitting from the surge of clinical trials on their way both in the United States and around the world.

I was diagnosed with MS in 1987 at the age of 28. I had just moved with my husband, Mark, to Maryland from Buffalo, New York. I was working with an accounting firm for a small business. At first my fingertips went numb, and then my hand, and finally the entire right side of my body. To continue to write and keep working I had to hold my left hand over might right hand to push my pen. Then, as suddenly as my symptoms came they went away. I changed jobs, and had my first child, Vincent, now age seven.

I experienced an MS attack not long after his birth and decided that it would be better if I could find a way to work at home so I got a license as a day care provider. I was fine for a while and my MS symptoms

disappeared. Then about three months after the birth of my daughter, Morissa, in June of 1991, I had the big one. Though this attack started like the others, with the numbness and tingling, one morning I woke up and I could not walk. I was terrified. My mom flew from Buffalo to help me with the kids but I could not even hold my three-month old daughter.

Then I learned about the double-blind clinical trial study for Copolymer-1 that my doctor was undertaking at the University of Maryland and the opportunity I had to participate. I had to admit that I had mixed emotions. I had no way of knowing whether I was going to get the real medication or not, or whether it would help me. I decided, if I was ever going to be able to arrest or cure this devastating disease, MS, people like myself had to take a proactive stand.

On January 30th, 1992, I took my first injection, and I am still injecting myself everyday. When the Copolymer-1 trial was unblinded several years later, I learned that I was actually on the medication. Though I would rather not need to take an injection everyday and I know that this certainly is not a cure for my MS, I am now back at work full-time, as an accounting manager for a printing graphic design company and have not had a serious MS episode in four years. For the first time in my life I

am filled with excitement and hope about the explosion in MS research which promises to slow the progression of my disease and perhaps even restore neurological function. Therefore, if the panel finds that the data supports the Copaxone study findings and recommends this medication for FDA approval, I implore the FDA, on behalf of all Americans who wrestle daily with the effects of this lifelong disease and to approve it quickly so that people like myself and those who will be diagnosed today and tomorrow will have new treatment options before they get any worse.

I would also like to ask -- the side effects that you were mentioning about the chest pains and --

DR. GILMAN: Flushing.

MS. DiCARLO: -- the palpitations, the flushings. I have experienced those side effects. So, if you have any questions or want any information on it --

DR. GILMAN: Thank you very much, Ms. DiCarlo.

MS. DiCARLO: Thank you.

DR. GILMAN: Next, Brian Bowersox.

MR. BOWERSOX: Good afternoon, ladies and gentlemen. My name is Brian Bowersox. I live in Westminster, Maryland. I am here representing the National Multiple Sclerosis Society and the more than one million individuals that it serves annually. There are certain dates that indelibly etched in each of our minds. For me it

was March 5th, 1988, when I was first formally diagnosed with MS. At the time I was about to graduate from the University of Baltimore School of Law and had my eye on a position with the Carroll County Government where I live. I also had a new wife. We had just been married the prior June, and I was in total control of my life.

During the four years that followed, while I built my career as an Assistant County Attorney with the Carroll County Government, and my life as husband and father of two young sons, I experienced an increasing number of unpredictable, disturbing, and debilitating MS effects. I saw the control over my life start to slip.

In 1991, thanks to my brother, who fashions himself a doctor, but he is really a dentist in the U.S. Navy, he brought to my attention the study taking place at the University of Maryland with Copolymer-1.

As someone who has played sports for most of his life, there was no offensive position I could take on this particular disease. The only thing I could do was step back and take a defensive position and react with steroids, or whatever treatment was available. There was nothing I could do myself to try to lessen the number of attacks. So I applied to get into the program. Fortunately, I was accepted. Even more fortunately, when the study was ultimately unblinded, I learned that I had been on the

medication all along.

Since 1991, I had not had a serious MS exacerbation. I have moved, with a colleague of mine, from my job with the county to establish my own private law practice and I have also become the father to a third child. My wife and I now have a beautiful daughter named Jenny who was conceived and born while I was on this particular drug.

With every new option obtained through advances in medical research, a measure of control has returned to my life and the lives of each and every person with MS. Each day that a person with MS misses access to a promising treatment is a date wasted that can never be recovered. Therefore, if the panel finds that the data presented supports the reported claims that Copolymer-1 can indeed reduce the number of acute attacks that hundreds of thousands of people like myself experience daily and perhaps improve neurologic function, I urge the FDA to expedite the approval of this product.

Now, that having been said, I will inform the Committee that I too was on the drug during the term of this study and that I had two episodes of chest tightening and pain in the back of my head and in my back. If anybody has any questions and wants to hear from somebody with firsthand knowledge of those incidents, I would be glad to answer any questions. If you have no questions, I thank you very much.

DR. GILMAN: Thank you, Mr. Bowersox.

Next, Elizabeth Dumbell.

MS. DUMBELL: Thank you for allowing me to speak with you today. I have multiple sclerosis. My name is Elizabeth Dumbell. I live in Charlotte, North Carolina. I work as a freelance writer and photographer. I work for nonprofit organizations because that is where my heart is.

There are well over a quarter of a million people like me walking around everyday trying to live their lives with MS, trying to live normal lives, as normal as they can be with MS. Not many of those people called you up today to see if they could talk to you, but I did, and I want to tell you why. I found out that I had MS in 1991. I was 34 years-old. I probably had the disease since the early 1980s. At first, I had on exacerbation every three years that mostly affected my eyes, a frightening thing for a photographer. Soon I was having on exacerbation every year. Then I had three exacerbations in four months. Before I had recovered completely from the attacks, at that point I began to accumulate disability on my eyes and one of my hands.

In January 1994, I went on Cop-1 under the FDA Treatment IND Program. I thank you for that program. It has made a tremendous difference in my life. The first year I was on Cop-1 I had one exacerbation. The second year I had one exacerbation. This year I have had zero -- zero.

What that means to me is that I can make photographs of children because I can see. It means that I can walk the campus of the treatment facility for abused children that my heart belongs to. It means that I can earn a living.

Other treatments for MS are available. The people I know on Betaseron have suffered side effects that make some of them stop the drug. Others who have stayed on it suffer. For me and for others I have talked to Cop-1 has had none of those effects.

People with MS are already giving everything they have to try to keep up with everybody else. The treatment for our disease is great. But treatment that has crippling side effects for some people ironically seems to me like it could hurt as much as it helps.

Cop-1 has no side effects that I have experienced or heard about. When I first started on the drug the injections hurt. That lasted a few months. Now it is only a matter of sticking a needle into my leg or my stomach everyday. I have gotten used to it. It is a regular part of my day, and it is something that I am happy to do given the benefits I receive from the drug.

Cop-1 has not only delayed the progression of my disease, but it has given me fewer and milder exacerbations which is what it is supposed to do and does do. What it has also done which it is not advertised to do, but surely has

done for me is make me feel better, less fatigued, less loss of balance, fewer days walking with a cane. I am better today than I was in January 1994.

Before I went on this drug I was on a downhill slide. My disease was getting worse every year. Today I work, I play, I contribute to the community I live in. That is what we all should have a chance to do. That is why I asked for the opportunity to talk to you today.

MS is a terrible disease and I am afraid of it. Cop-1 has given me a chance against it that I did not think I would get. Instead of an exacerbation now I get pins and needles in my feet and ankles. Instead of an exacerbation now I get a crawly feeling between my big toe and the one next to it. That was now where I was headed before I went on Cop-1.

I understand that as this disease progresses people, I can adjust. I may not be able to make photographs of children, but I can find a way to write to get whatever talents I have been given out into the world. What I am saying to you today is this. I hope you will help. I hope we will get every opportunity to fight against this disease. There are hundreds of thousands of people like me out there and we are scared. Please give us every chance you can.

Betaseron and Avenex, as I understand them, work in a different manner than Cop-1 does. It is good. It is

great. There are drugs now to slow the progression of the disease, but Cop-1 is a different approach, a new approach, an approach that I can swear to you today is working for me and without any side effects that keep me from my life. It is a chance that we all deserve. Please give us every chance you can.

Again, thanks for the opportunity to speak to you.

DR. GILMAN: Thank you, Ms. Dumbell.

Next, Maria Hardin.

MS. HARDIN: My name is Maria Hardin. I am Vice President of Patient Assistance Programs for the National Organization for Rare Disorders, also known as NORD. We are a patient group, and we advocate for people with rare disorders, including MS. I am here today to share with you NORD's experiences in administering the Copaxone Patient Assistance Program under the treatment IND for the past three years.

I want to say very clearly that the sponsor did not ask me to come; however, I feel very strongly that you need to know how important this drug is to the people with multiple sclerosis whom we have been able to help and the urgency of the FDA approval so that their insurance will begin reimbursing them for the cost of the drug.

The scenario I wish to present today is this. A drug was developed by a small pharmaceutical company to help

individuals suffering from MS. Under treatment IND regulations, they could charge for production costs. However, TEVA Lemongate was well aware that even if individuals wanted to try Copaxone their insurance would not cover the cost while it was in the experimental stage. In addition, many MS patients had no insurance of financial means to afford any drug. TEVA Lemongate set aside a generous amount of Copaxone to be given to the truly needy. NORD's role was to determine which medically-qualified patients deserved free Copaxone.

It was during this time that we began to hear patients praising the benefits of this drug and how it had restored their ability to function. Many had taken Betaseron or Avenex, received no benefit, and or experienced intolerable side effects. Copaxone is different. People take it and they feel better. Some feel so great that they resume a normal lifestyle. Some even wrote to tell us that they overdid it and actually ignored the fact that they had a chronic neurological condition. The testimonies, although anecdotal, give us pride that we had been involved with this drug and that NORD has been able to help people who would not otherwise have access because they could not afford it.

We urge this Committee to recommend approval of Copaxone because it gives another option to MS patients who cannot tolerate beta interferons. The company cannot be

expected to give the drug away for free indefinitely. So FDA approval is imperative for the sake of insurance reimbursement.

It is NORD's understanding that TEVA Marian plans to continue its charitable efforts by providing free drug to uninsured patients who cannot afford it after Copaxone is approved for marketing. At that time, insured patients will have unlimited access to the drug and TEVA Marian will know that many years of effort they have put in to developing Copolymer-1 was worth the massive effort.

Like any orphan drug, they could have given up a long time ago, considering the technical, financial, and scientific difficulties they faced. But their reward has been the letters and the phone calls from the grateful MS patients across the country who have experienced remarkable control and even remission of symptoms without the side effects of other available therapies.

Thank you very much.

DR. GILMAN: Thank you very much, Ms. Hardin.

Next, Anita Gowan was going to speak, but had to leave. She has left a note. I will just paraphrase it briefly. She states that she has relapsing/remitting multiple sclerosis which she has had for 10 years. In the last year she has been on Cop-1 and she considers the medication to be very helpful to her. She does urge that we

approve the medication.

Next is Kathleen Andes.

MS. ANDES: Hi. I want to thank everybody for allowing me to speak. I found out about this meeting about a day ago, so I am kind of here not representing anybody except myself. I have nothing really prepared except that the more I heard this morning about the Betaseron versus the Copolymer, I am an expert. I was on Betaseron. I gave it a year and a half of my life, and a year and a half of agony. But I did not want to go off of it because at that time my insurance would not cover Copolymer. It would cover the Betaseron 100 percent. Even though the Copolymer would be less expensive to the insurance company, they still refused to cover it. I finally had to take myself off of it. It got to the point that it was not the MS causing my inability to walk, but it was because of the Betaseron. Fortunately, my husband's company changed insurance companies, and they have agreed to cover the Copolymer. I have been on it for about a year. We are still fighting the amount of coverage at this point. So that is still in process. But they will pay part of it at least.

I was a ballet dancer when I was struck with MS and had to quit that career which I had spent approximately 20 years of my life preparing for. With MS I slowly progressed with the exacerbations and all, and remissions,

and was not really able to participate physically in too much of anything. I was also an amateur musician. The game plan was to be a musician after my dancing career was over. That game plan also went right out of the window. I am now back to playing my violin and swimming and that is with the Copolymer. So that is one of I think just a miracle to me that I could go back to something that I had not been able to do for many, many years.

