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 as Exhibit A, FOI Services' Document Number 143374 A, titled "[N20622] Copaxone (Teva Pharm): Approval Letter, Review & Evaluation of Clinical Data, Statistical Review, Pharmacology & Toxicology, Chemistry, FONSI, Environmental Assesment, Microbiology" was publicly available, incorporated into the FOI Services publicly available files, and was provided to a third party at least as early as April 8, 2005.

5. FOI Services provided the document attached as Exhibit A to Mylan Pharmaceuticals Inc. on July 17, 2007.

6. The record attached as Exhibit A was kept in the course of our regularly conducted business activity. Making the record was a regular practice of my job duties and our business activities.

7. I hereby declare that all statements made herein of my own knowledge are true and correct. I further declare that all of my statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Marlene S. Bobka

December 9, 2014
Date

SUBSCRIBED AND SWORN before me on December 9, 2014.

Notary Public

My commission expires: 7/21/2017

EXHIBIT A

20622

Copaxone

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-622

DEC 20 1996

Teva Pharmaceuticals USA
Attention: Deborah Jaskot
1510 Delp Drive
Kulpsville, PA 19443

Dear Ms. Jaskot:

Please refer to your June 15, 1995 new drug application and your resubmission dated October 11, 1995 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copaxone (glatiramer acetate) injection.

We also refer to an Agency Approvable letter dated October 4, 1996, and we acknowledge receipt of your response amendments dated:

October 2, 1996	October 21, 1996	October 31, 1996	November 6, 1996
November 11, 1996	November 27, 1996		

This new drug application provides for the indication of reduction of relapses in patients with relapsing-remitting multiple sclerosis.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the attached version of labeling. Accordingly, the application is approved effective on the date of this letter.

Accompanying this letter (ATTACHMENT) is the labeling that should be used for marketing this drug product. These revisions are terms of the NDA approval. Marketing the product before making the agreed upon revisions in the product's labeling may render the product misbranded and an unapproved new drug.

We have the following additional comments:

Chemistry:

We remind you of the following specifications agreed upon in a December 3, 1996 telecon between Dr. Paul Leber, Dr. Russell Katz, Dr. Stanley Blum, Dr. Martha Heimann, and Ms. Teresa Wheelous of the Division and Dr. Carol Ben-Maimon and Debbie Jaskot of your firm:

RRT at peak maximum:

RRT at -2SD:

RRT at -1SD:

RRT at +1SD:

The approximate molecular weight range of · is acceptable for use in the drug product labeling.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Phase 4 Commitments

We remind you of the Phase 4 commitments specified in the October 4, 1996 approvable letter. Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-622. Approval of this submission by FDA is not required before the labeling is used.

Additionally, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print.

Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Teresa Wheelous, R.Ph.
Regulatory Management Officer
(301) 594-2777

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

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

DATE: December 18, 1996

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

SUBJECT: NDA 20-622, Copaxone® [glatiramer acetate, formerly identified as copolymer-1]

TO: File NDA 20-622
&
Robert Temple, M.D.
Director, Office of New Drug Evaluation 1

This memorandum conveys the Division's recommendation that NDA 20-622 for the use of Copaxone® [glatiramer acetate, formerly identified as copolymer-1] in the management of patients with relapsing remitting MS be approved.

The sponsor has complied with the conditions of approval enumerated in the approvable action letter of October 4, 1996. Follow receipt of the agency's letter, the firm initially sought extensive revisions to the text of product labeling proposed in the approvable action letter. However, following discussions between its representatives and Division staff, the firm agreed that to accept, without substantive modification, the labeling that had been proposed by the agency.

Our Program Management staff have reviewed the latest draft of labeling, and find that, with the exception of a change in official generic name[1], it conforms in all but a few minor, and in my view ignorable, details to that conveyed in the agency's approvable action letter. The sponsor has seen all but our last revision of the final draft; again, I believe the labeling under which Copaxone will be approved for marketing of Copaxone differs in only minor details from that the firm last reviewed.

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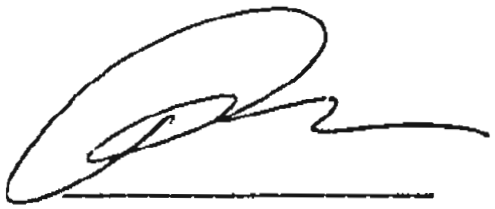
[1] necessitated by USAN's ruling that the original generic name, copolymer-1, was unacceptable.

Accordingly, the other requirements of approval having been satisfied, the application may be approved.



Paul Leber, M.D.
December 18, 1996

532

REQUEST FOR TRADEMARK REVIEW

TO: Labeling and Nomenclature Committee
Attention: Daniel Boring, Chair, (HFD-530) MPN II, (827-2333)

Thru: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

From: Teresa Wheelous, Regulatory Management Officer (594-5535)
Division of Neuropharmacological Drug Products, HFD-120

Date: December 19, 1995

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: COPAXONE **NDA#:** 20-622

Established name, including form: Copolymer-1 for injection (IND

USAN NAME

Other trademarks by the same firm for companion products: None

Indications for Use (may be a summary if proposed statement is lengthy):
Slowing progression of disability and reducing frequency of relapses in patients with relapsing-remitting multiple sclerosis.

Initial comments from the submitter: (concerns, observations, etc.)

None.

cc:
NDA 20-622
HFD-120/division file
HFD-120/Leber
HFD-120/Katz/Rouzer-Kammeyer
HFD-120/SBlum/MHeinman
HFD-120/Wheelous

m:dos\wpfiles\nda\nomen.con
final: Dec 19, 1995

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-622 Trade (generic) names COPAXONE (COPOLYMER-1)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&MC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

7/3/96 9/27/96
Date

cc: Orig NDA
HFD- /Div File
NDA Action Package

Consult #532 (HFD-120)

COPAXONE copolymer-1 for injection

A review revealed no names which sound like or look like the proposed name. However, the Committee was uncertain about the USAN name since it does not appear in the current USAN handbook nor does it seem to comply with the usual USAN nomenclature conventions.

The Committee has no reason to find the proposed name unacceptable, but would suggest that the sponsor contact USAN regarding the use of the proposed USAN name.

CDER Labeling and Nomenclature Committee

T.K. Boring, Chair

AUG 10 1995

Registered Mail
Return Receipt Requested

NDA 20-622

Teva Pharmaceuticals, USA
Attention: Stanley Scheindlin, D.Sc.
1510 Delp Drive
Kulpsville, Pennsylvania 19443

Dear Dr. Scheindlin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copaxone® (Copolymer-1) Injection.

On the basis of our initial review of your new drug application referred to above, received on June 13, 1995, and acknowledged on July 5, 1995, we have determined that the application is not acceptable for filing under 21 CFR 314.101(d)(3) in that it is incomplete because it does not contain information required under 21 CFR 314.50(d)(1)(i and ii). The critical deficiency resides solely in the chemistry, manufacturing, and control section. The deficiency is as follows:

The application fails to contain information necessary to evaluate the identity, quality, purity, and strength of the new drug substance/drug product (21 CFR 314.50(d)(1)(i & ii). Specifically, you have not submitted information describing the preparation and characterization of critical reference standards required for review of your application.

The materials described as Copolymer-1 markers and Copolymer-1 controls are critical primary reference standards for molecular weight determination in the methods listed below. No information about these materials, other than a brief paragraph (e.g. volume 1.3 pg. 038), has been provided.

Method No.

We are unable to evaluate the validity of these methods in the absence of information establishing the identity of the reference materials, i.e. the Copolymer-1 markers and controls. The following information is required for each reference sample.

a. A detailed description of the synthesis and purification of the marker.

b. Spectroscopic and physical data to establish the chemical structure and any pertinent conformational properties, e.g.∝-helical structure of the marker. This should include copies of actual spectra (e.g. NMR, IR, MS) for each marker.

c. All analytical data and relevant calculations used to determine the molecular weight distribution of the markers.

Although not reasons for this Refuse to File Action, we have completed a preliminary review of your application and have identified the following deficiencies:

Chemistry and Manufacturing:

2. We note that your application contains no evidence supporting your ability to scale up production of the drug substance. Should your application become approvable you will be limited to batches no larger than the pilot scale presently described until validated process scaleup information and detailed analytical data from production size batches of drug substance have been provided and reviewed.

3. Please submit a table linking drug substance lot numbers, drug product lot numbers, and study description and number for all lots of drug substance / product used in both preclinical and clinical studies. Additionally, we request full analytical data for all of these lots including copies of the reverse phase

4. The following applications and DMFs may not be referenced in support of the NDA until the IND and DMF holders submit Letters of Authorization (LoA) allowing the Agency to access their files on your behalf:

   a. IND . . Currently TEVA is authorized by to access these applications only for the treatment protocol submitted under IND

b. DMF Currently TEVA is authorized by Ben Venue to access this file for the treatment protocol IND only.

c. DMF submitted in the NDA is for Ben Venue, not TEVA. This LoA is not transferrable.

5. Please submit available analytical data tables for the drug substance and drug product lots on a 3.5 inch diskette in a spreadsheet format (i.e. Lotus or Excel).

6. In Section 3.2.6 Drug Substance Stability, please provide the following:

a. Supportive stability data referenced in this section.

b. Representative for non-stressed samples and for samples exposed to each stress condition.

c. Moisture content, acetate content, and amino acid analysis at the end of the proposed 6 month retest period or any longer period proposed as an expiration date.

7. In Section 3.3.7.4, for manufacture of the drug product at Ben Venue Laboratories, a Master Formula should be provided and the Formula Card should indicate amounts of drug substance, excipients, and batch scale.

Pharmacology:

We request that you submit any data you might have addressing the issue of whether or not the antibodies produced as the result of administration of Copolymer-1 are neutralizing antibodies with respect to drug activity.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file this application. To file this application over FDA's protest, you must avail yourself of this informal conference. We encourage you to avail yourself of a meeting with the Agency to discuss your resubmission. If you have any questions please call:

Teresa Wheelous, R.Ph.
Regulatory Management Officer
(301) 594-2777

If after the informal conference, you still do not agree with our conclusions, you may make a written request to file this application over protest, as authorized by 21 CFR

314.101(a)(3). The filing date will be 60 days after the date you requested the informal conference.

Under the Prescription Drug User Fee Act of 1992, FDA will refund one-half of the fee submitted with this application (25% of the total fee due). If you decide to file this application over protest, the filing of this application over protest will be regarded by the Agency as a new original application for user fee purposes, and you will be assessed a user fee applicable to new submission.

Sincerely yours,

8/10/95

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

t.e lw.S

NDA 20-622

OCT 20 1995

Teva Pharmaceuticals USA
Attention: Dr. Stanley Scheindlin
1510 Delp Drive
Kulpsville, PA 19443

Dear Dr. Scheindlin:

We have received your new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Copaxone® (Copolymer-1 for Injection)
Therapeutic Classification:	Standard
Date of resubmitted Application:	October 10, 1995
Date of Receipt:	October 11, 1995
Our Reference Number:	NDA 20-622

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on (60 days from receipt) in accordance with 21 CFR 314.101(a).

Should you have any questions, please contact:

Teresa Wheelous
Regulatory Management Officer
Telephone: (301) 594-2777

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and
Research

NDA 20-622

TEVA Pharmaceuticals USA
Attention: Stanley Scheindlin, Ph.D.
1510 Delp Drive
Kulpsville, PA 19443

AUG - 7 1996

Dear Dr. Scheindlin:

Please refer to your pending October 10,1995 new drug application resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Copaxone (copolymer-1) injection.

We also refer to your amendments dated January 10, 1996 and March 29, 1996.

We have completed our review of the microbiology and chemistry sections of your submission and have identified the following deficiencies:

Microbiology:

A. Provide the following information about the drug product manufactured at Teva Pharmaceutical Industries:

1. The bulk drug product prior to filtration is a peptide solution and does not contain a preservative.
   a) Indicate whether the bulk solution supports microbial growth.
   b) Submit information regarding the total bioburden load and volume of a batch of unfiltered bulk drug solution.
   c) Indicate the kinds of microorganisms that can be recovered from the bulk solution.
   d) Indicated the rationale for the limit number in the unfiltered bulk solution. We note that specification of for the bulk drug substance.
   e) Indicate the alert and action limits for the bulk solution at the Teva facility.

2. The sterilizing filters should ideally be validated with product inoculated with the challenge microorganism. Recirculation of drug product solution followed by a microbial filter challenge does not demonstrate the capabilities of the filter to sterilize the drug product solution. Please submit evidence that indicated that the sterilizing filters are capable of sterilizing the bulk solution. Indicted the actual CFU of P. diminuta used and recovered for assessing the microbial retentivity of the sterilizing filters.

3. Filtration conditions are not specified in the submission. Describe conditions including bulk solution volume and filtration time, temperature, pressure, and

the set-up used during the filtration process. Indicated whether one or two sterilizing filters are used to filter the bulk solution. In the event of a filter failure, what actions would be taken?

4. Indicated storage temperature and conditions during the holding periods for the bulk product. Describe the sterilization validation of the holding tanks and vent filters.

5. A description of the was omitted from the application. Please describe the includ

6. Describe the autoclave loading patterns, the placement of the thermocouples and biological indicators during the sterilization validation of the closures, equipment, containers and components. Identify the commercial source, the stability of the biological indicators used. Corroborate the microbial counts and resistance and provide performance characteristics.

7. Include a description of the bacterial endotoxin tests used for the product. The description should include qualification of the laboratory, inhibition and enhancement testing and results, determinations of noninhibitory concentration and maximum valid dilution.

8. Submit information on the sterilization validation of the freeze-drier.

B. Provide additional information regarding the manufacturing process at the Ben Venue Laboratories facility in Bedford, Ohio.