I guess the other thing are the side effects of the Copolymer. As I said, the Betaseron was just a nightmare. But, again, as an MS patient, there is nothing else out there. So you struggle and you try as hard as you can to stay on it. But when the cure becomes worse than the disease so to speak you have to go off.

For four months I had no other choice of any other medication. In that time I had several exacerbations. Since I have been on the Copolymer for one year, like I said, I feel like a brand new person. I am even thinking of taking a ballet class or two. I just want to thank you and hope you can approve this for us. Thank you.

DR. GILMAN: Thank you, Ms. Andes.

The final person requesting a hearing is Jan Sedlak, who has submitted a written testimony rather than appear here. I will just paraphrase to say that she is 45 years-old and has had her disease for four years. It

began with paraparesis to the point that she could not use her legs at all. She entered treatment with Copolymer-1 and she said that she is now able to carry out a full range of activities. She is essentially free of neurologic symptoms and has been for the last three years.

Is there anybody else in the audience who wishes to be heard?

[No response.]

DR. GILMAN: Again, does the sponsor wish to make any final statement about the issues presented before us?

[No response.]

DR. GILMAN: Does the FDA wish to make any statements?

[No response.]

Agenda Item: Committee Recommendations

DR. GILMAN: All right. Then it is time for the Committee to vote on this agent. Again, to provoke discussion, let me lead off. I feel convinced that the data we have heard today provides two well-controlled, double-blind studies indicating that the medication reduces the frequency of relapses. I have heard information suggesting that it is a safe drug, at least there is not enough information concerning these various untoward effects that we have discussed today to lead me not to vote approval. So I will start by saying that I will vote to

approve the drug. I would like to hear whether others wish to discuss their vote before we call for a vote.

Dr. Gennings?

DR. GENNINGS: I guess I just have one question about when you say something is efficacious, you just now said that you were defining that based on the relapse rate.

DR. GILMAN: Yes.

DR. GENNINGS: And this is not going to say anything about progression of the disease?

DR. GILMAN: Correct.

DR. GENNINGS: Is that correct?

DR. GILMAN: That is exactly right, yes. I should have maybe said that. I am convinced, as I said before, that I have seen data suggesting that it reduces the frequency of relapses and I am not convinced by the data suggesting that it slows progression of disability, yes. Are there other comments or points of view?

All right, Dr. Khachaturian?

DR. KHACHATURIAN: I second the motion.

[The motion was duly seconded.]

DR. GILMAN: Okay. Second the motion. Thank you. Okay. Since we are following Robert's Rules of Orders.

All in favor, please signify.

[Show of hands.]

DR. GILMAN: Opposed. Dr. Coyle?

DR. COYLE: I cannot vote.

DR. GILMAN: Are you abstaining? You cannot vote. I see. Okay. Then it is unanimous among those who can vote.

[The motion was approved unanimously.]

DR. GILMAN: Does the FDA want to ask any question of the Committee before we have some closing remarks?

DR. GENNINGS: Is that safety and efficacy?

DR. GILMAN: We have voted on approval combined for the two combined. That is our vote. I hope that is all right with you now. You did vote.

DR. GENNINGS: I did vote. I thought we were just voting about efficacy. There are a few questions here.

DR. LEBER: You can divide the question.

DR. GILMAN: We usually vote for safety and efficacy simultaneously.

DR. KATZ: There were two questions.

DR. LEBER: One thing to find out is whether anyone wants to say no to safety and yes to efficacy. If nobody wants to do that, I think the vote will stand.

DR. GILMAN: Yes.

DR. LEBER: If somebody does, we will revise it.

DR. GILMAN: I think that is a reasonable position. Does anybody wish to vote no for safety?

DR. TEMPLE: Or express reservations. I mean, we

go by what is said as much as by what the vote is. If anybody wants to communicate something, communicate it.

DR. GENNINGS: I honestly feel at a loss because I am not a physician. I guess I am reflecting some of the concern here about the safety. I actually feel better after hearing some of the actual patients stand up and say that I had these things happen and I still like the drugs. I am more reserved about the safety end of this than the efficacy end of the device right now.

DR. GILMAN: Well, if that is the case, let me go back again. Maybe we should take separate votes.

All in favor of approval with respect to efficacy signify by raising your hands now.

[There was a show of hands and the motion was approved unanimously.]

DR. GILMAN: That is unanimous. All right.

Let me see a show of hands on those who feel that it should be approved based upon the information concerning safety that we have heard.

[Show of hands.]

DR. GILMAN: It is unanimous except are you abstaining or are you voting no?

DR. GENNINGS: I am abstaining.

DR. GILMAN: One abstention. Let that so be recorded.

All right. Again, any further question or discussion? Dr. Temple?

DR. TEMPLE: The only comment I would make is that some of the patient testimony and some of the suggestions of benefit in retarding progression and other more global sensations seem to me need pursuit even after approval. We will be talking with the company about how to do that.

Agenda Item: Closing Remarks - Information and Followup

DR. GILMAN: Thank you.

All right. For the Committee, please keep the dates of November 14th and 15th open on your calendars. We will be meeting one or both of those days. Otherwise, thank you all. I thank the Committee very much. I thank the sponsor. Again, compliments on the beautifully presented series of studies.

[Whereupon, the meeting was adjourned at 2:54 p.m.]

Lemonco.

TEVA PHARMACEUTICALS USA
1510 Delp Drive
Kulpsville, PA 19443

TEL: 800 999 8382
FAX: (215) 513 0473

September 20, 1996

Ms. Ermona McGoodwin
Advisors and Consultants Staff
Food and Drug Administration (HFD-21)
1901 Chapman Avenue
Rockville, MD 20857

Dear Ms. McGoodwin:

As promised, we enclose herewith hard copy of the complete set of presentation slides employed by TEVA at the September 19, 1996 Advisory Committee meeting. Should you require any further information or additional materials, please do not hesitate to contact us.

Yours very truly,

Stanley Scheindlin

Stanley Scheindlin, D. Sc.
Senior Director, Regulatory Projects

SS/cs
Enclosures

COPAXONE®

Copolymer-1 for Injection

TEVA Pharmaceuticals USA

Agenda

- Introduction - Carole S. Ben-Maimon, M.D.
- Multiple Sclerosis - Kenneth P. Johnson, M.D.
- Clinical Overview: Efficacy and Safety - Carole S. Ben-Maimon, M.D.
- Medical Assessment - Jerry Wolinsky, M.D.
- Conclusion - Carole S. Ben-Maimon, M.D.

Multiple Sclerosis

- Pathogenesis
- Disease Management
- Outcome Assessments

Kenneth P. Johnson, M.D.

Professor and Chairman
Department of Neurology
University of Maryland School of Medicine
Baltimore, Maryland

Multiple Sclerosis
Epidemiology

Prevalence: 300,000-350,000 patients in USA

Age of onset: 18-45 years (peak: 30 years)

Gender: ± 70% women

Multiple Sclerosis
Stages of Clinical Disease

	Onset	Approximate Prevalence
Relapsing	65%	40%
Progressive	15%	40%
Benign	20%	20%

50% of patients will require walking aids or a wheelchair within 15 years of diagnosis

Multiple Sclerosis
Relationship Between Relapses and Fixed Disability*

Number of Relapses in First 2 Years	Years for 50% of Patients to Need Walking Aids
> 5	7
2 - 4	13
< 2	18

*Weinshenker et al, 1989; Weinshenker, 1995

Multiple Sclerosis
Pathology

- Discrete plaques consist of focal inflammation
- Demyelination
- Gliosis
- Axonal loss

Pathology confined to Central Nervous System white matter: brain, optic nerves and spinal cord

Multiple Sclerosis Pathogenesis

- Genetic predisposition
- T-lymphocytes sensitized to MBP, PLP, MOG
- Inflammatory foci in CNS damage myelin
  - Macrophages
  - Antibodies and complement
  - Cytotoxic T-cells
  - Pro-inflammatory cytokines
- Tri-molecular complex
  - Antigen presenting cell
  - Auto-antigen
  - T-lymphocyte

Multiple Sclerosis
Primary Disability Scale (Kurtzke)

DSS: 10 step scale - normal to death

EDSS: 20 half-step scale

- Non-linear
- EDSS 4 - able to walk 500 meters
- EDSS 6 - need for walking aid
- EDSS 7.5 - restricted to wheelchair

Multiple Sclerosis
Primary Disability Scale (Kurtzke) Cont'd.

Functional Systems (5-6 grades each)

Pyramidal	Brainstem
Sensory	Mental
Cerebellar	Visual
Bowel & Bladder	

Graded ability to perform in 7 functional systems plus walking distances used to determine EDSS

Kurtzke, JF Neurology 33:1444, 1983

Multiple Sclerosis
Major Management Issues

- Relapse Control
- Delay Disability
- Reverse Disability (Future)
- Modify Symptoms

Therapies must be safe for use in young adult life and well-tolerated during chronic treatment (many years).

Multiple Sclerosis
Relapse Control is a Major Therapeutic Goal

Relapses cause:

- **Loss of work days and ability to care for self, family and home**
- **Increased transient disability**
- **Increased fatigue**
- **Increased anxiety for patient and family**
- **Increased hospitalization**
- **Increased reactive depression**

Multiple Sclerosis
Ability to Delay or Modify Disability is Also of Major Importance

- Able to complete education, maintain employment or manage and care for self and family
- Delay need for walking aids or a wheelchair
- Reduce risk of cognitive decline
- Maintain quality of life

Clinical Overview

COPAXONE®
Copolymer-1 for Injection

Carole S. Ben-Maimon, M.D.

Copolymer-1

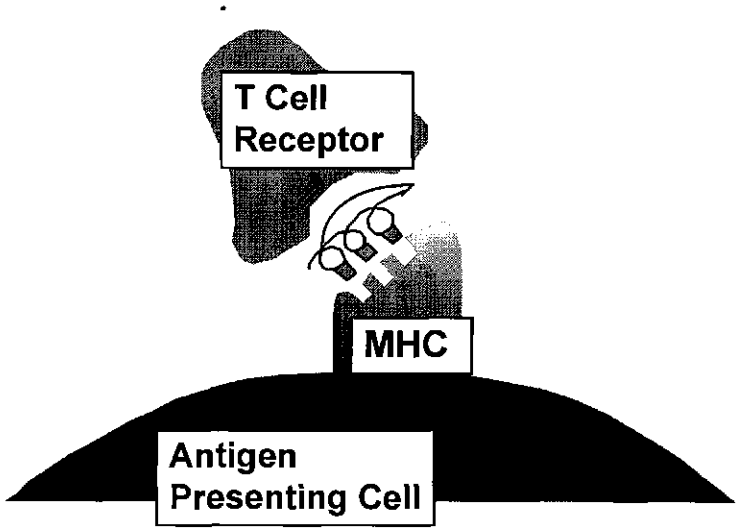
The acetate salt of synthetic polypeptides, containing four naturally occurring amino acids:

L-glutamic acid, L-alanine, L-tyrosine and L-lysine

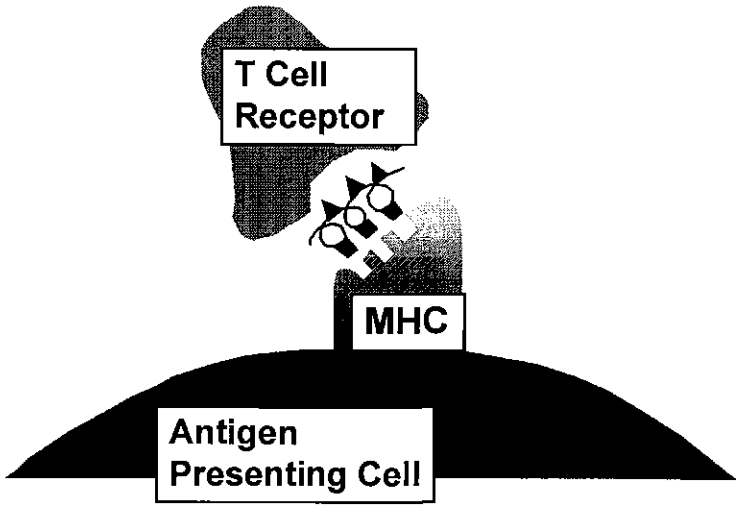
Discovery

- Discovered at Weizmann Institute in Israel in the labs of Dr. M. Sela and Dr. R. Arnon
- Designed to simulate myelin basic protein
- Reverses or prevents EAE