1. The validation of the sterilizing filters as conducted at the Teva manufacturing facility is inadequate. The sterilizing filters should ideally be validated with product inoculated with the challenge microorganism. Recirculation of drug product solution followed by a microbial filter challenge does not demonstrate the capabilities of. the filter to sterilize the drug product solution. Please submit evidence that indicates that the sterilizing filters are capable of sterilizing the bulk solution or that organisms cannot be tested by direct inoculation into the product. Indicate the actual CFU of P. diminuta used and recovered for assessing the microbial retentivity of the sterilizing filters.

2. Submit information on the sterilization of the freeze-drier.

3. Provide data on the sterilization of the sterilizing and vent filters.

4. Specify what are actions #AN-S-3087-1 (p.039 237,241), #AN-S-086 (p. 039 240), and #AN-S-3-077 (p. 139 250, 252,253).
5. Include a description of the bacterial endotoxin tests used for the product. The description should include qualification of the laboratory, inhibition and enhancement testing and results, determinations of noninhibitory concentration and maximum valid dilution.

Chemistry:

1. Please provide additional information about the synthesis of copolymer-1 drug substance:

6 Pages

Purged

f. Shelf-life instructions in patient insert (Vol. 3.14, p. 29)

> The shelf-life of COPAXONE® as packaged for sale is 18 months when stored in a freezer (-20°C to -10°C). This product contains no preservatives and should be used immediately after reconstitution or discarded. Protect COPAXONE® from light.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Teresa Wheelous, R.Ph.
Regulatory Management Officer
(301) 594-2777

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

TABLE OF CONTENTS

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 30 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. Sources for the Review

The Cop-1 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 PNs. 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% (5/844) 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 electively 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 clarification 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

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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*, 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

*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 68.2 ± 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
Rash	6	24.0	5	20.0
Sweating	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, dermatomycosjs, 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(5.1)
	≥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 ($x10^3/\mu L$)	$\leq 2.8 \times 10^3/\mu L$	5(2.5%)	1(0.4%)
	$\geq 16 \times 10^3/\mu L$	7(3.5%)	5(2.8%)
Platelets* ($x10^3/\mu L$) N=292	$\leq 75 \times 10^3/\mu L$	0	2(1.13%)
	$\geq 700 \times 10^3/\mu L$	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*
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	8537	41	20	72	Esophagitis
Hemic and Lymphatic	01-9001/9001E	707	26	20	-	Lymphadenopathy
Nervous	01-9002	5/2	26	20	75	Dizziness/vertigo

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 (Copoxane) 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: Kenneth 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 protocol, 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.

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, there 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					
P-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 subsquently 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 Last Date (dy-mo-yr)
		Bornstein		Teva				
		14,115	28,580	27,998	CRFs	Publication	Other	
CAL PHARMACOLOGY								
BR-OB	US	x		x[a]	x	x	x[b]	N/A[c]
BR-OA	Israel			x[a]		x		N/A
BR-OC	US			x[a]		x		N/A
BR-OD	Germany			x[a]			x[d]	N/A
S 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[e]	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[e]	2/6/95
PASSIONATE USE & TP (US)								
BR-3	US		x	x[a]	x		x[e]	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 14.2.7.1

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 14.1.1.1, 14.1.1.1

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

...s: Trial Results – Core and Extension	Core Trial (24 Months)				Core Trial including Extension (up to 35 Months)				Relevance (Vol/Pg)	
	COPAXONE (N=125)	Placebo (N=126)	Reduction vs. Placebo	P	COPAXONE (N=125)	Placebo (N=126)	Reduction vs. Placebo	P	Technical Section	Report
...Rate	1.19	1.85	-36%	0.007	1.34	1.89	-32%	0.002	157 001	042 107 084 074
...Rate	0.80	0.84			0.49	0.72				
...Relapse										
...of relapse-free patients	35.8%	27.0%		0.050	33.6%	24.6%		0.035	157 001	042 109 084 078
...Time to first relapse (days)	287	168		0.007	287	168		0.057	157 001	042 111 084 079
...of relapses per patient 0 1-2 ≥3	47 30 23	34 63 37		0.023	42 53 30	31 51 44		0.008	157 001	042 111 084 078
...Endpoints ...Progression-Free Patients	78.4%	75.4%		0.470	70.0%	70.6%		0.189	157 001	042 112 084 080
...EDSS change from baseline	-0.05	0.21		0.023	-0.11	0.34		0.020	157 001	042 113 084 081
...Ambulation Index Change from baseline	0.25	0.20			0.20	0.36			157 001	042 115 084 084
...Proportion of patients 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%	56.0%			54.4%	56.2%				
Worsened Disability (EDSS change ≥ 1)	20.8%	28.8%			10.4%	31.2%				

...Up to 35 months in the extension phase

	Core Trial (24 Months)				Core Trial Including Extension (up to 33 Months)				Reference (Vol/Pg)	
	COPAXONE (n=125)	Placebo (n=126)	Reduction vs. Placebo	P	COPAXONE (n=125)	Placebo (n=126)	Reduction vs. Placebo	P	Teitelbaum Boston	Paper
	1.19	1.85	-28%	0.007	1.34	1.88	-32%	0.002	157 001	042 107 084 074
	0.80	0.84			0.48	0.72				
	33.6%	27.0%		0.098	33.6%	24.6%		0.035	157 001	042 108 084 078
	257	198		0.087	287	193		0.057	157 001	042 111 084 079
0 1-2 ≥3	42 60 23	54 55 37		0.023	42 53 30	31 31 44		0.008	157 001	042 111 084 078
	70.4%	75.4%		0.473	70.6%	70.6%		0.188	157 001	042 112 084 080
	-0.05	0.21		0.023	-0.11	0.34		0.020	157 001	042 113 084 081
	0.20	0.20			0.28	0.38			157 001	042 115 084 084
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%	59.0%			54.4%	56.8%				
Worsened Disability (EDSS change ≥1)	20.8%	23.0%			18.4%	31.2%				

Up to 33 months in the extension phase

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 9, 1996

FROM: Glenna G. Fitzgerald, Ph.D.
Pharmacology Team Leader
Division of Neuropharmacological Drug Products, HFD-120

TO: NDA 20-622, TEVA Pharmaceuticals
Copolymer-1; Copaxone®
Subcutaneous Injection

SUBJECT: Pharmacology and Toxicology Overview

The pharmacology and toxicology studies which have been submitted in support of this NDA for injectable Copaxone, indicated for the treatment of patients with exacerbating-remitting multiple sclerosis, are comprehensively summarized and evaluated in the excellent review by Dr. John Jessop. The reproduction studies are reviewed by Dr. J. Edward Fisher in an attachment to Dr. Jessop's review. It is Dr. Jessop's conclusion, as well as mine, that these studies marginally support approval of this drug for this serious, chronic indication, as long as a Phase 4 commitment to submit two valid lifetime rodent carcinogenicity studies is honored.

Primary Issue Affecting Approvability:

The major concern about the adequacy of the preclinical package stems from the fact that the carcinogenicity studies have not been completed, although studies in mice (3, 15, 30, 60 mg/kg/day) and rats (3, 7.5, 15, 30 mg/kg/day) using the subcutaneous route are in progress. This deficiency exists even though the sponsor was informed in several meetings over the years, and in written communications (letter of Dec. 1, 1993 attached as example), that carcinogenicity studies would be required at the time of filing of the NDA unless they could provide a compelling argument for why such a requirement should be waived. Their argument (May 4, 1995 letter attached) was deemed inadequate. They have referred to the then Step 2 ICH document which recommended that for life-threatening diseases "carcinogenicity studies may be completed post-approval". In general, postponement of carcinogenicity studies to Phase 4 completion has been allowed for drugs for serious or life-threatening diseases with onset in the elderly, or for which there is no available therapy, or if survival is altered by the drug. Multiple sclerosis is a disease of relatively young people who could be exposed for a significant number of years, and there also is an available therapy. It should also be noted that Copaxone is not used to alter survival or progression of

the disease. At the time the Division learned that Teva was going to submit the NDA without the carcinogenicity studies it was Dr. Temple's recommendation that the application be filed (May 26, 1995 E-mail to Dr. Leber), with the understanding that " We cannot, however, in advance of reviewing the data, including the evidence of clinical benefit, conclude that carcinogenicity studies will not be needed prior to approval."

The sponsor has included in the NDA a survey of tumors reported in their toxicology studies in support of their contention that there is no evidence that Copaxone possesses carcinogenic potential. In a fertility and reproductive performance study in rats, one middle dose dam (6 mg/kg/day) of 180 females in the study was found to have two malignant mammary epithelial tumors, one discovered on day 7 postpartum in the dorsum of the neck and one on day 20 in the mammary gland region. No tumors were observed in rats receiving 30 mg/kg for 6 months, and it is considered that the finding in the reproduction study is most likely not drug related. In a 4 week dog toxicity study, 10 oral papillomas were found, appearing in control and dosed animals. The incidence was 3/6 controls, 1/6 low dose, 4/6 middle dose, and 2/6 high dose. Six of the 10 spontaneously regressed during treatment. The sponsor has stated that these neoplasms are not uncommon in young dogs and that they usually are considered to be of viral etiology. These tumors are undoubtedly not drug related findings. It should, however, be noted that Copaxone was clastogenic in two *in vitro* human lymphocyte assays (according to FDA review but not according to the sponsor, vide infra). Copaxone was not mutagenic in the Ames test and the *in vitro* mouse lymphoma assay, and it was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay. However, in light of the clastogenic response in lymphocytes, the possibility that Copaxone may be carcinogenic in lifetime bioassays must be considered.

Other Toxicology Issues:

1) Genetic Toxicology:
The findings in two *in vitro* chromosomal aberration assays in cultured human lymphocytes should be addressed, particularly since the sponsor has stated in the proposed labeling that the results were negative. The data from these assays are on pages 100 and 101 of Dr. Jessop's review. In the first assay a significant increase in "cells with aberrations excluding gaps" was seen in the presence of S9 rat liver microsomes at 20 hours, but not at 44 hours. The sponsor considered this to be a negative finding. Our experts have advised us that the 44 hour time point is used only if 20 hours is negative, and if one suspects that the drug might delay mitosis. With a positive finding at 20 hours, the assay is considered to be positive. In the second assay, a significant effect was reported for one of two replicates, and for the mean of the two replicates, at 20 hours in the presence of S9. The sponsor reported this as a negative finding as well. This would constitute a positive response by FDA standards. I have therefore considered the findings in both studies to provide positive evidence for clastogenicity in the human lymphocyte assay and recommend inclusion of the results in labeling.

2) Immunotoxicology:
Dr. Jessop's review provides an excellent, in-depth summary and discussion of the immunotoxicological characteristics of this drug (pages 125 through 139 and 144 through 146), to which I refer the reader. The sponsor has conducted a rather extensive battery of studies to characterize the immunotoxicity of Copaxone. It is apparent that, although anti-Copaxone antibodies are produced, they are not neutralizing antibodies. Also, repeated administration to rats, monkeys and humans does not result in a general immunosuppressive effect. However, several hypersensitivity and potential autoimmunity type findings were reported in the toxicology studies, and the following sections have been added to labeling to describe them (Pharmacological Properties, following Clinical Pharmacology):

"Hypersensitivity: 1). In a 6-month rat and a 1-year cynomolgus monkey study at doses up to 30 mg/kg/day (15-times greater than the human dose in rat and 29 times greater in cynomolgus monkey on a mg/m^2 basis) injection site lesions and immune complex deposition in the glomeruli of the kidney occurred. The monkey study also revealed a low incidence of active fibrinoid arterial lesions in various highly perfused organs and inflammatory cell foci in brain (choroid plexus), spinal cord and heart. Although immune complex deposition in kidney did not result in detectable pathology, these results are consistent with a hypersensitivity response, most likely due, in part, to consistent antigenicity of the drug in all species tested. 2) In a study of Copaxone in mice by the subcutaneous route of administration, 59 of 600 treated animals died in the first 14 weeks of the study. The animals were dosed with a maximum of 60 mg/kg/day Copaxone, which is 15 times greater than the human dose on a mg/m^2 basis. A large proportion of these animals (62%) died within 5 hours of receiving drug. At necropsy the most consistent findings were at the injection site and in the vasculature and hematopoietic system, and the cause of death was reported to be a Type 1 hypersensitivity

Anti-DNA and Anti-Histone Antibodies: In a 52-week study in cynomolgus monkeys receiving s.c. administration of 1, 10 or 30 mg/kg/day, a statistically significant increase in antibodies to double-stranded DNA occurred in male (10 and 30 mg/kg, weeks 8 and 13, $p<0.01$) and female (10 mg/kg; week 8, $p<0.05$) animals. In this same study, a statistically significant increase ($p<0.05$) in antibodies to histones was found in males (all doses at weeks 4, 8, and 13; 10 and 30 mg/kg/day a weeks 26, 39 and 52) and females (all doses at weeks 4, 8, 13 and 26; 30 mg/kg/day at week 2). Doses of 1, 10 and 30 mg/kg/day are in the same range, 10-fold and 29-fold greater, respectively, than the human dose on a mg/m^2 basis. These antibodies are often associated with autoimmune disease."

Dr. Jessop has directed several comments to the clinical reviewer about the potential problems associated with the immunotoxicological profile of Copaxone, as observed in animal studies (see page 148 of his review). I shall elaborate briefly on one of the issues, that of the lack of histopathological lesions in the kidneys of animals in which immune complex deposition occurred. Data (obtained by measurement of TCA precipitable drug) from the chronic rat (6 month) study indicated that there was a two-fold increase in large degradation products of Copaxone or of intact drug in plasma at the end of the study. Results obtained early in the study (day 28) showed a preponderance of small breakdown products. No measurements were taken between those two time points, so it is not known if increased exposure to high molecular weight products occurred early or late in the study. Since the large polymers or intact drug are the species associated with immune complex deposition, it is conceivable that, if that occurred late in the study, there was insufficient time for the renal pathology to develop. Drug was not measured in the one year monkey study, in which immune complex deposition also occurred, so it is not known if there was a correlation between these effects in that species as well. Dr. Jessop has therefore suggested that it would be appropriate to determine if systemic exposure to intact drug also increases with time in patients.

3) Cardiovascular Effects:

Copaxone produced hypotension in rats, rabbits, cats and dogs when administered intravenously. This effect appears to be mediated by histamine release, at least in part. It also caused the release of interleukin-2 from human blood cells, which can result indirectly in prolonged hypotension. Hypotension was not observed in the sub-chronic and chronic toxicology studies in which Copaxone was administered subcutaneously. The following "Cardiovascular Effects" section has been included in labeling under "Pharmacological Properties".

"**Cardiovascular Effects:** *In vitro* studies demonstrated that Copaxone directly induced histamine release from rat pentoneal cells and human penpheral blood basophils from healthy volunteers and multiple sclerosis patients. Safety pharmacology studies in rats, cats and Beagle dogs demonstrated that i.v. administration of Copaxone resulted in hypotension (decreased mean arterial pressure), and mechanistic studies revealed that the effect in rats and cats was probably due to histamine. Arrhythmias with increased T,R and S amplitudes occurred in dogs after intravenous dosing. The no effect dose in rats and dogs was 10 mg/kg and 5 mg/kg, respectively. This is 5 or 8 times greater than the human dose (20 mg), respectively, on a mg/m^2 basis."

Recommendations:

This application may be considered to be approvable for pharmacology/toxicology, with the understanding that draft reports of the two ongoing carcinogenicity studies will be submitted as soon as they are available. Subsequent submission of final reports should include a complete listing of any changes noted between the draft and final reports. If it is determined that the validity of the mouse study has been compromised by excessive early mortalities, a second mouse study may be required.

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA Original Review

NDA #: 20-622

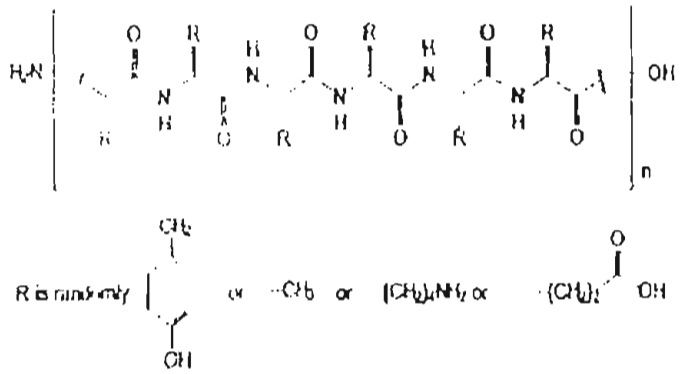
Review Date: February 21, 1995

Date of Submission: October 11, 1995

Sponsor: TEVA Pharmaceuticals USA
1510 Delp Drive
Kulpsville, PA 19443

Drug: Copolymer-1 for Injection (Copaxone®)

Structure:



Chemical Name Acetate salts of synthetic polypeptides containing 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.

Molecular Formula Poly[L-Glu$^{13-15}$, L-Ala$^{39-46}$, L-Tyr$^{8.6-10}$, L-Lys$^{30-37}$]nCH$_3$CO$_2$H

Molecular Weight

Pharmacological Category Immunomodulator (blocks myelin specific autoimmune response).

Indication: Slowing progression of disability and reducing frequency of relapses in patients with relapsing-remitting multiple sclerosis.

Related INDs/NDAs: IND

Proposed Clinical Use:

The recommended dose of Copaxone is 20 mg/day injected subcutaneously for slowing progression of disability and reducing the frequency of relapses in patients with relapsing-remitting MS. 20 mg/day for a 50 kg patient is about 0.4 mg/kg/day. (I used 50 kg because the majority of MS patients are female).

Previous Human Experience:

The total clinical program with Copolymer-1 (excluding the Clinical Pharmacology trials) consists of 11 clinical trials in which a total of 857 patients with MS have been exposed to the drug. 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/kg/day for at least 6 months. 490 received the drug for at least 12 months.

REVIEW AND EVALUATION OF PHARMACOLOGY TOXICOLOGY DATA
Original NDA Review

PHARMACOLOGIST: John J. Jessop, Ph.D., M.P.H.

NDA #: 20-622

DRUG: Copolymer-1 for treatment of relapsing-remitting multiple sclerosis.

TABLE OF CONTENTS

PHARMACOLOGY

Introduction

The pharmacology in this NDA is submitted in three parts, the first including information and studies pertaining to animal models of efficacy with respect to multiple sclerosis (MS), the second detailing studies to delineate the mechanism of action of the drug in treatment of MS, and the third describing the safety pharmacology. The pharmacology section of the NDA is quite extensive. The studies described in this section were performed over a period of about 25 years, primarily at the The majority of the studies were carried out by wrote the rather lengthy summary section included in the NDA concerned with the the mechanism of action and animal efficacy studies associated with Copolymer-1. For the purpose of this regulatory review, I will briefly summarize the more important pharmacological points included in the submission.

I. ***Copolymer-1 and Animal Models of Efficacy for Treatment of MS***

MS is a chronic inflammatory disease, affecting the central nervous system (CNS). In this disease, lymphocytes, predominantly T cells and macrophages, infiltrate the CNS and induce damage to the neuronal myelin sheath. Although the precise etiology of the disease has yet to be determined, there are at least two major hypotheses proposed to explain the pathogenesis of the disease:

1. MS results from a viral infection of the CNS and the resulting inflammatory condition is, mainly, an antiviral response.

2. MS is an autoimmune disease in which infiltrating T cells recognize self-antigens and attach normal nerve tissue.

These two hypotheses are not mutually exclusive, in that the autoimmune disease may actually be triggered by environmental factors, including viral infection or chemical or drug induction.

Multiple sclerosis and the EAE model

The putative autoantigen has not been identified in patients with certainty. Certain myelin-associated proteins are suspect, such as Myelin Basic Protein (MBP), Proteolipid Protein (PLP) and Myelin Oligodendrocyte glycoprotein (MOG). The animal model of human MS is "experimental allergic encephalomyelitis", or EAE (also termed "autoimmune encephalomyelitis"). This is widely recognized as a valuable model for studying MS.

There are basically two EAE animal models, the acute model and the chronic-relapsing model. In the acute model, EAE may be induced in animal species by the injection of CNS material, purified encephalitogenic proteins or their peptide fragments in Freund's adjuvant (CFA). Clinical signs such as paralysis of the hind legs generally appear in 10 to 21 days after challenge. This treatment usually ends in death, although some of the animals may recover spontaneously. In the chronic-relapsing EAE (CR-EAE) model, EAE is induced by injection of (SJL/J x BALB/C) F1 mice with mouse spinal cord homogenate (MSCH). Other CR-EAE models include the use of PLP in mice and in the juvenile strain 13 guinea pigs.

Immunological mechanisms in EAE and MS

In the EAE model, systemic injection of CNS tissue, purified encephalitogenic proteins, or their peptide fragments to experimental animals stimulates a population of autoreactive T cells which recognize the encephalitogenic determinants in association with Major Histocompatibility Complex (MHC) class II molecules. It is these autoreactive immune cells that migrate into the CNS and mediate the pathologic processes. The role of CD4+ cells in this process has been demonstrated by the fact that transfer of MBP and PLP-specific T cell lines and clones to naive recipients will induce EAE.

Immunological processes in EAE are similar to those shown in human MS patients. Several studies have implicated MBP-specific T cells as pathogenic in MS patients. Patients with MS as well as normal volunteers have been shown to respond to myelin autoantigens, suggesting MS may be related to a defect in immune regulation. These similarities indicate that the EAE animal model is a valuable one for human MS and for testing various immunomodulators as potential therapeutic agents.

Copolymer-1 is thought to interfere with the immunological processes presumed to induce MS in patients. Therefore, to determine the potential utility of this drug for the treatment of MS, the Sponsor first studied the efficacy of the drug in the EAE animal model.

Study of Copolymer-1 in the EAE model

The Sponsor states that there are basically three different possible effects of Copolyer-1 on both acute and CR-EAE, a) suppression, b) prevention and c) blocking. According to the Sponsor, **suppression** occurs when the drug is given to the animals **after** the challenge with CNS material, and involves a combination of the drug blocking autoantigen:MHC-II interactions and the drug treatment resulting in activation of T suppressor cells that specifically inhibit the function of autoantigenic T helper cell population. **Prevention** occurs when the drug is given to the animals **prior** to the myelin challenge, and probably involves generation of antigen-specific T suppressor cells. This is purported to be the most specific mechanism by which Copolymer-1 acts. Finally, **blocking** of EAE occurs when the drug is **co-injected** with the encephalitogenic CNS tissue and is most probably mediated by competition between Copolymer-1 and the autoantigen for binding to MHC-II molecules on the APC. This has been shown to be a relatively non-specific mechanism.

According to the Sponsor, adminstration of Copolymer-1 to animals in which EAE was induced by a number of antigens (e.g. MBP, MSCH or PLP) and in a number of different species (mice, rats, guinea pigs, rabbits and monkeys) resulted in preventing, blocking or suppressing of the disease, depending on the schedule of administration relative to the progression of EAE. These encouraging results were apparently found with both acute and CR-EAE. Apparently a number of other synthetic polypeptides also shared similar activity. However, Copolmer-1 was apparently not encephalitogenic and was the most active of the lot at mediating a protective effect on the EAE animals.

Reviewer's comments:

The fact that the drug demonstrated efficacy in the EAE animal model provides a valid scientific rationale for further study of the drug for use in the treatment of MS. However, one desirable characteristic of an immunosuppressive drug for the treatment of disease is a specificity for suppression of only the specific immune mechanism responsible for the disease. The sponsor acknowledges in this section that by at least one mechanism of action, that of blocking the binding of antigen to MHC-II molecules on APC, the drug action is not specific for myelin basic protein. Therefore, one might predict that the drug would act, at least in part, as a general immunosuppressant, which over time could impair the ability of the patients to resist infectious disease.

Theoretical Mechanism of Copolymer-1 in MS therapy

One theoretical approach to the treatment of MS is the autoantigen-based approach, which is aimed at the trimolecular complex formed by the antigen, MHC and the T cell receptor (TCR). The theory is that some, as yet undefined, autoantigen interacts with the MHC molecule on the surface of the Antigen Presenting Cell (APC) and, concomitantly, with the TCR of the autoreactive T cell, thus stimulating the autoreactive T cell to act against "self" tissue, such as the CNS. The therapeutic approach based on autoantigens is designed 1) to interfere in the activation of the T cell by preventing binding of the autoantigen to the MHC-II molecule on the APC, 2) to allow binding of the autoantigen to the TCR, but without providing the necessary signal for T cell activation (anergy) or 3) to allow binding to both MHC-II and TCR, but inducing T-suppressor cells instead of T helper cells. Number 1 and 2 would inhibit the activation of autoreactive T cells that damage the CNS, while number 3 would activate a population of T cells that would act to specifically inhibit the autoreactive immune response to the CNS.

II. ***Studies to determine the actual mechanism of action of Copolymer-1 in EAE***

Studies relating to the mechanism of action of Copolymer-1 in the blocking, suppression and prevention of EAE related to five areas, 1) cross reactivity between MBP and Copolymer-1, 2) activation of T suppressor cells specific for inhibition of autoantigen-specific T helper cells, 3) effects of Copolymer-1 on cellular responses to various antigens, 4) competition between Copolymer-1 and other antigens for binding to the MHC-II molecules and 5) studies carried out on human lymphocytes *in vitro*.

1) Cross-reactivity: One possibility is that Copolymer-1 could affect MBP-induced EAE through some cross-reaction with MBP. In fact, Copolymer-1 and MBP cross-reacted in delayed-type hypersensitivity reactions in guinea pigs, in which animals were sensitized with one antigen and then challenged with the heterologous antigen. Cellular cross-reactivity was demonstrated by direct cross-stimulation of lymphocytes *in vitro* in several species (mice, guinea pigs and rabbits). Finally, cross-reactivity between Copolymer-1 and MBP was demonstrated using both polyclonal and monoclonal antibodies to these antigens. A large proportion of the anti-MBP mouse monoclonal antibodies cross reacted with Copolymer-1, and a few of the anti-Copolymer-1 antibodies also cross-reacted with MBP.

Reviewer's comments:

Although the Sponsor contends that there are these immunological cross-reactions between Copolymer-1 and MBP, which could explain how Copolymer-1 might inhibit the induction of EAE by MBP administration, they also insist that Copolymer-1 is not, itself, encephalitogenic.

2) Induction of T suppressor cells: Adoptive transfer studies demonstrated that the ability to suppress EAE induced in mice by pretreatment with Copolymer-1 could be transferred to naive untreated animals by transfusion of spleen cells from treated animals. The cells that mediated this suppressive state were identified as suppressor T cells sensitive to low doses of cyclophosphamide and to anti-thy 1 antibodies plus complement. Further characterization was achieved using hybridoma technology. Hybridomas were established from the spleen cells of Copolymer-1-treated mice by fusion with a lymphosarcoma T cell line (BW), and some of these T-cell hybridomas were able to transfer and confer unresponsiveness to encephalitogenic stimulus in naive animals. These T-cell hybridomas were also capable of inhibiting antigen-specific proliferation of MBP-specific T cell lines *in vitro* and inhibiting the MBP-specific induction of T cell line proliferation and IL-2 secretion. These data all point to a T suppressor cell line with a specificity for inhibition of MBP-induced immune response in T cells.