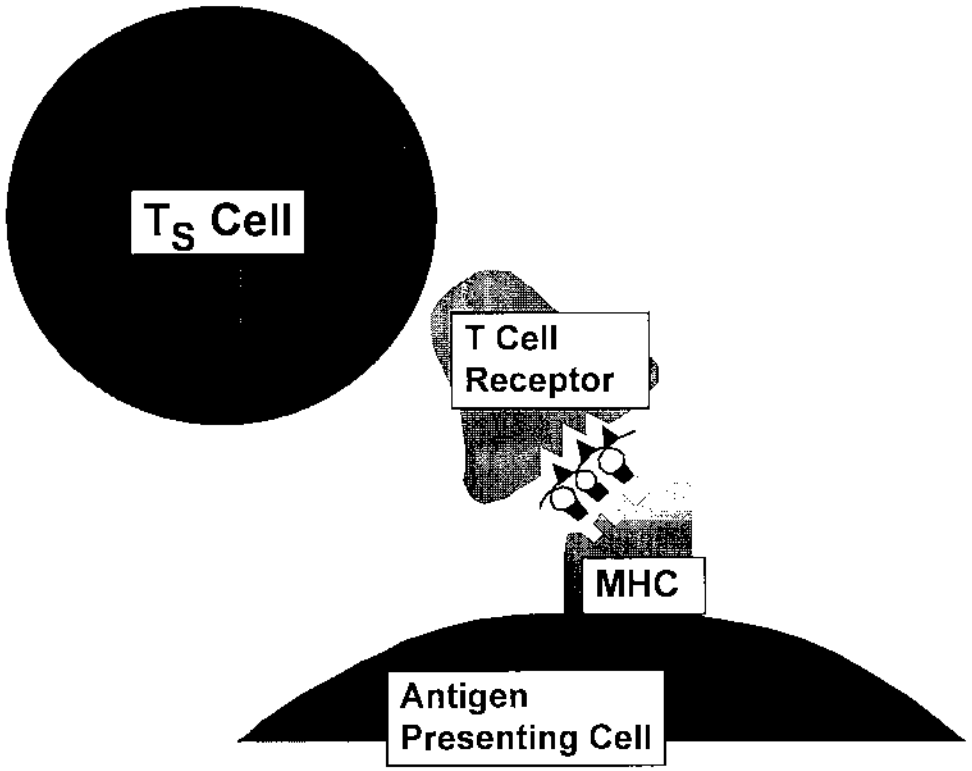
Mechanism of Action



Mechanism of Action



Mechanism of Action



Regulatory History

- 1985 - Trial BR-1 (pivotal) completed
- 1987 - FDA orphan drug designation
- 1987 - FDA audits Trial BR-1
- 1993 - FDA approves Treatment IND
- 1994 - Trial 01-9001 (pivotal) completed
- 1995 - NDA submitted

Clinical Pharmacology Trials

Trial	Number of Patients	
BR-OA (Abramsky)	7	(4 with unspecified MS, 3 with other neurological disease)
BR-OB (Bornstein)	16	(4 with relapsing MS, 12 with chronic-progressive MS)
BR-OC (Baumhefner)	5	(all with chronic-progressive MS)
BR-OD (Bauer)	21	(6 with relapsing MS, 15 with chronic-progressive MS)
Total Number of Patients	49	

Preliminary Dosing Trial
Trial BR-OB

- **Dose:**
  - Initial dose: 5 mg daily 5x per week
  - Titrated: 2 to 30 mg daily for up to 6 months

- **Results:**
  - 3 patients (C-P) stabilized with improvement
  - 2 patients (relapsing) stabilized
  - 11 patients (2 relapsing, 9 C-P) no effect
  - 4 injection site reactions
  - 13 other adverse reactions (no serious/severe)

Toxicology Studies

Single dose:		
Rat, Dog	400, 100 mg/kg	No Effects
Repeated dose:		
Mouse (13 wks)	0,20,60 mg/kg	Inj. site inflammation
Rat (4 wks)	0,2,10,20,40 mg/kg	Facial swelling, inj. site inflammation
Rat (26 wks)*	0,3,10,30 mg/kg	inj. site inflammation
Dog (4 wks)	0,2,10,20 mg/kg	Inj. site inflammation
Dog (90 days)	10 mg/kg	Inj. site inflammation
Monkey (28 days)	0,2,10,20 mg/kg	Inj. site inflammation
Monkey (52 wks)*	0,3,10,30 mg/kg	Inj. site inflammation

*Copolymer-1 reactive antibodies

Toxicology Studies: Reproduction

Species,Strain	Copolymer-1 (mg/kg/day)	Results
Segment I, Rat	0, 1, 6, 36	No adverse effects on fertility or reproduction
Segment II, Rat	0, 0.3, 1.5, 7.5, 37.5	No adverse effects in dam or fetus
Segment III, Rat	0, 0.3, 1.5, 7.5, 37.5	No adverse effects on perinatal and postnatal development
Segment II, Rabbit	0, 0.3, 1.5, 7.5, 37.5	No adverse effects in dam or fetus

Toxicology Studies: Mutagenicity

---

in vitro Tests

Ames Assay
Mouse Lymphoma Assay
Human Lymphocyte Assay

in vivo Test

Mouse Micronucleus Assay

Carcinogenicity Studies

- Rapidly degraded to small polypeptides
- Chronic toxicology studies
  - -120 rats: 6 months
  - -24 monkeys: 1 year
- Two life-span studies (mice/rats) ongoing

Number of Patients in the Clinical Program

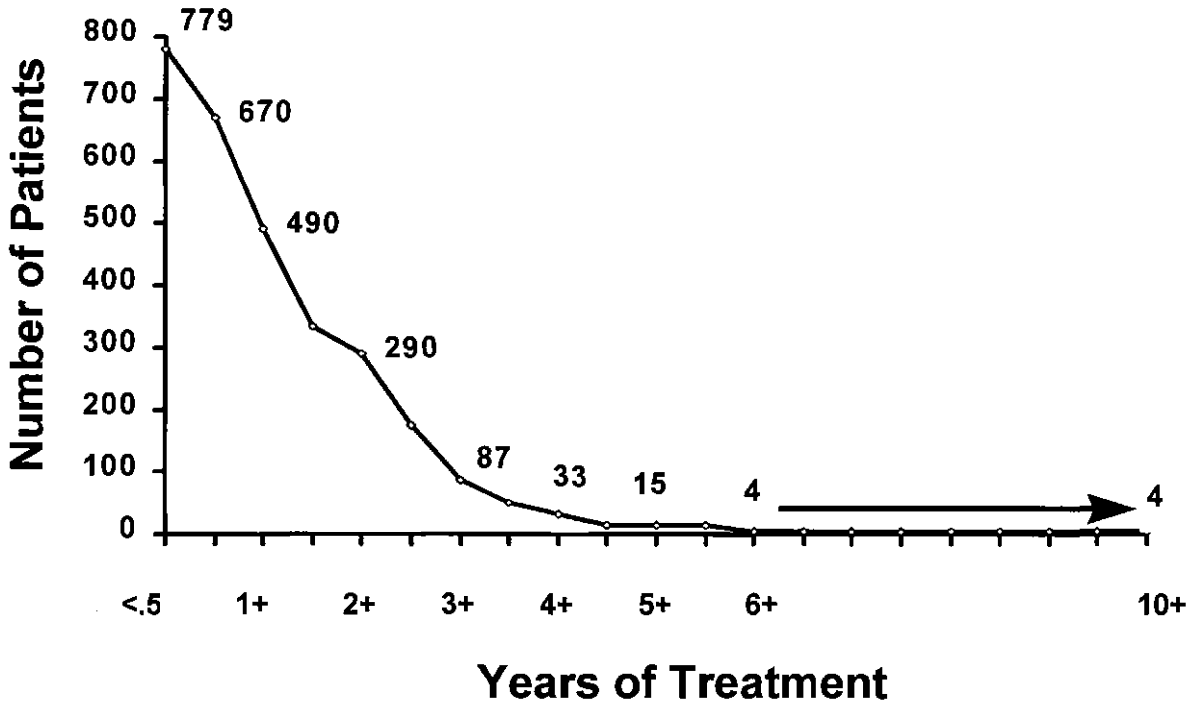
	COPAXONE®	Placebo
Controlled Trials	201	206
Uncontrolled Trials	656	
Subtotal	857	206
Clinical Pharmacology	49	
Total	906	206

Number of Patients in Clinical Trials*

	COPAXONE®	Placebo
Relapsing MS	779	151
C-P MS	73	55
MS Unspecified	5	
Total	857	206

*Excludes clinical pharmacology

More than 1000 Patient-Years of Exposure in Relapsing MS



Two Double-Blind, Placebo Controlled Trials in Relapsing Multiple Sclerosis

Trial	Dose mg/ Route	Duration	Number of Patients COPAXONE®	Number of Patients Placebo
BR-1	20/SC	24 Months	25	25
01-9001/ 9001E	20/SC	24 Months (plus extension)	125	126
	Total Number of Patients		150	151

Trial BR-1

Supported by:

National Institutes of Health

Publication
Trial BR-1

Bornstein, MW, Miller AJ, Slagle S. et al.

A pilot trial of COP 1 in exacerbating-remitting multiple sclerosis.

N Eng J Med 317:408-414, 1987.

External Advisory Committee
Trial BR-1

John Kurtzke, MD, Chief of Neurology Service, VAMC, Washington, DC

Joel Verter, PhD, NIH Office of Mathematics and Applied Statistics

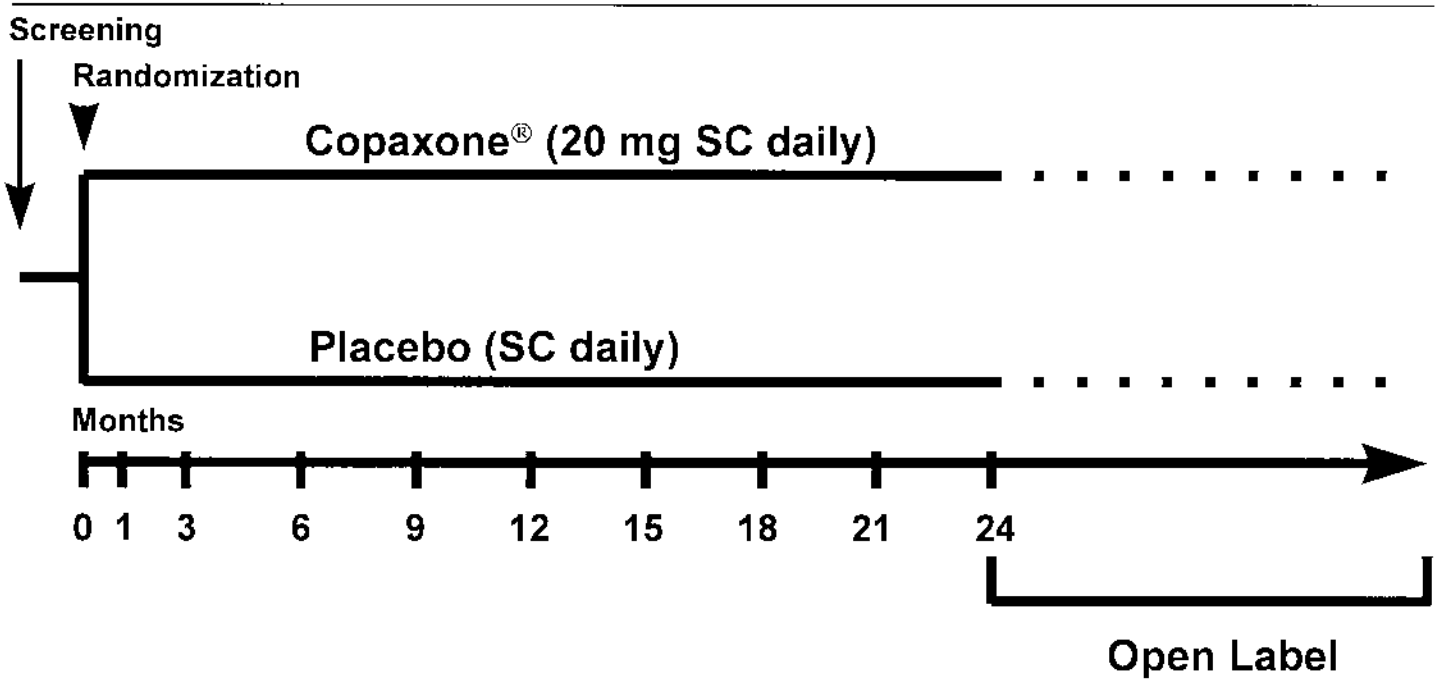
William Weiss, Chief Officer of Biometry and Field Studies, NINCDS