3) Effects of Copolymer-1 on cellular responses to various antigens:

The immunological assays used to examine the ability of Copolymer-1 to inhibit T cell response (cellular response) included the delayed-type hypersensitivity reaction (DTH), both *in vivo* and *in vitro*, and the MBP-induced secretion of interleukin-2 and gamma interferon. Copolymer-1 treatment caused inhibition of the MBP-induced delayed-type hypersensitivity (DTH) reaction in mice and rats using different doses, schedules and routes (oral, s.c., i.v.), when drug was administered at the same time as the antigen. The drug failed to inhibit development of DTH response to MBP under similar conditions in the guinea pig. Copolymer-1 also inhibited the *in vitro* sensitization of guinea pig and rabbit isolated lymphocytes to MBP by blocking recognition of the antigen during the primary macrophage-lymphocyte interaction. Finally, Copolymer-1 inhibited the MBP-induced secretion of cytokines such as interleukin-2 and gamma interferon in a dose-dependent manner. It also inhibited the proliferation of MBP-specific and PLP-specific T cell lines of different MHC restrictions and epitope specificities in response to their homologous antigen.

4) Competition between Copolymer-1 and other antigens for binding to MHC Class II molecules:

The other mechanism of action proposed by the Sponsor for Copolymer-1 involved the ability of the drug to interfere with the interaction between the autoantigen and the MHC-II molecules on the APC. A number of studies were carried out to test this theory. First of all, the inhibitory effect of Copolymer-1 on MBP and PLP specific T cell lines was dependent on the number of APC, suggesting competition for the MHC complex. In an ovalbumin (OVA)-specific T cell hybridoma, addition of Copolymer-1 could not inhibit antigen-dependent stimulation when the drug was added after the APC were fixed following prolonged exposure to OVA, indicating that no effect of drug was found when the drug could no longer compete for MHC class II molecules.

Studies using biotinylated proteins and peptides confirmed the specific binding of Copolymer-1, MBP and MBP-derived peptides to MHC class II molecules of a number of different APC populations *in vitro*. Neither Copolymer-1 nor MBP bound to APC that did not express MHC class II. Furthermore, treatment with anti-A (MHC class II molecules) but not anti-H2K or anti-H2D (MHC class I molecules) abolished the binding, confirming that Copolymer-1 and MBP both bind to MHC class 2 molecules. Finally, Copolymer-1 showed competition for MBP binding on APC. However, Copolymer-1 was also able to compete with other myelin-associated proteins (PLP, MOG) for binding to MHC class II on APC, again emphasizing the lack of specificity for this particular mechanism of action.

Reviewer's comments:

These data outlined in #1-4 above are consistent with an immunological mechanism of action for Copolymer-1 in which the drug 1) induces a population of T suppressor cells that inhibit the function of the MBP-specific T helper cells and 2) interferes with the interaction between MBP and MHC class II molecules on APC. While the T suppressor cells induced by the drug are probably specific in their inhibition of only the T helper cell population that specifically recognizes MBP, the immunosuppression due to the blocking of binding of the MBP to MHC class II on APC appears to be fairly non-specific. These data, again, raise the question of whether or not Copolymer-1, by at least one of its proposed mechanisms of action, is a general immunosuppressant, and whether or not this drug might decrease the patients ability to resist infections.

5) Studies carried out in human lymphocytes *in vitro*.

Apparently, a number of studies demonstrated that human peripheral blood mononuclear cells (PBMNC) from both healthy donors and MS patients with different HLA haplotypes proliferated and released interleukin-2 (IL-2) and interferon-gamma (IFN-γ)-like activity in response to Copolymer-1, in the absence of prior sensitization. As the Sponsor concludes, **this suggests a cross-reaction between Copolymer-1 and some common undefined natural antigen**.

Reviewer's comment:

The Sponsor suggests that release of IL-2 and IFN-γ upon treatment of human PBMC with Copolymer-1 supports the theory that a cross-reaction exists between Copolymer-1 and some common undefined naturally occurring antigen. They further indicate that these data support the theory that the mechanism of action for Copolymer-1 in the treatment of MS or EAE (animal model) somehow involves this cross-reaction. However, the results of these studies in human PBMC raise a number of concerns.

First, these data in human PBMC suggest that initial administration of the drug might actually induce release of IL-2 and IFN-γ *in vivo*, even in patients that have never received the drug (no prior sensitization). It is interesting that administration of Copolymer-1 early in clinical trials often results in what the Sponsor terms a "systemic response", characterized by vasodilatation, chest tightness with palpitations, anxiety and/or dyspnea. It is known that the administration of IL-2 to patients also results in a "systemic response", in this case described as including fever, chills, fatigue, nausea and vomiting. These effects of IL-2 are thought to be due to its induction of production of a whole cascade of other cytokines, including interleukin-1 and TNF-α, which are also known to mediate hypotension and decreased cardiac output. Therefore, one must wonder if the "systemic effects" associated with Copolymer-1 administration might be, at least in part, due to it's ability to induce release of these cytokines.

Second, I am concerned that administration of Copolymer-1 will sensitize the immune system, resulting in induction of release of increasing amounts of these cytokines with repeated Copolymer-1 administration. Another adverse effect of repeated IL-2 administration is potentially life-threatening capillary leak syndrome. This is the result of endothelial cell destruction and perturbation of the vasculature, possibly due to either a direct action of IL-2 activated host cells and/or the result of an IL-2-mediated cascade of other cytokines (e.g. IL-1, TNF). Among other symptoms, vascular leak syndrome can lead to a dramatic decrease in blood pressure, shock, and eventually death.

Consistent with animal data was the fact that Copolymer-1 competed for binding sites on MHC-class II molecules on human-derived APC with MBP. However, also consistent with animal data was the fact that Copolymer-1 also competed with MOG and PLP-derived peptides for these binding sites, indicating that this action of the drug is non-specific in nature.

Reviewer's comments:

These data in human PBMC are consistent with animal data in suggesting that, at least with the mechanism of action involving inhibition of binding of autoantigen with MHC-class II molecules on APC, Copolymer-1 could be expected to act as a non-specific immunosuppressant. This again raises the concern that repeated administration of the drug might decrease the patient's resistance to infection. Also, induction of interleukin-2 production and release is of concern because the resulting cytokine cascade could potentially result in vascular leak syndrome.

Reviewer comments:

No data were submitted to evaluate binding of Copolymer-1 to the standard battery of receptor types, including adrenergic, cholinergic, etc.

Potential interaction between Copolymer-1 and interferon-beta (IFN-ß)

Apparently IFN-ß, a know modulator of the immune response, was shown to inhibit various T cell lines of human origin with respect to inhibition of proliferation and cytokine release. Its effects on MBP-specific T cell lines were found to be additive to those of Copolymer-1. This is consistent with the fact that Copolymer-1 has been shown to inhibit binding of antigen to MHC-class II molecules, while IFN-ß has been shown to decrease expression of MHC-class II molecules on the surface of APC. It is, therefore, likely that the two compounds would act synergistically to inhibit immune function mediated through MHC-class II molecules. The Sponsor suggests that the two drugs might be used together to treat MS at some point.

III. Safety Pharmacology

Cardiovascular pharmacology

Pharmacology data indicate that Copolymer-1 could potentially affect the cardiovascular system by a couple of different mechanisms. First of all, studies involving Copolymer-1 treatment of human PBMC revealed that the drug could induce release of IL-2 from immune cells that were not previously exposed to the drug. IL-2 has been shown, in turn, to induce release of IL-1 and TNF-α, cytokines that are known to induce hypotension, decreased cardiac output, and in the extreme, capillary leak syndrome. The Sponsor also demonstrated that Copolymer-1 administration could directly induce release of histamine, by a purported "non-immune" mechanism. Histamine is also known to mediate hypotension, probably at least in part through increasing vascular permeability. Therefore, the Sponsor was concerned about the potential effects of drug administration on the cardiovascular system, and they carried out a number of preclinical safety pharmacology studies to examine this issue. The following is a Table summarizing the *in vivo* safety pharmacology studies carried out by the Sponsor to determine the effects of Copolymer-1 on the cardiovascular system.

Table 22. Summary of In Vivo Studies on the Cardiovascular Effect of Copolymer-1

Species/Strain	No. Animals/dose	Dose mg/kg	Route of Admin.	Results	Ref
Rats, Wistar NON-GLP	9 males	10, 20 (Batch #TEVA/290021)	i.v.	1. No effect on H.R. or respiratory rate. 2. Hypotensive effect max at 20 mg/kg (194mm/Hg) 3. Hypotension blocked by combo H1 and H2 blockers 4. No tachyphylaxis 5. NOEL 10 mg/kg	TUP-1 Vol. 18, pg. 310
Cats TF NON-GLP	11 females	1, 2, 5, 10, 20, 40 (Batch #TEVA/290021)	i.v.	1. No effect on HR 2. Hypotension, max at 5 mg/kg. 3. Hypotension blocked by combo H1 and H2 blockers. 4. Tachyphylaxis. 5. Early pressor response at ≥20 mg/kg) 6. Histamine blockers increased pressor responses. 7. NOEL 1 mg/kg	TUP-1 Vol. 18, pg. 310.
Rabbits NON GLP	4 females	approx. 7 (Batch #TEVA/123-133)	i.v. bolus	1. Slight decrease (5%) in MAP between 2-3 hours after admin. 2. Increase in HR (13%) during same time period.	TUP-2, Vol. 17, pg 008.
Beagle dogs	2 males, 2 females	20 (Batch # TEVA/12+13+17B)	i.c.	Slight decrease in blood pressure within 15 minutes of drug admin.	TEV/042/COP, Vol 18, pg. 181.
Beagle dogs	3 males	0.4, 2, 5, 10, 20 (Batch #TEVA/RE-8781/1 and RE-8845)	i.v.	1. Decreased MAP (about 20% @ 10 mg/kg for 30 min.) 2. Decreased H.R (about 10%). 3. NOEL of 2-5 mg/kg	TEV/044/COP, Vol. 18, pg. 221
Beagle dogs	3 males	0.4, 2.5, 5, 10, 20 (Batch #TEVA/990168/II)	i.v.	1. Decreased MAP (about 67% @ 10 mg/kg, 37% at 10 mg/kg) 2. Decreased H.R. about 21%. 3. Arrythmias in all dogs at 10 and 20 mg/kg NOEL of 5 mg/kg	TEV/051/COP, Vol. 18, pg. 267.

1. Cardiovascular effects of copolymer-1 in rats and cats, TUP-1 (016 304), February 1994 (report), NOT GLP, Batch #TEVA/29021.

Objective: This was a non-GLP study in which the Sponsor examined the effects of Copolymer-1 administration on the cardiovascular system in rats and cats.

Study Description: Chronic indwelling catheters were implanted into the caudal artery of anesthetized Wistar rats and femoral artery and vein of anesthetized cats to measure blood pressure. Copolymer-1 was administered i.v. and blood pressure and respiration rates were recorded. The experiments also included use of histamine H1 and H2 receptor antagonists to determine if the cardiovascular effects were due to Copolymer-1-induced histamine release.

Results:

Rats:

Copolymer-1 was tested on two different batches of Wistar Rats at doses of 10 or 20 mg/kg. 20 mg/kg i.v. Copolymer-1 induced a 20.7 mmHg (first batch of rats) and 34 mmHg (second batch) drop in MAP in rats with latency periods for maximum effect of 112.9 and 79.6 seconds, respectively. There was little tachyphylaxis to this depressor effect with repeated administration of drug. Histamine blockers mepyramine (H1 receptors) and famotidine (H2 receptors) were shown to block histamine-related drops in MAP. 10 mg/kg i.v. mepyramine blocked the Copolymer-1 (20 mg/kg)-induced fall in blood pressure by about 54%. A combination of 10 mg/kg i.v. mepyramine and 35 mg/kg cimetidine (H2 blocker) blocked the response to Copolymer-1 completely. 4 mg/kg i.v. famotidine reduced the depressor response to Copolymer-1 (20 mg/kg) about 65%. A combination of i.v. famotidine (4 mg/kg) and mepyramine (5 mg/kg) blocked the response to 20 mg/kg Copolymer-1 about 94%.

Reviewer's comments:

Histamine is known to mediate a drop in blood pressure due to action of both H1 and H2 receptors found in various vascular beds. The H1 receptors are reported to be responsible for a more rapid drop in blood pressure, while the H2 receptors reportedly mediate a more long-term drop in blood pressure with slower onset. The data reported in this study are consistent with a histamine-mediated drop in blood pressure due to Copolymer-1 administration, in that administration of either H1 or H2 receptor antagonists alone only partially inhibited the Copolymer-1-induced drop in blood pressure, while use of the two antagonists together completely inhibited the depressor response.

Cats:

Depressor responses to i.v. administration of Copolymer-1 were considerably greater in cat than rat, with an i.v. administration of 1 mg/kg drug resulting in a mean fall in blood pressure from 38 to 95 mmHg. In the cat there was pronounced tachyphylaxis, with the depressor effect almost completely disappearing with repeat administration of Copolymer-1. With respect to use of histamine antagonists, results were similar to those in rat, with partial block of the Copolymer-1-induced depressor response with either H1 or H2 antagonist alone, and complete block with the use of a combination of the two.

In the cats, an immediate **pressor response** to Copolymer-1 administration was also found. Repeated i.v. dosing with 10 or 20 mg/kg of the drug resulted in transient increases in MAP of 25-35 mmHg. When animals were pre-treated with H1 or H1 and H2 antagonists, the increase in MAP was found to be up to 55 mgHg, and therefore, blocking histamine receptors actually increased the pressor response. In further studies to attempt to determine the mechanism for this pressor response, the Sponsor tried the use of an α-blocker (phentolamine) 1 mg/kg, which successfully blocked the pressor response to phenylephrine but not Copolymer-1. They were unable to determine the mechanism for the pressor response to Copolymer-1 administration in the cat.

Reviewer's comments:

The depressor response to Copolymer-1 in this NON-GLP study appeared to be mediated by the release of histamine, while the Sponsor was unable to determine the mechanism for the pressor response. However, data in human PBMC from both normal volunteers and MS patients demonstrated that treatment with Copolymer-1 resulted in production and release of IL-2. Release of this lymphokine can, in turn, cause release of a whole cascade of other cytokines, including the inflammatory cytokines IL-1 and TNF-α. Additionally, since Copolymer-1 is thought to interact with MHC-II molecules on APC (monocytes), it would not be surprising to discover that the drug directly induces release of IL-1 and TNF-α from monocytes. It is known that administration of TNF-α can result in an initial pressor response, followed by a depressor response thought to be due to induction of vascular leak syndrome. Administration of this inflammatory cytokine has also been shown to result in a decrease in peripheral blood neutrophils, as was reported in both subchronic rat (3-month) and monkey (28-day) studies. Therefore, it is possible that, in addition to histamine-mediated effects of Copolymer-1 on the cardiovascular system, administration of Copolymer-1 might also result in cardiovascular effects due to induction of release of TNF-α. This may be of concern, because long-term effects of continued TNF-α are known to be at least partially responsible for such serious conditions as the vascular leak syndrome and severe hypotension associated with septic shock.

It might be a good idea to recommend to the Sponsor that they monitor for plasma TNF-α in patients receiving the drug on a daily basis for life, as increased production of this cytokine can result in severe hypotension and death.

2. Effect of a single intravenous injection of COP-1 (20 mg) in the conscious rabbi . NON-GLP, July 1994, Batch #TEVA/123-115.

Objective: To assess the acute efect of an intravenous injection of Copolymer-1 on mean arterial pressure (MAP) and heart rate in the rabbit.

Study description: Copolymer-1 was injected I.v. by bolus into the marginal ear vein of 4 conscious female rabbits at a dose of 20 mg/rabbit (about 7 mg/kg). Blood pressure was monitored with a pressure transducer, implanted (under local anesthesia) into the central ear artery via a catheter. Heart rate was monitored by the same system. Rabbits were monitored for 3 hours after drug injection.

Results: No effects were seen up to 2 hours after drug injection. Between 2 and 3 hours after drug administration, MAP decreased about 5% (8 mmHg) and HR tended to increase slightly (300 beats/min in Control versus 339 in Treated animals). The Sponsor concluded that these effects were not drug-related, but were due to restraint of the conscious rabbits for an extended period of time.

Reviewer's comments:

I disagree that these effects were due to extended restraint of the rabbits. The Control animals were also restrained, and yet there were differences between Control and Treated animals. The decrease in MAP was minimal, but only a single dose of drug was used.

3. Cop-1 acute physiology study in beagle dogs by subcutaneous injection, June 1988, NON-GLP, Batch #TEV/12+13+17B (a mixture).

Objective: To assess the acute effects of Copolymer-1 on the cardiovascular system in Beagle dogs, as a result of a high dose subcutaneous injection.

Study description: Copolymer-1 dissolved in saline was injected subcutaneously into two male and two female dogs at a dose of 20 mg/kg body weight. Blood pressure and heart rate were recorded in the conscious dogs with the aid of a pressure transducer, at scheduled intervals for a period of 24 hours. Values were compared to those obtained before injection. Dogs were connected to the pressure transducer through their cannulated carotid artery.

Results: The Sponsor reports that there were no effects of the drug on blood pressure or heart rate. However, in three of the four animals (two males and one female) the blood pressure decreased about 7, 13 and 16% in the first 15 minutes, and in two of these animals remained at the lower level for at least 6 hours after drug injection.

Reviewer's comments:

This study is NON-GLP and includes only four animals, and therefore it is difficult to form any conclusions with respect to the results. However, it would appear that blood pressure did decrease slightly about 15 minutes after drug injection in three of the animals, and remained at these decreased levels for at least 6 hours. These data are consistent with cardiovascular effects in other animal species.

4. Copolymer-1: effects of I.v. injection on the cardiovascular system and respiration of Beagle dogs,

NON-GLP, November 1989, Batch #TEV/RE-6781/1 and RE-6645.

Objective: To assess the acute effects of Copolymer-1 on selected cardiovascular parameters and respiratoin in conscious Beagle dogs following intravenous injection of various doses.

Study description: Copolymer-1 dissolved in saline was administered i.v. to 3 conscious male dogs at doses of 0.4, 2, 5 and 10 mg/kg. Drug was injected successively to each dog at the various doses, after stabilization of the baseline. Direct blood pressure, heart rate, respiratory rate and ECG (lead II) were measured at time 0 (before treatment) and at 0-5, 15, 30, 45 and 60 minutes after treatment.

Results: Administration of 5 mg/kg resulted in marginal effects including a 17% decrease in H.R. at 30 minutes after injection, and virtually no effect on MAP. 10 mg/kg Copolymer-1 resulted in a 21% decrease in MAP lasting for about 30 minutes following drug administration and a 19% decrease in H.R. lasting for about the same period of time. Two of the dogs also exhibited increases in the T waves and in the R and S amplitutes at 10 mg/kg.

The Sponsor concluded that the results showed a "transient reduction in mean arterial pressure and heart rate and increases in the T, R and S amplitudes of ECGs."

The NOEL was listed by the Sponsor as 2-5 mg/kg for this study.

Reviewer's comments: These data are consistent with other studies in demonstrating that administration of Copolymer-1 results in a decrease in blood pressure. No attempt was made in this study to determine whether these effects were due to histamine release or some other mechanism of action. These data further demonstrated ECG effects of the drug.

5. COP-1: effects of intravenous injection on the cardiovascular system and respiration in conscious Beagle dogs,

NON-GLP, January 1990, Batch #TEVA/99016/II.

Objective: To assess the acute effects of Copolymer-1 on selected cardiovascular parameters and respiration in conscious Beagle dogs as a result of intravenous injection of various doses.

Study description: Copolymer-1 dissolved in saline at 10 mg/ml was administered i.v. to 3 conscious male dogs at doses of 0.4, 2, 5, 10 and 20 mg/kg. The various doses were injected successively to each dog, after baseline stabilization. Direct heart rate, blood pressure, respiratory rate and ECG (lead II) were measured at time 0 (before treatment) and at 5, 15, 30, 45 and 60 minutes after treatment.

Results:

Following injection of Copolymer-1, reduced mean arterial blood pressure (MAP) and heart rate were observed at 10 and 20 mg/kg for about the first 15 minutes after drug administration. At 10 mg/kg, MAP dropped an average of 63% below baseline, while heart rate decreased about 21% below baseline. At 20 mg/kg MAP dropped about 37% and H.R. about 24%.

Furthermore, ECG results demonstrated that all dogs exhibited increases in the T-wave and, in some cases, in R and S amplitudes at 10 and 20 mg/kg. And finally, arrhythmia was noted in all dogs at doses of 10 and 20 mg/kg, mostly up to 15 minutes after administration.

The Sponsor estimated the NOEL for Copolymer-1 in this study to be 5 mg/kg.

Reviewer's comments:

It is of some concern that these animals experienced arrythmias after a single i.v. injection of the drug. The Sponsor did not attempt to determine the mechanism of action for this phenomenon. However, in keeping with their hypothesis that the drug is a direct inducer of histamine release, it is known that histamine can directly affect the heart. Apparently, H1 receptors can be involved in the slowing of AV conduction, H2 receptors can be involved in both heart contractility and electrical conduction. High dose histamine is also known to induce arrhythmias. Therefore, one possible explanation for these effects could be a direct induction of histamine release by the drug.

Analysis of dose at which cardiovascular effects occurred compared to human dose

The clinical dose of Copolymer-1 proposed for use in this NDA is subcutaneous injection of 20 mg/day of drug for the life of a patient with relapsing-remitting MS. For a 50 mg patient (MS is predominantly found in women) this translates into about 0.4 mg/kg/day. The NOEL for the safety pharmacology studies in dogs was reported to be 5 mg/kg. Since there are few pharmacokinetics data presented for this drug, we are left with a comparison on either a mg/kg or a mg/m^2 basis. With respect to mg/kg, the NOEL in dogs is about 12.5-fold greater than the proposed clinical dose. With respect to a surface area comparison, thought by some to be a more accurate means of comparing comparable doses between the species, a 5 mg/kg dose in dog is equivalent to about a 2.5 mg/kg dose in man. Therefore, on a surface area basis, the NOEL in the dog (5 mg/kg) is about 6.25-fold greater than

the proposed clinical dose. The major concern is that, in the dog, a two-fold increase in dose (from 5 mg/kg to 10 mg/kg) took us from the NOEL to dramatically decreased blood pressure, alterations in ECG patterns, and arrythmias. These data do not provide for much of a safety margin for the drug.

However, one must also consider the fact that the route of administration in the dog studies was different from the proposed clinical dosing. In the dog studies, i.v. bolus administration was used, while subcutaneous administration is proposed for the clinic. It is often true that i.v. administration of a drug results in greater toxicity than other routes, usually due to the fact that drug reaches the plasma more rapidly by i.v. administration, and plasma Cmax levels are usually higher by this route of administration, often resulting in greater toxicity. In fact, in the one dog study in which s.c. administration was used (2 males, 2 females), only a slight decrease in blood pressure was reported, and there were no direct effect on the heart seen.

Effects of Copolymer-1 on Smooth Muscle Preparations

The effects of Copolymer-1 on smooth muscle preparations were examined in a NON-GLP study (Study #TUP-3, January 1994). The smooth muscle preparations tested included ileal strips derived from male guinea pigs, tracheal strips derived from male guinea pigs, and stomach fundic tissue extracted from CR rats.

Results in guinea pig ileum demonstrated that Copolymer-1 showed a phasic response that developed within a few seconds, followed by a tonic contraction that built up and lasted for about 30-50 minutes. In most cases the supramaximal dose of Copolymer-1 for this response was 1.6 mg/ml, while the contractile potency in terms of an EC50 was about 0.4-0.8 mg/ml. These contractions were inhibited by H1 nd H2 histamine antagonists and by inhibitors of the prostaglandin/leukotrienes pathways. A combination of H1 plus H2 blockers accomplished a maximum inhibition of about 54%. Ultimately, the contractile response most likely depended on calcium mobilization, as complete inhibition of contraction was mediated by calcium blockers such as verapamil and nifedipine.

In rat stomach strips, Copolymer-1 treatment resulted in a contractile response which generated a pattern of mixed phasic contractions superimposed upon tonic contractions. The response was strongly suppressed by atropine (0.1 μM) and indomethacin (1 μM).

Copolymer-1 at a concentration of up to 1.6 mg/ml failed to induce a contractile response in tracheal preparations from non-sensitized animals. However, a contractile response, though somewhat inconsistent, could be evoked in preparations from animals that had been sensitized to the drug in advance. Furthermore, in the presence of indomethacin (3 μM), a consistent and uniform contractile response could be elicited from preparations from sensitized animals. The Sponsor states that this response, though not particularly relevant with respect to drug efficacy, could be important when the drug is administered in high dose by the i.v. route of administration.

Effects of Copolymer-1 on histamine release in two types of cells: rat peritoneal mast cells and human peripheral blood basophils

In a NON-GLP study to assess the effect of Copolymer-1 to stimulate release of histamine from rat peritoneal mast cells (study #HAP-1, Hadessah Medical Center, Jerusalem, Israel, August 1994), mast cells were incubated in the presence of various concentrations of Copolymer-1, with 3 µg/ml of compound 48/80 as a positive control and with vehicle as a negative control. The cells were exposed to the drug for 20 minutes at 37° C., pelleted, and histamine was measured in the cell pellet after sonication and in the supernatant through the use of a radioenzymatic assay. The percent histamine release was calculated, and results are shown in the following table:

Histamine release from rat peritoneal cells

Inducer	Conc. (µg/ml)	Net histamine release* %	SD
48/80	3	57.4	8.2
Copolymer-1	0.01	Lower than Control	
	0.1	6.5	1.2
	1.0	8.9	3.8
	5.0	19.7	8.8
	10.0	27.1	5.9
	100	43.9	3.9
	250	58.8	4.2
	500[b]	75.0	4.7

*Net histamine release was calculated by subtraction of the value obtained in vehicle control incubations. The latter was below 5%.
[b]At 500 µg/ml, a cytotoxic effect of 10-20% was noted by staining with trypan-blue.

As seen in this table, Copolymer-1 directly induced release of histamine from rat peritoneal cells, with measurable histamine beginning at about 0.1 µg/ml drug. Histamine release was induced by Copolymer-1 in a dose-related manner, with over 50% release at 250 µg/ml drug. The Sponsor states that according to the scientific literature, rat peritoneal mast cells resemble human mast cells of the connective-tissue type, and it can therefore be inferred from these data that Copolymer-1 will also directly induce release of histamine from human mast cells.

Effects of Copolymer-1 on histamine release from human peripheral blood basophils was also examined in PBMC from either healthy volunteers or Copolymer-1 treated MS patients. Apparently some measurable histamine release was seen at 100 µg/ml Copolymer-1, with about 20% release at 1000 µg/ml. Therefore, these human basophils were not as sensitive to Copolymer-1 induced histamine release as the rat mast cells. The Sponsor reported that this histamine release was found in human PBMC from both healthy volunteers and Copolymer-1 treated MS patients.