I. Herbert Scheinberg, MD, Professor and Chair, AECOM Committee on Clinical Investigations

Design
Trial BR-1

- Double-blind
- Placebo-controlled
- Randomized
- Matched-pair

Design
Trial BR-1



Inclusion Criteria
Trial BR-1

- Males or females
- 20-35 years of age
- Clinically definite MS
- Diagnosed at least 1 year prior to screening
- At least 2 relapses in the 2 years prior to screening
- Ambulatory with DSS score between 0 and 6
- Emotionally stable as determined by psychosocial evaluation

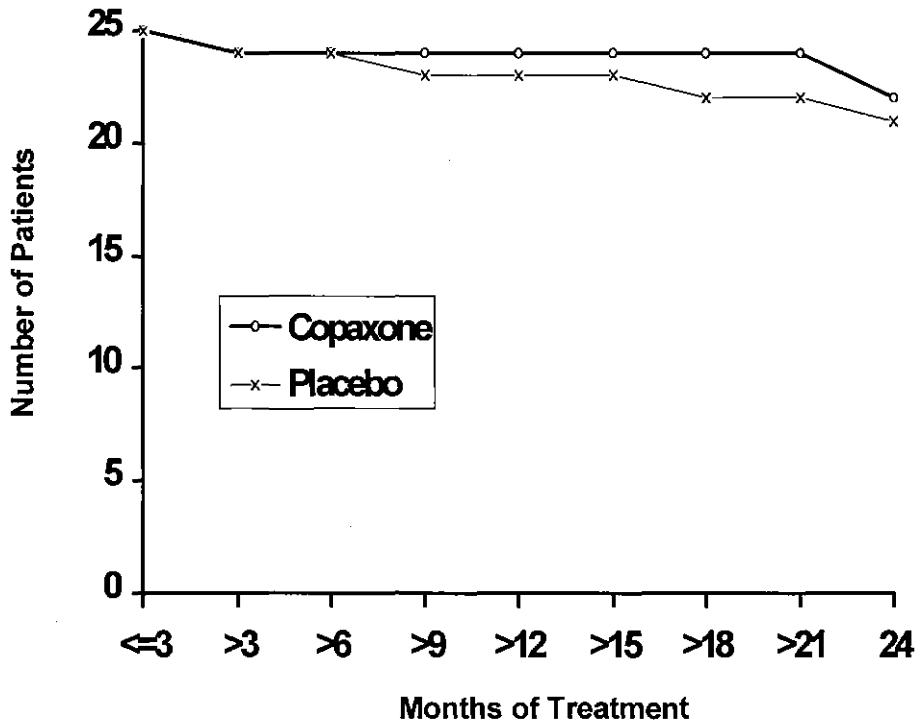
Demography
Trial BR-1

	COPAXONE® (n=25)	Placebo (n=25)
Male	11 (44%)	10 (40%)
Female	14 (56%)	15 (60%)
White	23 (92%)	25 (100%)
Black/Other	2 (8%)	0 (0%)
Age (yrs.) Mean (SD)	30.0 (3.2)	31.0 (3.5)
Min-Max	20-33	25-35

Baseline Characteristics: Trial BR-1

	COPAXONE® (N=25)	Placebo (N=25)
Duration of MS (yrs)		
Mean (SD)	4.9 (2.7)	6.1 (3.9)
Min-Max	2.0-10.0	1.0-13.0
Prior 2-Year Relapse Rate		
Mean (SD)	3.8 (1.4)	4.0 (1.2)
Min-Max	2-8	2-7
Baseline DSS Score		
Mean (SD)	2.8 (1.9)	3.2 (2.0)
Min-Max	1-6	0-6

Comparable Exposure Time Between Groups: Trial BR-1



Cohorts for Analysis
Trial BR-1

- ***Publication*** **(evaluable) cohort: 48 patients**
  Copaxone®: 25 Placebo: 23*

- ***All Patients*** **(Intention-to-treat) cohort: 50 patients**
  Copaxone®: 25 Placebo: 25

*Two patients in the placebo group considered non-evaluable

Relapse Criteria
Trial BR-1

- Neurological Abnormalities: Worsening
- Duration: At least 48 hours
- Objective Symptoms: Objective neurological changes.
  Increase of one point in at least one functional system score
- Exclusion criteria: Sensory symptoms unaccompanied by a objective findings did not represent relapse

Primary Endpoint
Proportion of Relapse-Free Patients
Trial BR-1

	% Relapse-Free	
Publication Cohort		
COPAXONE®	56.0% (14/25)	p=0.039*
Placebo	26.1% (6/23)	
All Patients Cohort		
COPAXONE®	56.0% (14/25)	p=0.180*
Placebo	32.0% (8/25)	

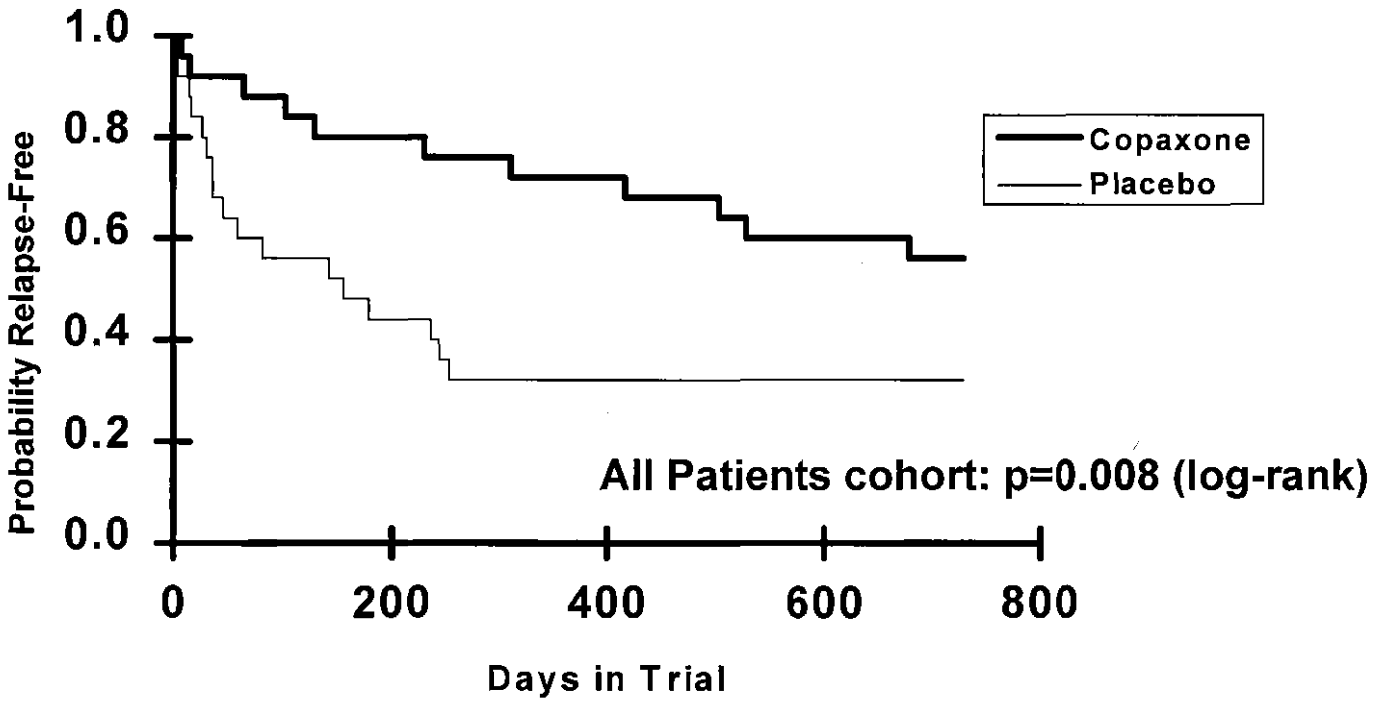
*McNemar (Matched Pair) Test based on 22 and 24 pairs, respectively

Distribution of the Number of Observed Relapses Over 24 Months: Trial BR-1

Number of Relapses:	0	1-2	≥3	Mean(SE)
Publication Cohort				
COPAXONE®	14 (56.0%)	10 (40.0%)	1 (4.0%)	0.6 (.18)
Placebo	6 (26.1%)	6 (26.1%)	11 (47.8%)	2.6 (.50)
		p=0.002*		
All Patients Cohort				
COPAXONE®	14 (56.0%)	10 (40.0%)	1 (4.0%)	0.6 (.18)
Placebo	8 (32.0%)	6 (26.1%)	11 (47.8%)	2.4 (.48)
		p=0.004*		

*Exact probability test on the categorical distribution

Kaplan-Meier Survival Distribution of Time to First Relapse: Trial BR-1

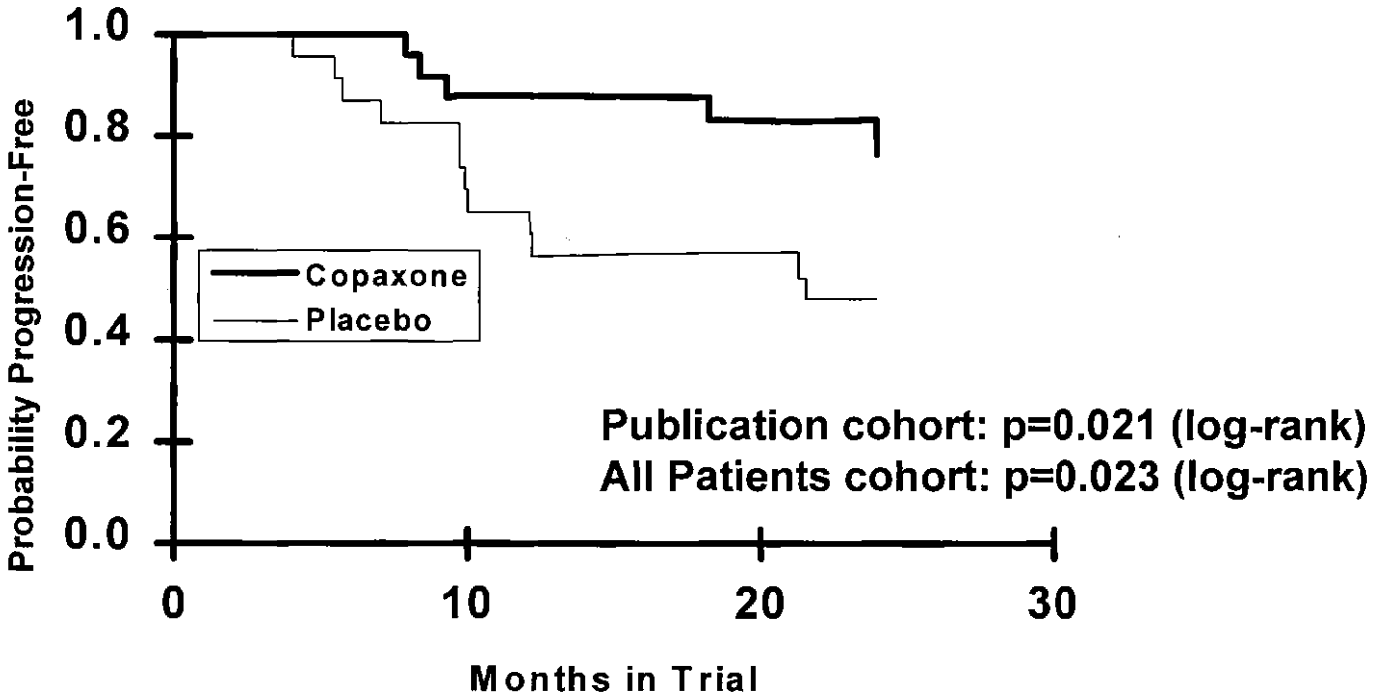


DSS Categorical Change from Baseline to Last Visit: Trial BR-1

	% Unchanged/Improved	
Publication Cohort		
COPAXONE®	80.0% (20/25)	p=0.066*
Placebo	52.2% (12/23)	
All Patients Cohort		
COPAXONE®	80.0% (20/25)	p=0.128*
Placebo	56.0% (14/25)	

*Exact probability test

Kaplan-Meier Survival Distribution of Time to Progression: Trial BR-1



Proportion of Progression-Free Patients
Trial BR-1

	% Progression-Free	
Publication Cohort		
COPAXONE®	80.0% (20/25)	p=0.034*
Placebo	47.8% (11/23)	
All Patients Cohort		
COPAXONE®	80.0% (20/25)	p=0.072*
Placebo	52.0% (13/25)	

*Exact probability test

Trial 01-9001/9001E
Multicenter Phase III Trial

Supported by:

Orphan Drug Division of FDA
National Multiple Sclerosis Society

Publication
Trial 01-9001/9001E

Johnson, K.P., Brooks, B.R., et al.

Copolymer-1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind, placebo-controlled trial.

Neurology 45:1268-1276, 1995.

Participating Centers
Trial 01-9001/9001E

Project Director: K. Johnson, MD, University of Maryland

Name	Location
B. Brooks, MD	University of Wisconsin
J. Cohen, MD and F. Gonzalez-Scarano, MD	Hospital of the University of Pennsylvania
C. Ford, MD	University of New Mexico School of Medicine
R. Lisak, MD	Wayne State University School of Medicine
L. Myers, MD	UCLA School of Medicine
H. Panitch, MD	University of Maryland
J. Rose, MD	University of Utah V.A. Medical Center
R. Schiffer, MD	University of Rochester
T. Vollmer, MD and J. Goldstein, MD	Yale University School of Medicine
L. Weiner, MD	USC Healthcare Consultation Center
J. Wolinsky, MD	University of Texas Heath Sciences Center

Steering Committee
Trial 01-9001/9001E

Kenneth P. Johnson, MD
University of Maryland Hospital

Yafit Stark, PhD
Senior Director of Clinical Trials
TEVA Pharmaceutical Industries, Ltd.

Irit Pinchasi, PhD
Deputy Corporate Vice President
Teva Pharmaceutical Industries, Ltd.

Nina Spiller, PharmD
National Medical Research Corporation

Safety Committee
Trial 01-9001/9001E

Neurologists

Stanley Van Den Noort, MD, PhD
University of California, Irvine

Aaron Miller, MD
Maimonides Medical Center

Clinical Pharmacologist

Irving H. Gomolin, MDCM, FRCPc, FACP
Gurwin Jewish Geriatric Center

Statistician

David Mellits, PhD
Johns Hopkins University

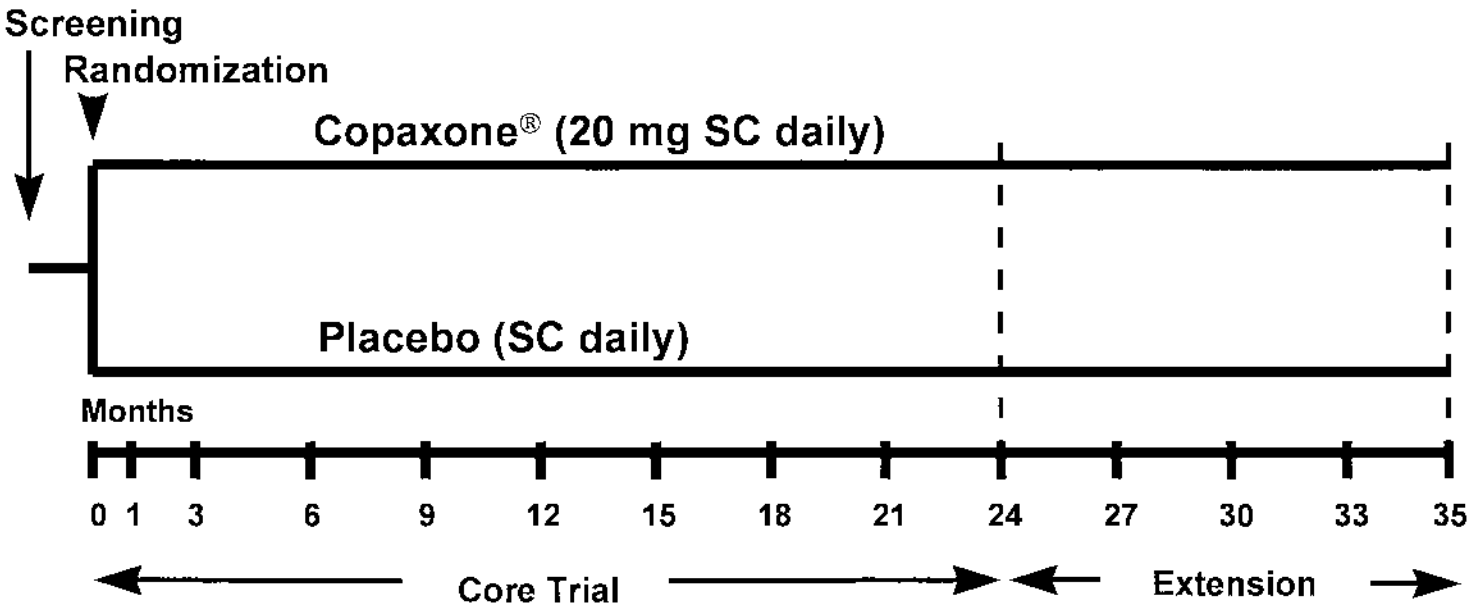
National MS Society

Stephen Reingold, PhD
Vice President of Research

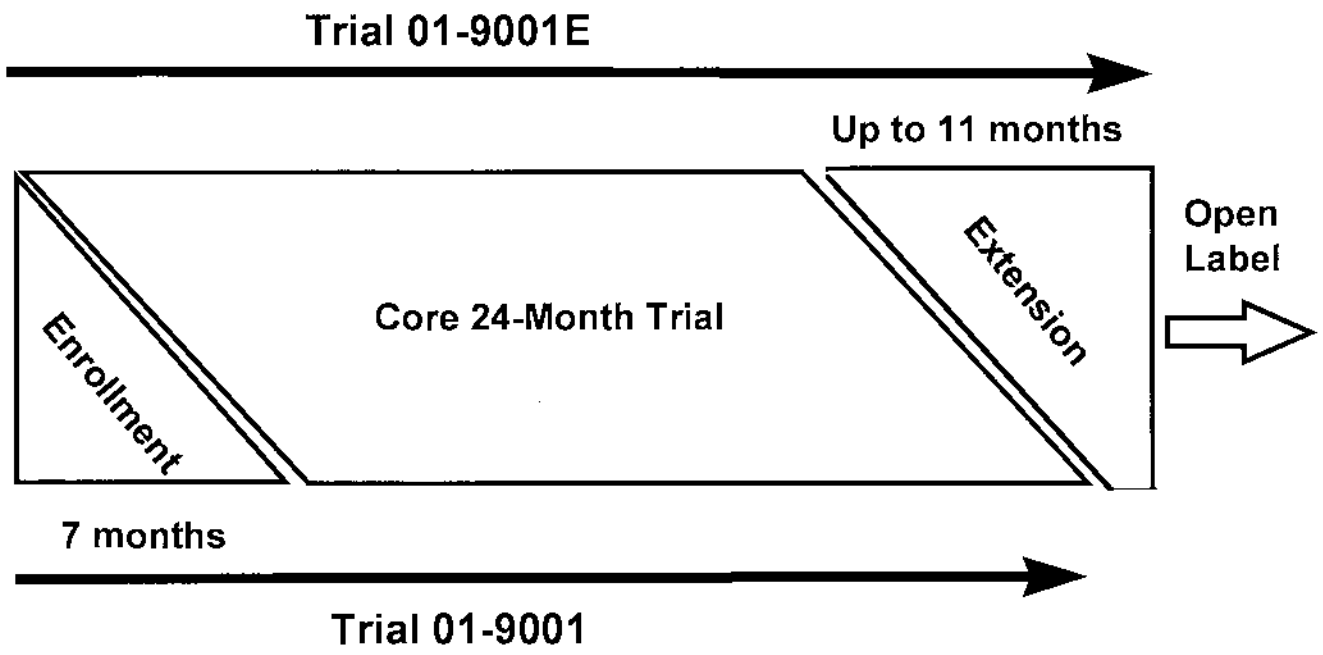
Design
Trial 01-9001/9001E

- Multicenter (11 sites)
- Double-blind
- Randomized
- Placebo-controlled

Design
Trial 01-9001/9001E



Design
Trial 01-9001/9001E



Inclusion Criteria
Trial 01-9001/9001E

- Males or females
- 18-45 years of age
- Clinically definite MS (Poser criteria)
- Diagnosed at least 1 year prior to screening
- At least 2 relapses in the 2 years prior to screening
- Ambulatory with EDSS score between 0 and 5.0
- Stable for at least 30 days prior to enrollment

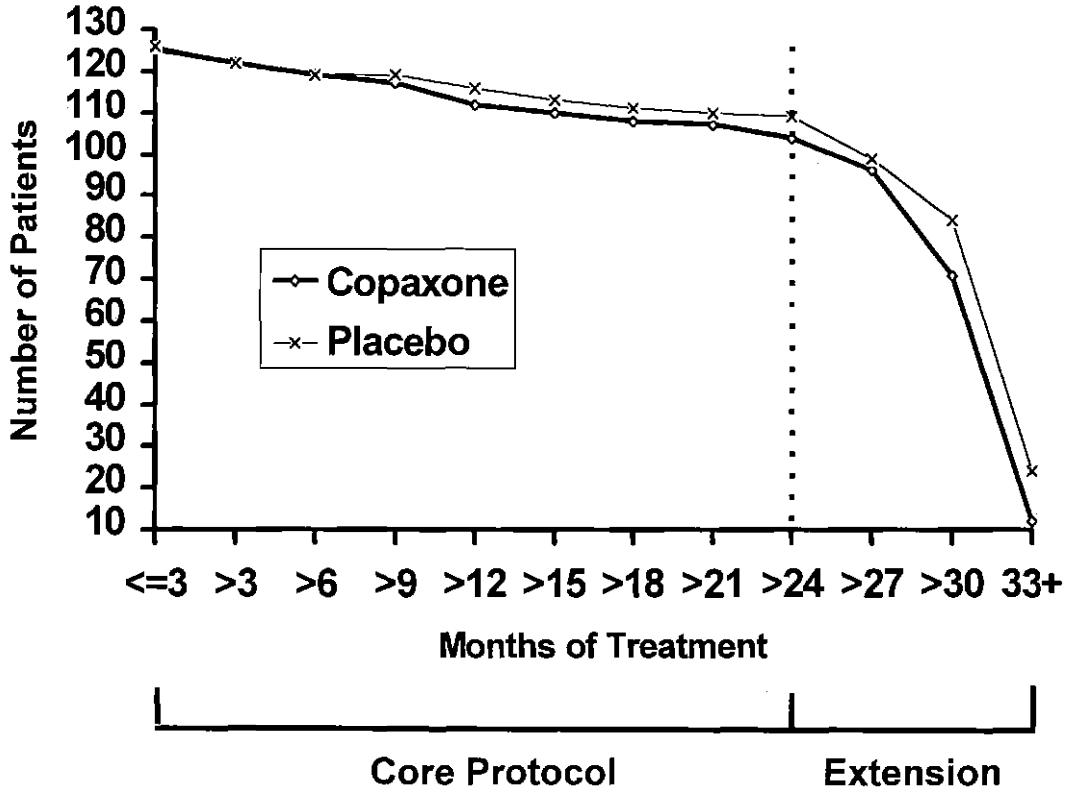
Demography
Trial 01-9001/9001E

	COPAXONE® (N=125)	Placebo (N=126)
Male	37 (30%)	30 (24%)
Female	88 (70%)	96 (76%)
White	118 (94%)	118 (94%)
Black/Other	7 (6%)	8 (6%)
Age (yrs) Mean (SD)	34.6 (6.0)	34.3 (6.5)
Min-Max	19-46	19-46