ADME

Copolymer-1 is a synthetic "immunoregulatory" peptide, designed to prevent the autoimmune response in MS in which T cells are primed to specifically destroy myelin. In fact, although not specifically stated by the Sponsor, Copolymer-1 is actually a "peptide vaccine". Therefore, the most appropriate drug bioavailability is probably that intact Copolymer-1 drug that reaches the local lymph nodes that drain the tissues of the subcutaneous injection site (see Summary and Evaluation Section–ADME for further discussion). However, the Sponsor did not address this issue, but rather they presented data describing the systemic exposure of drug in animals.

The PK of Copolymer-1 was examined in terms of systemic exposure by administering radiolabelled drug. Data with respect to systemic exposure were problematic in that ^{125}I-labelled Copolymer-1 was used in the studies. Two problems are associated with this methodology, 1) ^{125}I-labelling is known to change the PK properties of a peptide and 2) this methodology did not allow them to clearly differentiate between plasma concentrations of intact parent drug, degradation products, or free radiolabelled iodide (see Summary and Evaluation Section–ADME for further discussion).

Absorption

Absorption studies after subcutaneous administration were carried out two ways, 1) extent of absorption was determined indirectly by measuring residual radioactivity at the injection site over time and 2) the rate of absorption was evaluated based on the plasma concentration-time curves for drug-related radioactivity. With respect to the extent of absorption, in mice, <14% of the total radioactivity remained at the injection site 1 hour after s.c. injection, and <5% of the dose remained after 8 hours at the injection site. This low residual radioactivity at the injection site within 1 hour following s.c. administration was interpreted by the Sponsor to mean that ^{125}I-Copolymer-1 was rapidly absorbed, and the 8 hour data indicated that the drug was extensively absorbed.

With respect to rate of absorption and elimination, plasma concentration-time curves in Sprague-Dawley rats administered Copolymer-1 by the s.c. route of administration were constructed based on "total plasma radioactivity". These data revealed K_{ab} (absorption rate constant) of about 0.1min^{-1} and a $T_{1/2}$ of about 10-20 minutes. Maximum plasma radioactivity after s.c. injection (both rats and monkeys) was attained in most animals in 2 hours (see Table 41 below). Therefore, based on these data, the drug was apparently both absorbed and eliminated fairly rapidly.

Table 41. Mean absorption parameters based on total plasma radioactivity after subcutaneous administration of ^{125}I-Copolymer-1.

Species/Strain	Group (M/F)[a]	Sampling Time	Copolymer-1 Dose (mg/kg)	Tmax[b] (H)	K_a[c] (Min^{-1})	$T_{1/2ab}$[d] (Min)
Rat/ Sprague Dawley	8/0	0.25, 0.5, 1, 2, 4, 6, 8, 10 12 h	0.5 50	1.2 2.5	0.09 0.04	9.0 18.8
Rat/ Sprague Dawley	14/0	3, 5, 8, 12, 15, 20, 30, 45, Min. 1, 1.5, 2, 3, 4, 5, 6, 7, 8 h	0.5	1.3	0.08	9.8
Rat/Drt:CD (SD)BR	5/5	2, 5, 10, 20, 30, Min, 1, 2, 4, 6, 8, 24 h	3 10 30	2[e] 2[e] 2[e]	ND[f]	ND
Monkey/Cynomolgus	1/1	2, 5, 10, 20, 30, Min, 1, 2, 4, 6, 8, 24, 72 h	20 40 60-h[h] 60-iso[i]	2[e] 2[g] 4[e] 2[g] 2 4 2 2	ND	ND

[a] M=Male; F=Female.
[b] T_{max}=time to maximal plasma concentration.
[c] K_a= Absorption rate constant.
[d] $T_{1/2ab}$=Absorption half-life.
[e] Median.
[f] ND=Not determined in this study.
[g] Data from individual animals.
[h] 60-h=Hyperosmotic formulation.
[i] 60-iso=Isosmotic formulation.

Pharmacokinetics

Due to the fact that it was impossible to know the proportion of the "total plasma radioactivity" that was made up of intact parent drug versus various degradation products versus free radiolabelled iodide, pharmacokinetics parameters were calculated based on: 1) the total radioactivity in plasma, and 2) the radioactivity in TCA-precipitable fractions of plasma.

Total radioactivity in plasma

Data for studies in rat and monkey, based on total radioactivity, are summarized in the following Table 44.

Table 44. Absolute values for pharmacokinetic parameters based on total plasma radioactivity following single subcutaneous doses of ^{125}I-Copolymer-1.

Report	Species	Gender	Dose (mg/kg)	Cmax [a] (µg/ml)	AUC $_{0\text{-}\infty}$ [a] (µg.h/ml)	AUC$_{0\text{-}t}$ [a] (µg.h/ml)
1028/21-1050 (037 217)	Monkey	Male	20	46.7	606.7	1391
			40	96.4	1513	3581
			60	141.5	2324	5425
		Female	20	50.3	691.9	1555
			40	78.0	1106	2930
			60	138	2289	5467
1028/19-1011 (037 114)	Rat	Male	3	5.1	58.3	61.4
			10	20.1	235.9	267.7
			30	54.4	642.3	699.1
		Female	3	5.5	66.5	71.8
			10	20.9	258.3	283.3
			30	60.9	719.6	766.6
BS/PK-2 (037 034)	Rat	Male	0.5	0.969	-	9.79
			50	73.96	-	773.9
BS/PK-3 (037 062)	Rat	Male	0.5	0.64	-	5.38[b]

[a] Cmax=maximum plasma concentration; AUC=area under the concentration-time curve.
[b] Original data were 322 µgxmin/ml; 322 µgxmin/ml converts to 5.36 µgxh/ml

Data shown in Table 44 above are pharmacokinetics data for total radioactivity found in plasma. These data show that, with respect to total radioactivity, plasma C_{max} and AUC levels after ^{125}I-Copolymer-1 s.c. injection in both rats and monkeys were linear and dose-dependent. No sex differences were found.

The Sponsor also carried out studies by the oral, i.v. and i.m. routes of administration. They state that the PK profiles for i.m. and oral administration were similar to that for s.c., although absorption was somewhat lower. They report the **absolute bioavailability for Copolymer-1 in the rat by the s.c. route of administration to be 46%** (relative to i.v. administration). However, this bioavailability figure is based on total radioactivity, and is therefore somewhat misleading.

Reviewer's comment:

The Sponsor gives a bioavailability figure for ^{125}I-Copolymer-1 of 46%. However, this figure pertains to total radioactivity determined in plasma. This figure is not really relevant to the mechanism of action because 1) as shown in the following "metabolism" section of this review, most of the total radioactivity found in plasma is actually metabolized/degraded drug 2) the drug is proposed by the Sponsor to act at the injection site, and therefore the systemic exposure is not required for the drug to work. As stated previously, my assessment is that Copolymer-1 is acting as a peptide vaccine, and the appropriate bioavailability is constituted by the intact drug that reaches the immune system through the lymph nodes that drain the area of the local s.c. injection site.

TCA-precipitable fraction

A problem with using radiolabelled drug is that the radiolabelled iodide can become dissociated from the drug and incorporated into other plasma proteins or remain free in the plasma. Furthermore, the intact peptide drug can become extensively degraded and still maintain the radiolabel. Therefore, determination of total plasma radioactivity will most likely yield an overestimation of systemic exposure to intact drug. The Sponsor reports that Copolymer-1 is approximately 80% TCA precipitable, and it is the high molecular weight drug that is detected by this methodology. Therefore, in an attempt to obtain a more meaningful value for systemic exposure, the Sponsor also determined plasma drug concentration using TCA precipitation. This methodology is also limited, in that the radiolabelled Copolymer-1 is incompletely precipitated by TCA and TCA will also precipitate some portion of the larger MW degraded drug as well as the parent. Furthermore, some free iodide will be incorporated into plasma proteins that are also TCA-precipitable.

The Sponsor reported that the TCA-precipitable radiolabelled material in plasma accounted for 20-40% of the total radioactivity at C_{max}. When the Sponsor used the TCA-precipitable radiolabelled material in plasma for PK calculations and extrapolated values for 0.3 mg/kg dose (the human dose; the Sponsor arrived at this figure by dividing the 20 mg/day dose by 70 kg person), they determined the predicted plasma C_{max} to be between 52 and 240 ng/ml. This extrapolation assumed linearity of PK and similarities across species (rat, monkey, human).

The Sponsor also pointed out that the $T_{1/2}$ for the TCA-precipitable material was about 50 hours, much longer than for total radioactivity (about 10 hours in rat). The Sponsor's interpretation of these results is that "...the elimination of total radioactivity from plasma is probably of no relevance to Copolymer-1, since it detects primarily the disposition of free iodide or of label which was further incorporated into other, unrelated molecules..." They point out that "...the elimination from plasma of TCA-precipitable radioactivity, with $T_{1/2}$ greater than 50 hours, supports a secondary association or incorporation of the radiolabel into other macromolecules..." Therefore, the Sponsor seems to suggest that, while TCA-precipitable material probably provides the best estimation of PK of the drug, this methodology is also flawed.

Extrapolation to therapeutic dose using "total radioactivity"

The Sponsor also used the "total radioactivity" values to predict the plasma C_{max} and AUC for the proposed human dose, 20 mg/day, which they calculate to be 0.3 mg/kg/day using a 70 kg patient. This extrapolation was accomplished by dividing the pharmacokinetic parameters (plasma C_{max} and AUC) for the PK data reflecting total radioactivity by the ratio of the experimental dose to the human therapeutic dose. Using this methodology, the Sponsor reported a predicted plasma C_{max} of 380-710 ng/ml for the proposed human dose of 20 mg/day (0.3 mg/kg/day for 70 kg person) (Table 45, 001 206, not included here).

However, then the Sponsor makes the following statement, "While a 50 mg/kg dose of ^{125}I-Copolymer-1 resulted in detection of radioactivity by means of HPLC paired with gamma counts (see figure 3, page 152) the same dose of unlabelled Copolymer-1 produced no detectable levels via HPLC fluorescence detection (Study GAD/PK-6). **Based on these animal studies, serum concentrations of Copolymer-1 are presumed to be low or not detectable following subcutaneous administration of 20 mg once daily to man."** This is a somewhat confusing statement, in light of the fact that they spent a great deal of time and effort in predicting the plasma C_{max} and AUC for a human dose of 0.3 mg/kg and arrived at the values mentioned above. However, I interpreted this statement to mean that the drug is not detectable in plasma, even when 50 mg/kg is administered s.c., unless the drug is radiolabelled. Normal HPLC fluorescence detection techniques are apparently not sufficient to detect drug, even when 50 mg/kg (which should result in about 150 µg/ml in plasma by radiolabelled studies) of drug is administered s.c.

Distribution

There were basically three NON-GLP studies submitted with the NDA that dealt with the issue of tissue distribution of Copolymer-1. Those studies are summarized in the following:

1. Copolymer-1, a single dose pharmacokinetic study, tissue distribution of ^{125}I-Copolymer-1 in healthy and experimental autoimmune encephalomyelitis (EAE) mice

NON-GLP, 1991.

Objective: Compare the tissue disposition pattern of Copolymer-1 related radioactivity in a murine model of MS with that of healthy mice after a single s.c. dose of ^{125}I-Copolymer-1.

Study Description: Healthy (21) and EAE-induced (16) female mice were given a single s.c. dose of 0.5 mg/kg ^{125}I-Copolymer-1, and one group was sacrificed 1 hour after dosing and a second group 8 hours after dosing. After decapitation, blood

(plasma), stomach, intestine, kidney, liver, spleen, brain, diaphragm, lung, heart, thymus, adrenal, urinary bladder and skin were all collected and examined for radiolabelled drug. Radioactivity was determined in plasma (total radioactivity), in TCA-precipitated plasma (TCA-precipitable drug), and in tissue homogenates using a gamma counter. Results were expressed as percentage of dose and as µg equivalents of intact Copolymer-1.

Results:

One hour after administration of rabiolabelled drug, the mean total concentration of Copolymer-1 related radioactivity in plasma was 43.15 µg/ml in healthy mice and 46.99 µg/ml in EAE mice. These concentrations declined to 28.2 and 17.4 µg/ml, respectively, after 8 hours. The TCA precipitate radioactivity, representing free drug and macromolecule-bound label, was 12.7 and 17.3% at 8 hours, for healthy and EAE mice, respectively.

Among the tissues examined, the stomach showed highest levels of radioactivity at both time points. The mean concentrations at 1 hour (272.7 and 282.2 µg/g in healthy and EAE mice, respectively) were about 6-fold higher than those for plasma. All other tissues showed levels lower than plasma. The brain exhibited the lowest uptake of drug-related radioactivity, and the difference in brain concentration between healthy and EAE mice (2.07 µg/g versus 45.5 µg/g) was statistically significant at the 1-hour time point.

The Sponsor stated that the fairly high levels of radioactivity in the stomach were probably due to a sequestration of free radiolabelled iodide released from the radiolabelled drug upon administration. The Sponsor concluded that there were no major differences between the tissue disposition pattern for drug-related radioactivity between the healthy and EAE-induced mice.

2. Copolymer-1, a single dose pharmacokinetic study, disposition of ^{125}I-Copolymer-1 in the rat,

NON-GLP, December 1994.

Objective: To assess the absorption, distribution, metabolism and excretion pattern of Copolymer-1 related radioactivity in rats after a single subcutaneous dose of ^{125}I-Copolymer-1.