Baseline Disease Characteristics
Trial 01-9001/9001E

	COPAXONE® (N=125)	Placebo (N=126)
Duration of MS (yrs)		
Mean (SD)	7.3 (4.9)	6.6 (5.1)
Min-Max	0.6-21.2	1.0-23.0
Prior 2-Year Relapse Rate		
Mean (SD)	2.9 (1.3)	2.9 (1.1)
Min-Max	2.0-11.0	0.0-6.0
Baseline EDSS Score		
Mean (SD)	2.8 (1.2)	2.4 (1.3)
Min-Max	0.0-5.0	0.0-5.0

Comparable Exposure Time Between Groups: Trial 01-9001/9001E



Patient Disposition
Trial 01-9001/9001E

Patients Screened:	**284**	
	COPAXONE®	**Placebo**
Randomized	**125**	**126**
Completed Core 24 Months	**106 (85%)**	**109 (87%)**
Entered Extension	**100 (80%)**	**106 (84%)**
Completed Extension	**91 (73%)**	**94 (75%)**

Relapse Criteria
Trial 01-9001/9001E

- Neurological Abnormalities: Appearance or reappearance
- Duration: At least 48 hours
- Stabilization Duration: Stability or improvement 30 days before deterioration
- Objective Symptoms: Increase of at least 0.5 in EDSS or 1 point in each of two functional system scores or 2 points in one functional system score
- Exclusion criteria: Not undergoing any metabolic change. Sensory or cognitive dysfunction alone could not be entirely responsible

Primary Endpoint
Mean Number of Observed Relapses
Trial 01-9001/9001E

	Core 24 Months Mean(SE)	Core+Extension Mean(SE)
COPAXONE® (n=125)	**1.29** (0.12)	**1.47** (0.14)
Placebo (n=126)	**1.67** (0.14)	**1.97** (0.16)

P-values for core 24-month analysis:

ANOVA	**p=0.055; 0.025**	**ANCOVA**	**p=0.007**
T-test	**p=0.04**	**Mantel-Haenszel**	**p=0.02**

Time to First Relapse
Trial 01-9001/9001E

Median Time to First Relapse (Days from Baseline)

	Core 24 Months	Core+Extension
COPAXONE® (N=125)	287	287
Placebo (N=126)	198	198
	p=0.233*	

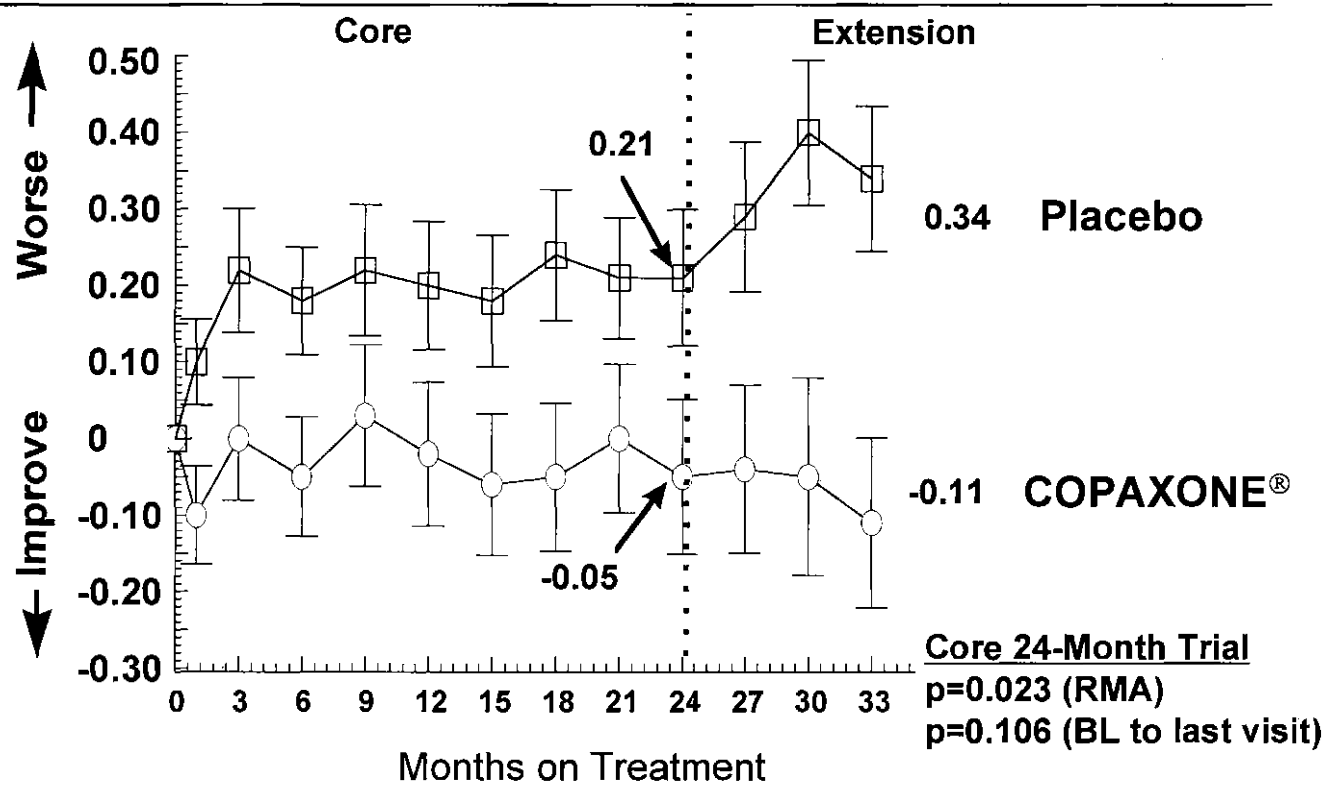
*Log-rank test of time to first relapse

Proportion of Relapse-Free Patients
Trial 01-9001/9001E

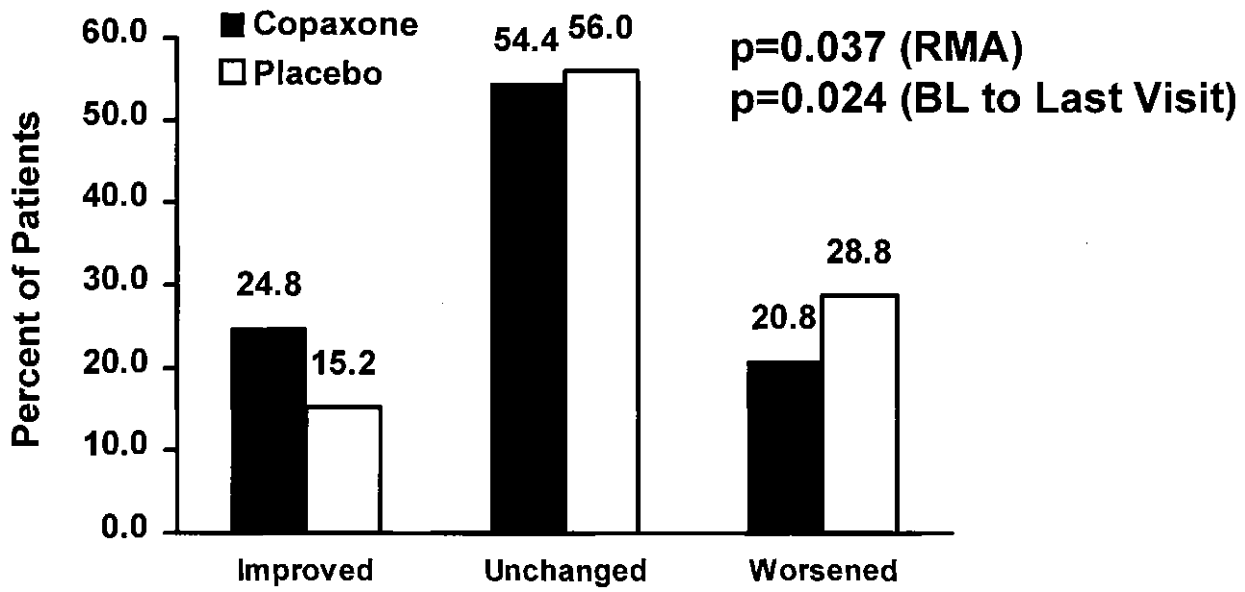
	Core 24 Months	Core+Extension
COPAXONE® (N=125)	33.6%	33.6%
Placebo (N=126)	27.0%	24.6%
	p=0.188*	

*CMH test

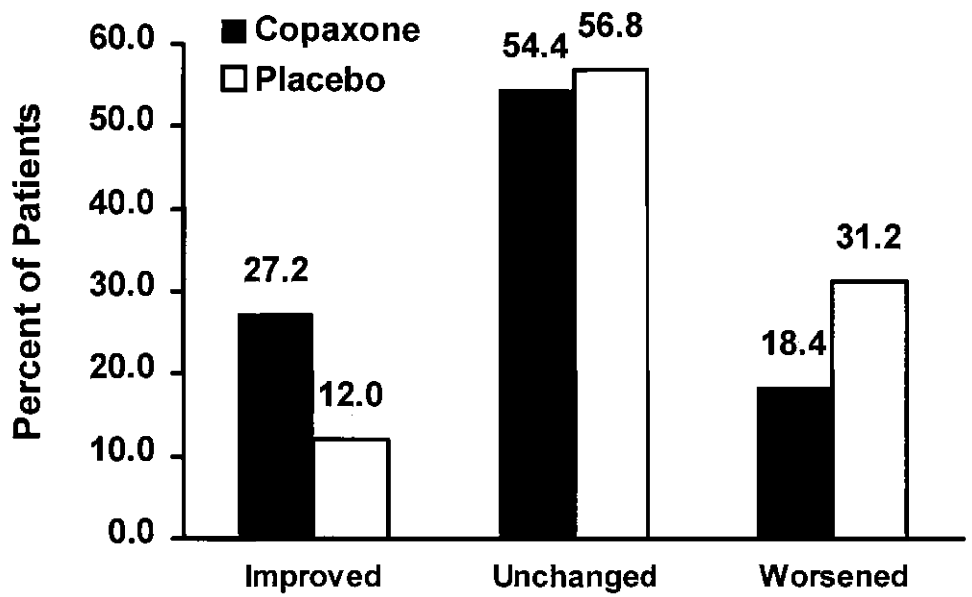
EDSS Change From Baseline
Trial 01-9001/9001E



EDSS Categorical Change at End of Core 24 Months Trial 01-9001/9001E



EDSS Categorical Change at End of Extension Trial 01-9001/9001E

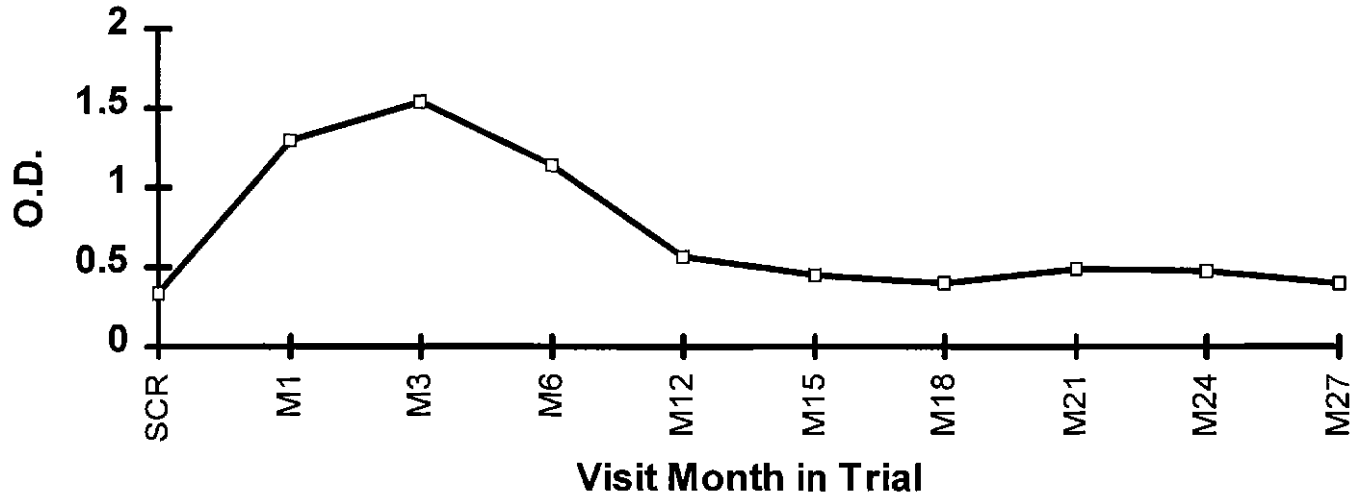


Proportion of Progression-Free Patients
Trial 01-9001/9001E: All Patients

	Core 24 Months	Core+Extension
COPAXONE® (N=125)	78.4%	76.8%
Placebo (N=126)	75.4%	70.6%
	p=0.476*	

*CMH test

Antibodies
Trial 01-9001/9001E



Safety

Complete Safety Database

	Copaxone®	Placebo
Number of Patients Exposed	906	206
Number of Patients With At Least One Post-Baseline Evaluation	893	206
Number of Patients in Clinical Pharmacology Studies	49	
Number of Patients in Clinical Trials Evaluated for Safety	844	206

Deaths
All Trials

Trial	Patient	MS Type	Dur. of Treatment	Cause of Death
1110-1	8417	Rel	26 months	Respiratory arrest
1110-1	8501	Rel	3 months	Cardiorespiratory insufficiency
BR-2	01-578	C-P	11 months	Glioblastoma
BR-3	2049	C-P	36 months	Pneumonia
BR-3	2051	C-P	36 months	Colon malignancy
BR-3	2038	C-P	22 months	Intra-operative: tracheostomy tube change
BR-3	2039	C-P	19 months	Pulmonary failure due to progressive MS

Premature Withdrawals Due to Adverse Events: Trials in Relapsing MS

	COPAXONE®	Placebo
Controlled Trials	12.7% (19/150)	2.7% (4/151)
Trial 01-9001/9001E	13.6% (17/125)	3.2% (4/126)
Trial BR-1	8.0% (2/25)	0.0% (0/25)
Uncontrolled Trials	7.5% (46/617)	
Across Trials	8.5% (65/767*)	2.7% (4/151)

*excludes clinical pharmacology trials

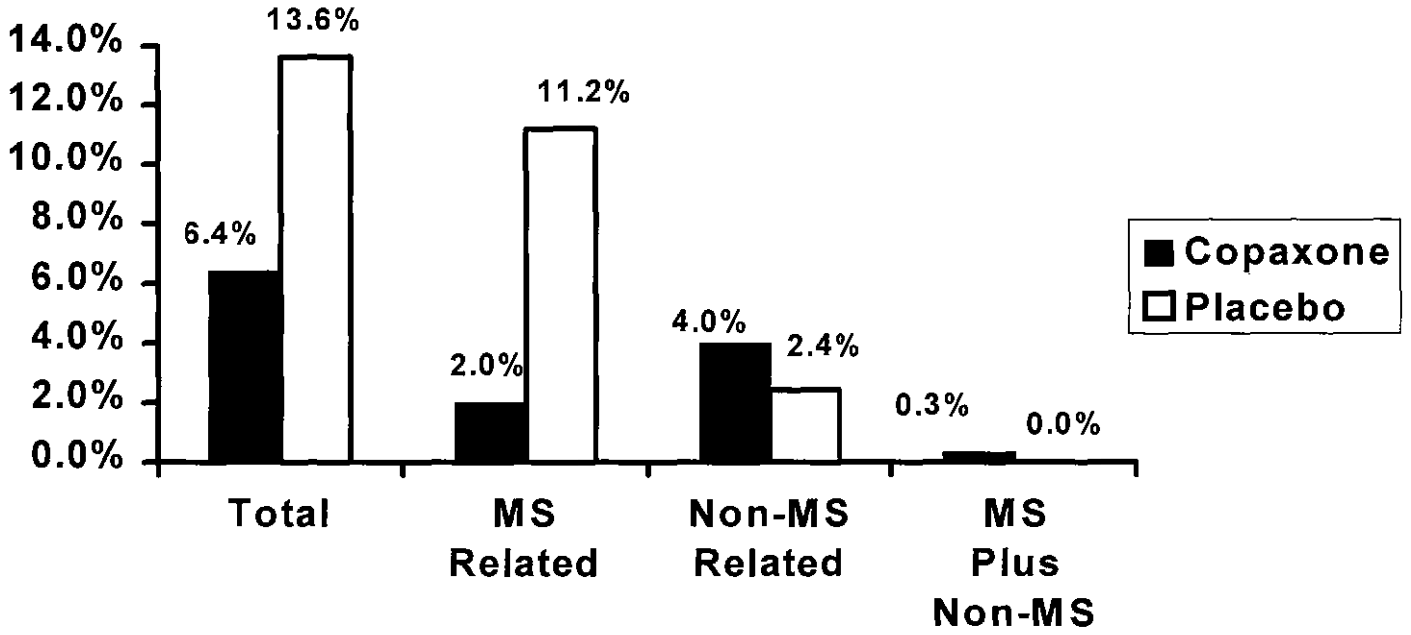
AEs Associated with Premature Withdrawal Controlled Trials in Relapsing MS

	Number of Patients	
Adverse Experience	Copaxone	Placebo
Local injection site reactions	4	1
Unspecified	4	0
Unintended pregnancy	3	0
Dyspnea	2	0
Urticaria	2	0
Vasodilatation	2	1
Infection	2	0

Occurring in one Copaxone patient only:
Chest pain, face edema, nausea, syncope, vomiting, lymphadenopathy, rash, splenomegaly, depression

Occurring in one placebo patient only:
Increased salivation, sweating, taste perversion, elevated liver function test, insomnia, abnormal gait, anxiety, dizziness, dysphagia

Hospitalizations
All Trials



Adverse Events: Largest COPAXONE® Frequencies Greater Than Placebo Trial 01-9001/9001E

	COPAXONE®	Placebo	
Injection site pain	66.4%	36.5%	<
Asthenia	64.8%	61.9%	
Injection site erythema	58.4%	13.5%	<
Injection site pruritus	38.4%	4.0%	<
Hypertonia	35.2%	29.4%	
Flu-like syndrome	30.4%	27.0%	
Injection site inflammation	28.0%	7.1%	<
Vasodilatation	27.2%	11.0%	<
Back pain	26.4%	22.2%	
Chest pain	26.4%	10.3%	<
Arthralgia	24.8%	17.5%	

Injection Site Reactions: Incidence
Trial 01-9001/9001E

	COPAXONE®	Placebo
Pain	66.4%	36.5%
Erythema	58.4%	13.5%
Pruritus	38.4%	4.0%
Inflammation	28.0%	7.1%
Mass	26.4%	7.9%
Ecchymosis	22.4%	34.9%
Induration	20.0%	0.8%
Welt	15.2%	4.0%
Hemorrhage	7.2%	3.2%
Urticaria	7.2%	0.0%
Unspecified	3.2%	0.8%

COPAXONE® Injection Site Reactions
Severity: Trial 01-9001/9001E

	No. of Patients	Mild	Moderate	Severe
Atrophy	3	100.0%		
Ecchymosis	28	85.7%	14.3%	
Erythema	73	89.0%	11.0%	
Fibrosis	1	100.0%		
Hemorrhage	9	100.0%		
Induration	25	96.o%	4.0%	
Inflammation	35	77.1%	22.9%	
Mass	33	90.9%	9.1%	
Melanosis	1	100.0%		
Pain	83	79.5%	19.3%	1.2%
Pruritus	48	91.7%	8.3%	
Unspecified	4	75.0%	25.0%	
Urticaria	9	100.0%		
Welt	19	89.5%	10.5%	

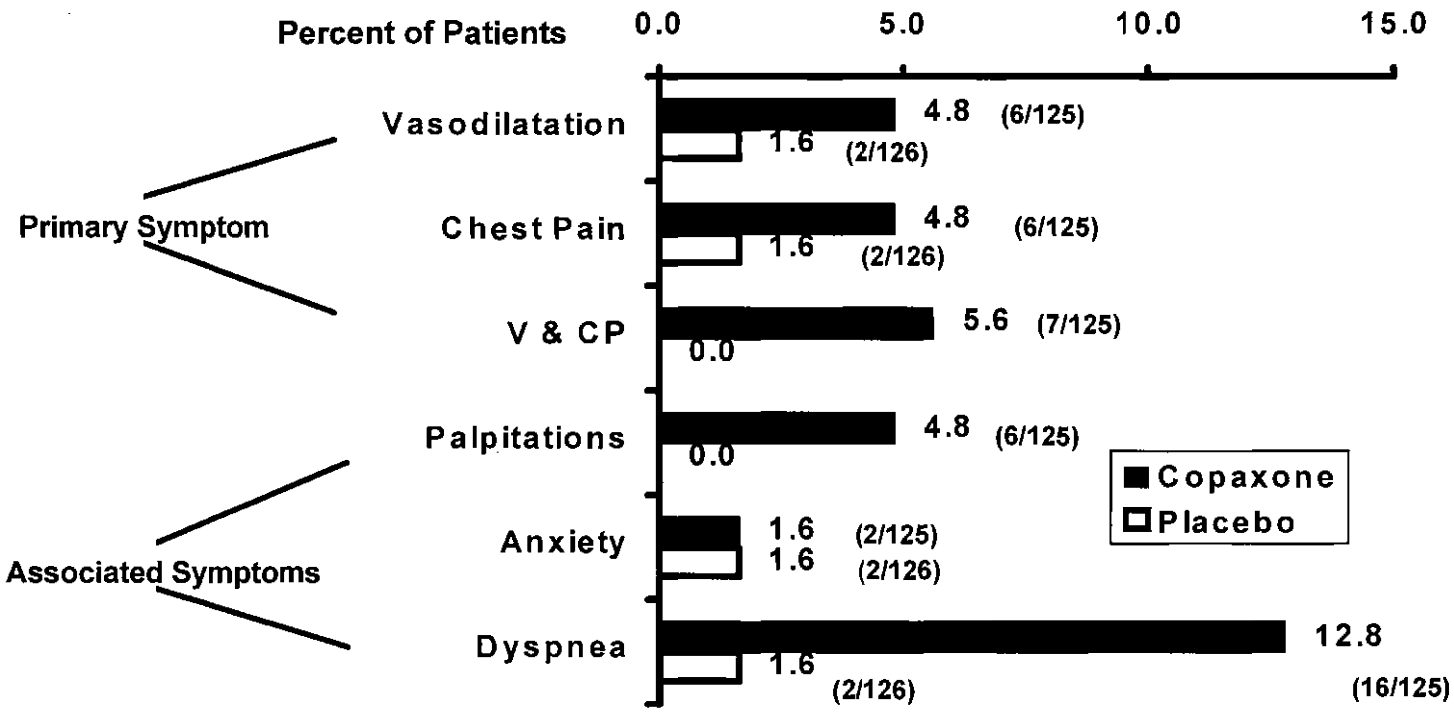
Systemic Reactions
Trial 01-9001/9001E

Definition: vasodilatation and/*or* chest pain *with at least one of the following:* palpitations, anxiety or dyspnea