Study description:

A single s.c. dose of 50 mg/kg ^{125}I-Copolymer-1 was administered to each of 24 rats. The rats were divided into three groups of eight rats each and sacrificed at 4, 8 or 12 hours after dosing. Blood, stomach, intestine, kidney, liver, spleen, brain, diaphragm, lung, heart, thymus, testicles, adrenals, and urinary bladder were collected for radioactivity determination in plasma, TCA-precipitated plasma and tissue homogenates.

Results:

The only organs demonstrating higher concentrations of the drug were the stomach and the intestines, consistent with the mouse study. 11.4% and 6.1% of the dose was found in the stomach and intestine, respectively, after 4 hours. This declined to about 1% of the dose after 12 hours in both organs. These were the only organs to demonstrate greater concentrations of the drug-related radioactivity (stomach, 308.8 µg equiv/g; intestines, 62.3 µg equiv/g; both at 4 hours) than plasma (59.5 µg equiv/g at 4 hours). The brain contained the lowest concentration of drug-related radioactivity. The Sponsor stated that this is probably due to drug difficulty crossing the blood-brain barrier.

3. Copolymer-1, a single dose PK study in the rat: an 8-hour monitoring of plasma radioactivity and tissue distribution after i.v., s.c., i.m. and oral administration,

NON-GLP, December 1994.

Objective:

To assess the bioavailability and tissue distribution pattern of Copolymer-1 and its metabolites in rats after oral, s.c., i.m. or i.v. administration of a single dose of ^{125}I-Copolymer-1.

Study description: 41 male rats were cannulated in their left femoral vein and artery, divided into four groups and administered a single dose of 0.5 mg/kg ^{125}I-Copolymer-1 by one of the following routes: i.v., i.m., s.c. or oral. Blood was withdrawn from the arterial cannula at 3, 5, 8, 12, 15, 20, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours after dosing. Plasma was prepared and TCA-precipitated, and the TCA-soluble fraction was further precipitated using silver nitrate. Animals were sacrificed at the end of the 8 hours and organs collected for tissue determination of drug-related radioactivity.

Results:

In this study, the Sponsor also examined the thyroid. A large proportion of the total drug-related radioactivity was found in the thyroid (>400 ng equiv/ml versus 220 ng equiv/ml in plasma after s.c. administration). The Sponsor makes the point that this is consistent with iodide concentration in the thyroid, and is probably due to a large amount of free radiolabelled-iodide that is released from the drug as the result of extensive metabolism associated with s.c. administration. Consistent with the other rat and mouse studies, the only other organ to demonstrate concentration of the drug was the stomach. In this study, by the s.c. route the stomach contained 4-fold higher concentrations of drug-related radioactivity than plasma. Brain contained the lowest concentration of drug-related radioactivity.

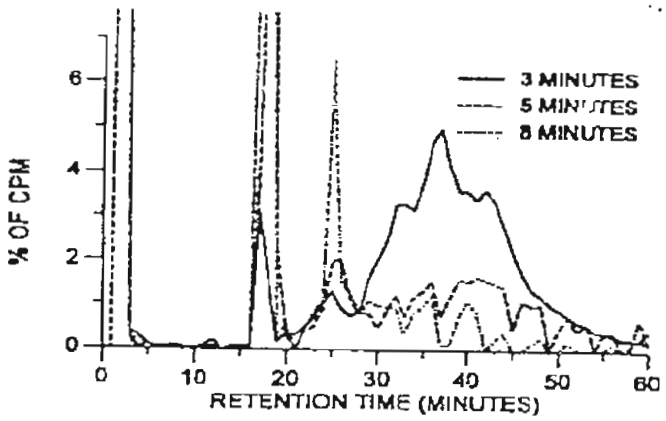
Metabolism

Studies were carried out both *in vivo* (rats and monkeys) and *in vitro* (rat and human tissues) to examine the metabolism of Copolymer-1. Various methodologies were used. In one study, the metabolism of Copolymer-1 was investigated using HPLC and combined HPLC/radiotracer techniques to monitor the disappearance of intact drug. In other studies, methods including radiotracer techniques and protein precipitation with TCA and precipitation of the TCA soluble fraction with silver nitrate ($AgNO_3$) were employed. The radioactivity in the TCA precipitate reflects high molecular weight material (including parent drug), the $AgNO_3$-soluble fraction contains the low molecular weight fraction, and the free iodide is contained in the $AgNO_3$ precipitate.

In Vivo Studies

Results from the studies in rats demonstrated that Copolymer-1 undergoes rapid degradation *in vivo*. The chromatographic profile of total radioactivity in plasma shown in Figure 3 below (001 218) demonstrates that at 3 minutes after s.c. administration of ^{125}I-Copolymer-1, a large proportion of intact drug, eluting with a retention time from about 30–45 minutes, was still present in plasma. However, at the 5 and 8 minute time points, additional plasma sampling demonstrated that the majority of the intact Copolymer-1 drug was already degraded to distinctly smaller fragments and free iodide. It is unclear whether these smaller species are Copolymer-1 metabolites or other unrelated species iodinated as the result of iodide exchange.

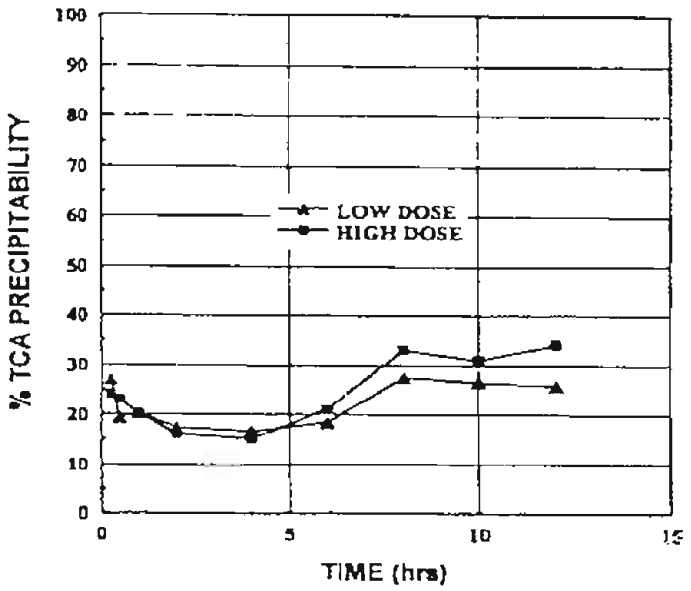
FIGURE 3. CHROMATOGRAPHIC PROFILE OF TOTAL RADIOACTIVITY IN PLASMA AFTER SUBCUTANEOUS ADMINISTRATION OF A 50 mg/kg SINGLE DOSE OF ^{14}C-COPOLYMER-1 TO RATS



In another rat study including s.c. administration of the radiolabelled drug, it was found that 4 hours after s.c. injection of ^{125}I-Copolymer-1 that only 20% of the total plasma radioactivity was TCA-precipitable (see Figure 5 below, 037 054). These data are consistent with degradation of the intact drug to smaller, non-precipitable species. However, the percentage of total radioactivity that was TCA-precipitable steadily increased over the next 41 hours to a maximum of about 80% of plasma radioactivity being TCA-precipitable (see Figure 6 below, 037 055). The Sponsor explains this phenomenon as incorporation of degraded radiolabelled peptide and amino acids into newly formed plasma proteins and binding of these radiolabelled degradation products as well as free radiolabelled iodide to plasma proteins that are also TCA-precipitable.

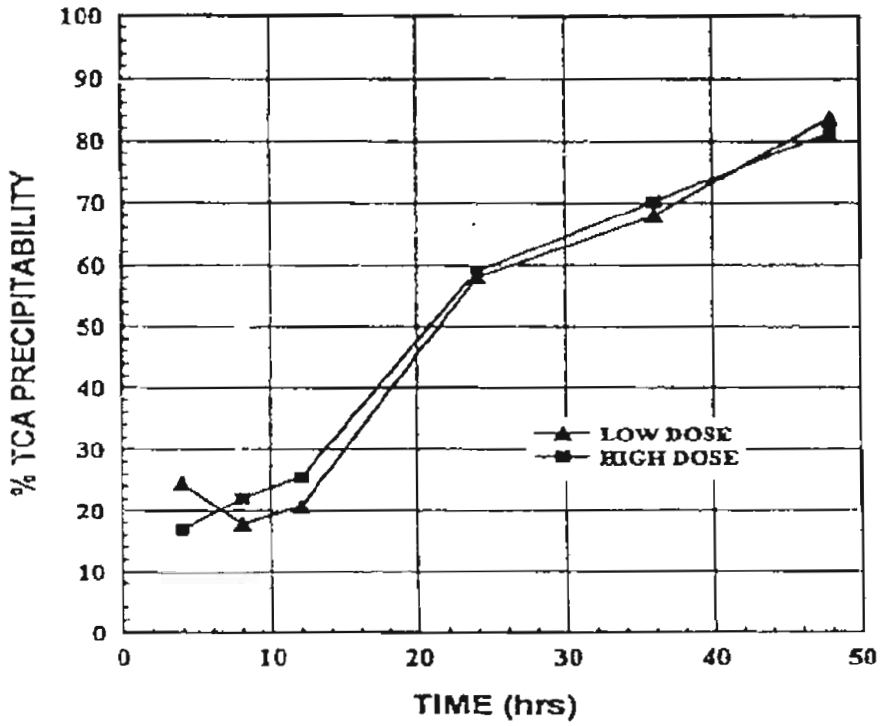
PK-24 21

FIGURE 5 TCA PRECIPITABILITY OF RADIOACTIVITY IN THE PLASMA AFTER S.C. INJECTION OF [illegible]-COPOLYMER-1 TO RATS



037 054

FIGURE 6 TCA PRECIPITABILITY OF RADIOACTIVITY IN THE PLASMA AFTER S.C. INJECTION OF ^{125}I-COPOLYMER-1TO RATS



037 055

In Vitro Studies

In one *in vitro* study, ^{125}I-Copolymer-1 was incubated with Sprague-Dawley rat plasma or tissue homogenates, and TCA-precipitable radioactivity was subsequently determined to examine the extent to which these various tissues were able to degrade the drug. Data, shown in the following table, demonstrated that rat plasma actually had a somewhat stabilizing effect on the drug (70% radioactivity recovered in TCA-precipitate from Control incubation versus about 77% from rat plasma incubation). However, subcutaneous tissue (19.4% TCA-precipitable radioactivity recovered), striated muscle (35.4%) and other tissues were shown to result in rapid degradation of the drug.

Table: In vitro stability of Copolymer-1 in rat plasma and tissue homogenates

Tissue	TCA Precipitate (% radioactivity recovered)
Control	70
Plasma	76.97
Liver	53.28
Stomach	53.41
Subcutaneous tissue	19.39
Small intestine	26.2
Striated muscle	35.37
Kidney	38.9

These data indicate that the drug was metabolized or degraded by enzymes associated with various tissue homogenates, with the greatest effect occurring in subcutaneous tissue. The involvement of a protease in the hydrolytic degradation of Copolymer-1 was examined by coincubation of small intestine and subcutaneous tissue homogenates in presence or absence of a protease inhibitor. PMSF, a peptidase inhibitor, was reported to reduce the degradation seen with subcutaneous tissue homogenates but did not effect the degradation of drug associated with small intestine homogenate, suggesting that different enzymes were involved in the two tissues.

Similar effects were seen with human plasma and tissue homogenates, as seen in the table below:

In vitro stability of Copolymer-1 in human plasma and tissue homogenates

Tissue	Radioactivity Recovered (% recovered[a])		
	TCA precipitate	Soluble [b]	Free Iodide [c]
Control	82.78	17.38	19.84
Plasma	89.18	2.82	8.30
Subcutaneous tissue	16.06	36.41	47.51
Striated muscle	18.66	48.3	33.04

[a] Results are presented only for a 10 µg/ml concentration of Copolymer-1.
[b] Silver nitrate soluble fraction.
[c] Silver nitrate precipitable fraction.

Both rat and human plasma appeared to have somewhat of a stabilizing effect on Copolymer-1, as evidenced by the fact that a greater percentage of total radioactivity was associated with TCA-precipitated plasma (intact drug) in plasmas from both species than from Controls in the respective studies. Also, subcutaneous tissue from both rat and human appeared to be the tissue that demonstrated the largest effect to degrade Copolymer-1 *in vitro*.

The Sponsor states that these data are consistent with the *in vivo* finding that higher TCA precipitability and slower disappearance of characteristic HPLC profile occurs following i.v. injection compared to s.c. injection.

Excretion

Excretion of radioactivity after s.c. administration of radiolabelled Copolymer-1 to rats occurred primarily in the urine, with almost no radioactivity detected in the feces. The Sponsor proposes that the radioactivity found in the urine constitutes mainly the excretion of free iodide, as intact Copolymer-1, as with most high molecular weight peptides, is too large to be filtered through the kidney glomeruli.

The residual radioactivity in the rat carcass after 24 hours was about 16-20%, which the Sponsor concludes is probably from the incorporation of the degradation products into newly-synthesized peptides or from accumulation of the released iodide in the thyroid and stomach. The Sponsor concludes that, once radiolabelled Copolymer-1 is injected s.c., it is rapidly degraded in the subcutitus to a combination of smaller peptides, amino acids and free radiolabelled iodide. They state that the free radiolabelled iodide is excreted in the urine or incorporated into newly synthesized proteins, while the smaller peptides and amino acids bind to plasma protein and other tissues in the body. However, they state that, due to the nature of the breakdown products, it is virtually impossible to track the pathway of the breakdown products.

Finally, twenty-four hours after each radiolabelled dose, the injection site contained <2% of the dose. The Sponsor stated that this suggests that a major portion of the dose was systemically available in some form.