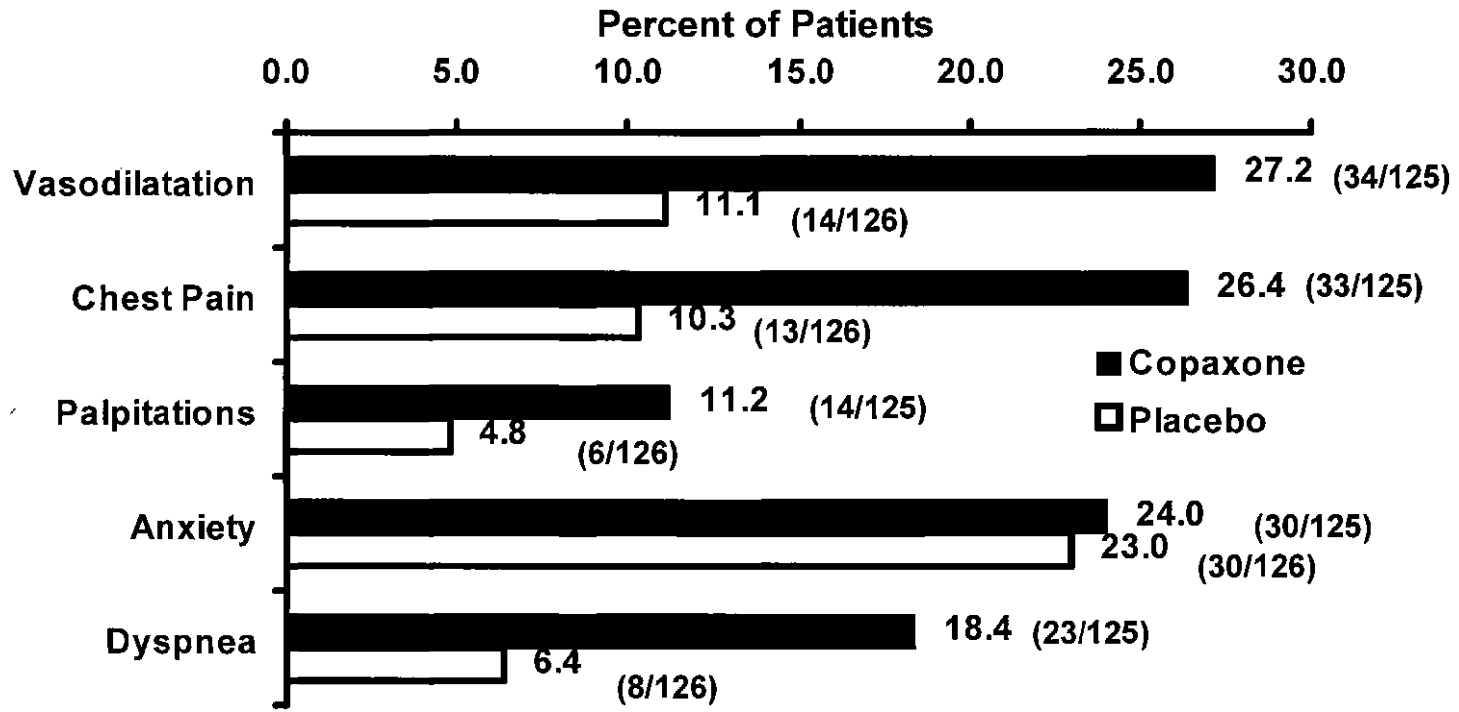
COPAXONE®: 19 patients (15.2%)
- **10 with 1 episode**
- **4 with 2 episodes**
- **3 with 3 episodes**
- **2 with 4 or more episodes**

Placebo: 4 patients (3.2%)
- **All with 1 episode**

Systemic Reactions: Incidence of Individual Components Among Affected Patients , as a Percentage of All Patients: Trial 01-9001/9001E



Systemic Reactions: Incidence of Individual Components Among All Patients Trial 01-9001/9001E



COPAXONE® Systemic Reactions Incidence in Relapsing MS Patients

Number of Episodes	Number of Patients (N=844)
1	52 (6.2%)
2	17 (2.0%)
3	11 (1.3%)
4	4 (<1%)
5	2 (<1%)
6	0
7	1 (<1%)

Total Number of Patients: 87 (10.3%)
Total Number of Events: 152

Conclusions from Two Adequate and Well-Controlled Trials: Data Supporting Efficacy

Statistical Significance for the Frequency of Relapses

	Mean Number of Relapses			
	Trial 01-9001/9001E		Trial BR-1	
	Core (24 Months)	Core+Extension	All Patients	Publication
COPAXONE®	1.29	1.47	0.6	0.6
Placebo	1.67	1.97	2.4	2.6

P-values for core 24 month analysis:
ANOVA: p=0.055; 0.025 ANCOVA: p=0.007
T-test: p=0.04 M-H p=0.02

Categorical analysis
exact probability test:
All patients: p=0.004
Publication: p=0.002

Other Endpoints Supporting Efficacy

- Mean change in EDSS score achieved statistical significance - Trial 01-9001
- Categorical analysis of change in EDSS achieved statistical significance - Trial 01-9001
- Time to progression achieved statistical significance - Trial BR-1

Other Relapse-Derived Endpoints Supporting Efficacy

	Trial 01-9001/9001E		Trial BR-1	
	Core	Core+Ext	All Patients	Publication
Proportion Relapse-Free				
COPAXONE®	33.6%	33.6%	56.0%	56.0%
Placebo	27.0%	24.6%	32.0%	26.1%
	p=0.188		p=0.180	p=0.039
Median Time to !st Relapse(Days)				
COPAXONE®	287	287	312[a]	
Placebo	198	198	156	
	p=0.233		p=0.008	

[a]25th percentile; median estimated to be over 700 days

Disability Endpoints Supporting Efficacy

	Trial 01-9001/9001E		Trial BR-1	
	Core	Core+Ext	All Patients	Publication
(E)DSS Mean Change from Baseline				
COPAXONE®	-0.05	-0.11		
Placebo	0.21	0.34		
(RMA)	p=0.023			
(BL to Last Visit)	p=0.106			

Disability Endpoints Supporting Efficacy

	Trial 01-9001/9001E		Trial BR-1	
	Core	Core+Ext	All Patients	Publication
(E)DSS Categorical Change from BL				
COPAXONE®				
Improved	24.8%	27.2%	28.0%	28.0%
No change	54.4%	54.4%	52.0%	52.0%
Worsened	20.8%	18.4%	20.0%	20.0%
Placebo				
Improved	15.2%	12.0%	12.0%	13.0%
No change	56.0%	56.8%	44.0%	39.2%
Worsened	28.8%	31.2%	44.0%	47.8%
(RMA)	p=0.037			
(BL to Last Visit)	p=0.024		p=0.128[a]	p=0.066[a]

[a]Improved/no change categories combined

Disability Endpoints Supporting Efficacy

	Trial 01-9001/9001E		Trial BR-1	
	Core	Core+Ext	All Patients	Publication
Proportion Progression-Free				
COPAXONE®	78.4%	76.8%	80.0%	80.0%
Placebo	75.4%	70.6%	52.0%	47.8%
	p=0.476		p=0.072	p=0.034
Median Time to Progression (Days)				
COPAXONE®	NON-EST*	NON-EST	NON-EST	NON-EST
Placebo	NON-EST	NON-EST	656	656
	p=0.604		p=0.021	p=0.023

*NON-EST: Non-estimable

Conclusion

COPAXONE® is effective in patients with relapsing multiple sclerosis, as demonstrated in two adequate and well-controlled trials.

Conclusion

COPAXONE® has been tested in 857 patients with multiple sclerosis, 779 with relapsing multiple sclerosis, and has been found to be safe and well-tolerated.

Medical Assessment

Jerry S. Wolinsky, MD

Professor of Neurology
Director of MS Research Group
University of Texas Health Sciences Center

Medical Assessment

Multiple Sclerosis: Tangible Costs

- Include personal services, home alterations, special equipment and transportation, lost earnings and disease-specific medical costs
- $9.7 billion annually in 1994 dollars
- $35,000 annually per patient
- $50,000 annually if progressive; $30,500 if relapsing

Whetten-Goldstein et al. MS Management 3:33, 1996

Medical Assessment

Multiple Sclerosis: Lost Days

- 39% of all MS patients had at least 1 day of restricted activity in the last 2 weeks
- 16% of MS patients' activities were restricted for 8 or more of the last 14 days
- 27% of all MS patients spent at least 1 day bed-confined in the last 2 weeks
- 10% Spent the last year bed-confined

Minden et al., Multiple Sclerosis: A Statistical Portrait, 1993

Medical Assessment

Multiple Sclerosis: Hospitalizations

- 27% of all MS patients are admitted to hospitals at least once annually
- About 1 in every 500 hospital stays is for MS
- 50% of MS admissions are acute or urgent, precipitated mostly by relapses
- Care extends beyond hospitalization
  - 9% are discharged with home health care follow-up
  - 8% require additional intermediate care facilities
  - 10% are discharged to skilled nursing facilities

Minden et al., Multiple Sclerosis: A Statistical Portrait, 1993

Medical Assessment

Benefits of COPAXONE® :

- Reduces the frequency of relapses and slows the progression of disability
  - Relapse finding maintained across all levels of disability; more pronounced in less disabled patients
  - Changes in EDSS: more patients on COPAXONE® remained stable or improved compared to those on placebo

Medical Assessment

Benefits (cont'd):

- Neutralizing Antibodies
  - No evidence that daily treatment with COPAXONE® induces formation
  - Clinical efficacy maintained throughout the dosing period (up to 35 months) even in the presence of copolymer-1-reactive antibodies, regardless of changes in antibody titers

Medical Assessment

Benefits (cont'd):

- Tolerability
  - 1092 patient years of exposure; over 10 years of treatment in some patients
  - Fewer MS-related hospitalizations for COPAXONE® patients
  - No known product-related lab abnormalities in 844 patients evaluated across all studies
  - Animal studies show no effects on fetotoxicity or teratogenicity

Medical Assessment

Benefits (cont'd):

- Tolerability (cont'd)
  - Trial 01-9001/9001E
    - »Five women conceived during prolonged COPAXONE® treatment: three continued pregnancies; all three delivered healthy babies
    - »No abnormal ECG changes seen
    - »No significant overall changes in vital signs

Medical Assessment

Benefits (cont'd):

- Tolerability (cont'd)
  - COPAXONE® does not appear to be associated with depression, suicide attempts or the occurrence of flu-like symptoms

Medical Assessment

Risks of COPAXONE®:

- Local Site Reactions
  - Most commonly observed adverse experiences in patients receiving COPAXONE®
  - Included erythema, pain, inflammation, pruritus and mass (also observed in patients receiving placebo)
  - Majority were reported as mild

Medical Assessment

Risks (cont'd):

- Systemic Reactions
  - Self-limited, occurring following subcutaneous injection
  - Defined as chest pain and/*or* vasodilatation *with one or more of the following:* palpitations, anxiety or dyspnea

Medical Assessment

Risks (cont'd):

- Systemic Reactions (cont'd)
  - Unpredictable in occurrence
  - Majority of patients who reported a systemic reaction experienced it only once
  - Resolution usually occurred within 15 minutes
  - No therapy required; no sequelae have been reported

Medical Assessment

Conclusion:

COPAXONE® represents a novel clinical option for multiple sclerosis, a serious disorder with no known prevention or cure

- **Well-tolerated**
- **Potential for maintaining long-term efficacy**