TOXICOLOGY

Acute

I. Subcutaneous route of administration

Following is a summary table of the acute toxicology studies by the subcutaneous route of administration submitted in support of this NDA:

Table 1. Summary table of acute toxicology studies and results by the subcutaneous (s.c.) route of administration.

Species	Lab [a]/Report #/GLP status/ start date	No. Animals per group (M/F)[b]	Dosing Regimen/ Duration	Cop-1 Dose (mg/kg) and Batch #	Effects	NOEL/LD_{50}
Rat (Sprague-Dawley)	TEVA/B37/1/ 92, 21 004. NOT GLP 7-21-92	4/4	s.c., single dose, observe 14 days	0, 400 mg/kg	No deaths. No effects.	None calculated.
Dog (Beagle)	WIS/WZT/3, 21 022. NOT GLP 6-76	1/1	½ dose s.c. ½ dose i.m. observe 48 h	100 mg/kg #4, 5, 7, 8.	No deaths. No effects.	None calculated.

[a] Lab= Laboratory where study conducted:
TEVA = TEVA Pharmaceutical Industries, Ltd., Netanya, Israel.
WIS = Weizmann Institute of Science, Rehovot, Israel.

[b] M/F=Male/Female

Following is a summary of the parameters that were examined for each of the acute toxicology studies listed in Table 1 above:

1. Toxic response of rats to COP-1 after subcutaneous injection of 400 mg/kg, report #B37/1/92.

The following parameters were examined: mortality, clinical signs and body weight.

2. Acute intramuscular and subcutaneous toxicity to beagle dogs of COP-1, report #WZT/3.

The following parameters were examined: gross pathology, histology (brain, hypophysis, lungs, liver, spleen, lymph nodes, kidneys, adrenals, intestines, muscles, gonads, tissue removed from injection site and cytological smear of bone marrow), body weights, clinical signs, mortality. The differential count of bone marrow included myeloid cells, lymphocytes, monocytes and eosinophils.

Reviewer's comments:

1. Neither of these studies (rat or dog) were done under GLP guidelines.
2. No attempt was made to find a lethal dose of the drug.
3. In the dog study, only one animal/sex/group was used at 100 mg/kg, and there were no Control animals included in the study.
4. In the dog study, half of the dose of drug was given s.c., but the other half of the dose was administered i.m.

Due to these inadequacies, these studies are essentially worthless as acute toxicology studies for the purpose of determining NOEL or LD_{50} or for calculating a margin of safety with respect to the human dosing regimen. It is encouraging that at 400 mg/kg, about a 1000-fold higher dose than the 0.4 mg/kg human dose, no mortality or toxic effects were seen in the rats. (Note: by surface area, 400 mg/kg is equivalent to about 57 mg/kg in man, which is about 142-fold higher than the human dose). However, the lack of GLP compliance, small number of animals, lack of Control dogs, and fact that dogs were administered half the dose by the i.m. route render these studies invalid from the Agency's perspective.

II. Other than subcutaneous route of administration

Following is a summary table of the acute toxicology studies and results by routes of administration other than s.c. that were submitted in support of this NDA:

Table 2. Summary table of acute toxicology studies and results by routes of administration other than the subcutaneous (s.c.) route.

Species	No. Animals per group (M/F)[b]	Dosing Regimen/ Duration	Cop-1 Dose (mg/kg) and Batch #	Effects	NOEL/LD_{50}
Mouse, ICR strain	5/5	I.m. [c], single dose, observe 14 days	0, 100, 500, 2500 mg/kg #12	No deaths. No effects.	None calculated. 2500 mg/kg=6000-fold>human (520-fold by surface area)
Mouse, ICR out-bred CD-1	3/3	I.p., single equal doses on two consecutive days	41.42-2000 mg/kg #19035A	Deaths: all animals @>232.1 mg/kg died within 2 h after last treatment. [d]	LD_{50}=232 mg/kg 580-fold> human dose [f] (by surface area is 48-fold>man)
Rat, Lewis	5/5	I.v., single dose, observed 14 days	0, 1500 mg/kg #3	No deaths. No clinical or pathological effects	None calculated. 1500 mg/kg is 3750-fold> human (125-fold by surface area)
Rat, ICR Sprague-Dawley	5/5	I.v., single dose [g], observed for 14 days	Copolymer-1 0, 40, 200 #99018/II Bromo-contaminated Cop-1: 40, 200. #99020/II	Deaths: (see Table 2B below) Cop-1: tremor, hepatic discoloration. Bromo Cop-1 unconscious, ataxia, bradypnea, gastric mucoid congestion, duodenal, jejunal and pulmonary congestion, splenic enlargement and hemorrhage.	COP-1 *NOEL*=40 (100-fold>human; 14-fold>human by surface area) LD_{50}=>200 (500-fold> human, 71-fold>human by surface area) Bromo *NOEL*-none LD_{50}=between 40 and 200.
Rat, Sprague-Dawley	5/5	I.v., single dose, observed 14 days.	0, 40, 200 mg/kg #00593 #06492	Deaths: 2F, 1M@200 Dead by 2h, showed ataxia, bradypnea, gasping, dec activity before death. Lower wt gain@200 in females.	LLD (lowest lethal dose)=200 (500-fold> human; 71-fold by surface area) NOEL 40 mg/kg (100-fold> human; 14-fold by surface area)
Dog, Beagle	1/1	½ dose I.m. ½ dose s.c. Observe 48 hrs	100 mg/kg #4, 5, 7, 8	No deaths. No effects	None calculated.

ous

[d] Note: this study was actually designed as a combination range-finding study and mouse micronucleus test. The sponsor chose to also present as an acute toxicology study in mice.

[e] Cause of death was not determined. No toxicities were determined, as animals were examined as part of mouse micronucleus test.

[f] Human dose=20 mg = 0.4 mg/kg for 50 kg patient (majority MS patients female)

[g] This experiment also included a group of animals receiving a COP-1 preparation containing 12-14% bromotyrosine, a bromide-containing contaminant, to examine the toxic effects of this contaminant.

Table 2B. Mortality associated with rat study TEV/050/COP

Dose level (mg/kg)	Mortality * Male	Female	Combined
Saline	0/2	0/2	0/4
COP-1 40	0/5	–	0/5
200	2/5	0/5	2/10
Bromo Cop-1			
40	0/5	0/5	0/10
200	3/5	4/5	7/10

* Deaths occurred within 3 hours after treatment.

Following is a summary of the parameters that were examined for each of the acute toxicology studies listed in Table 2 above:

1. Acute intramuscular toxicity to mice of "COP-1", repor. . January, 1976.

The sponsor examined body weights and looked for "signs of toxicity". No further details were given in the report of this NON-GLP study.

2. Study to evaluate the potential of COP-1 to induce micronuclei in the polychromatic erythrocytes of CD-1 mice, report . January 14, 1992.

The study was designed as a combination range-finding study to determine the LD_{50} and as a mutagenicity study (mouse micronucleus assay). Mortality, body weights and micronuclei were examined.

3. Acute intravenous toxicity to rats of "COP-1", June 1973.

The report is very sketchy for this NON-GLP study. Apparently animals were observed for 14 days after treatment, and mortality, body weights, and gross pathology and histology were determined. Organs examined histologically included brain, heart muscle, thymus, lungs, intestinge, liver, spleen, kidneys, adrenals and gonads.

4. COP-1 and its impurity: acute intravenous toxicity study in rats, report , November 19, 1989.

Animals were observed for 14 days after treatment, inspected four times on the day of dosing and once daily thereafter. The type, time of onset and duration of reactions to treatment were recorded. Body weights were recorded on the day of dosing and on Days 2, 5, 8 and at sacrifice. Animals were killed at termination of the study and examined at necropsy to detect pathological changes. All body cavities were opened and larger organs were narrowly sectioned and the G.I. tract was opened at intervals for examination of the mucosal surface.

5. Comparative study in rats of the acute toxicity of two batches of COP-1 drug substance, report May 12, 1993.

Experimental observations for 14 days after treatment for this GLP study included clinical signs, mortality, body weights, gross pathology and organ weights (heart, lungs, liver, kidneys, thymus, spleen, brain and adrenals from each rat).

6. Acute intramuscular and subcutaneous toxicity to beagle dogs of COP-1, repon

The following parameters were examined: gross pathology, histology (brain, hypophysis, lungs, liver, spleen, lymph nodes, kidneys, adrenals, intestines, muscles, gonads, tissue removed from injection site and cytological smear of bone marrow), body weights, clinical signs, mortality. The differential count of bone marrow included myeloid cells, lymphocytes, monocytes and eosinophils.

Subchronic

Table 3a. Summary table of rodent subchronic toxicology studies and results by the subcutaneous (s.c.) route of administration.

Species	Lab [a]/Report #/GLP status/ start date	No. Animals per group (M/F)[b]	Dosing Regimen/ Duration	Cop-1 Dose (mg/kg) and Batch #	Effects	NOEL/LD_{10}
Mouse (Crl:CD-1)		12/12	s.c., 13 weeks, daily injection into dorsal skin shoulder/thigh-rotate 4 sites.	0, 20, 40 or 80 mg/kg/day #05994	Not available.	None available.
Rat (CD Sprague Dawley)		12/12	s.c., 4 weeks, daily injection into supra-scapular region.	0, 2, 10, 20, 40 mg/kg/day #RT-1	Deaths: None Blood chem: slight ↑ ALPH, ALT, AST; slight ↑ urea. Macroscopic: slight liver pallor; red and swollen ears, swollen face, nose and limbs; injections site lesions (due to antigenicity?).	No deaths. No NOEL, but minor symptoms.
Rat, CR		5/5	i.m./s.c., 3+3 months	0, 250 (i.m.) or 200 (s.c.) mg/kg. #36	Deaths: None. Macroscopic: edema at injection site. Bone marrow: ↓ lymphocytes. Histopathology: ↑ red pulp activity.	No deaths. Only single dose used in study; no NOEL calculated.
Rat, Crl:CD Charles River		20/20	s.c., daily injection for 26 week study; 4 sites: left & right shoulder; left & right thigh.	0, 3, 10, 30 mg/kg/day. #03992	Deaths: None treatment-related. Clin. Chem.: slight ↑ creatnine and urea. Immunotoxicology: antigenicity, evidence of immune complex deposition at kidney glomeruli, production of anti-nuclear antibodies. Macro/Micropath: injection site wounds/inflammation.	No deaths. No NOEL with respect to antigenicity or anti-nuclear antibody production. NOEL for immune complex deposition=3 mg/kg/day (7.5-fold > proposed human dose by mg/kg; in same range by mg/m^2)

Table 3b. Summary table of dog subchronic toxicology studies and results by the subcutaneous (s.c.) route of administration.

Species	Lab [a]/Report #/GLP status/ start date	No. Animals per group (M/F)[b]	Dosing Regimen/ Duration	Cep-1 Dose (mg/kg) and Batch #	Effects	NOEL/LD$_{50}$
Dog, beagle		3/3	s.c., 4 weeks, daily injection into dorsal region of dog, 3 different sites.	0, 2, 10, 20 mg/kg/day RE 6551/I and RE 6551/II	Death: None Ophthalmoscopy: hypo-reflective points in the eye. Blood chemistry: increased gamma globulin, indicating antibody production. Microscopic: lesion site inflammation.	No LD or LD$_{50}$ NOEL for eye effects=2 mg/kg/day=6-fold-human dose. No NOEL for injection site lesions.
Dog, beagle		5/5	s.c., daily injection for 36 (1/sex/group) or 90 days 4/sex/group)	10 mg/kg/day 4, 5, 7, 8.	Study was NOT GLP, and data was in narrative form only. Reported no histological effects.	None

[a] male and 1 female were sacrificed at 36 days and the remainder of the animals at 90 days.

Table 3c. Summary table of monkey subchronic toxicology studies and results by the subcutaneous (s.c.) route of administration.

Species	Lab [a]/Report #/GLP status/ start date	No. Animals per group (M/F)[b]	Dosing Regimen/ Duration	Cop-1 Dose (mg/kg) and Batch #	Effects	NOEL/LD$_{10}$
Monkey, Cyno		1/1	Dose-ranging study, s.c., 28 days, daily injection into 4 different sites (left and right shoulder, left and right back)	0, 20, 40, 60 mg/kg/day 600593	Deaths: None. Cardiovascular: ↓ HR. HD animals. Hematology: HDM & HDF decreased WBC, lymphocytes, neutrophils. Urinalysis: ↓ urine volume HDM & HDF. Organ wts.: ↑ kidney weights HDM. Pathology: injection site lesions.	NO LD$_{10}$ NOEL 40 mg/kg for ↓HR, ↓lymphocytes (males), and injection site lesions. (100-fold-human dose by mg/kg; 33-fold>by mg/m^2) No NOEL for lymphocytes (Female), kidney weights.
Monkey, Cyno		6/4	s.c., 52 weeks, daily single injection into one of 7 sites (right & left upper and lower back, left and right flank of abdomen, area between shoulders.)	0, 3, 10, 30 mg/kg/day 602093, 04493, 01394.	Deaths: 1 F@10 mg/kg/day. Antigenicity: anti-COP-1 antibodies; anti-DNA- and anti-histone antibodies; Urine analysis: ↓ creatinine clearance (GFR)-HDF. Histopathology: fibrinoid arteritis in several visceral organs; inflammatory cell foci in several organs including eye, heart, kidney, CNS and spinal cord. Immunohistochem: HDM positive stain in glomeruli for COP-1 and Complement C3; HDF positive stain in glomeruli for COP-1. Symptoms consistent with immune complex formation and deposition.	No LD$_{10}$. No NOEL determined. Antibody response is not dose-related phenomenon.

1. COP-1: 13 week subcutaneous range-finding toxicity study in the mouse, study 1028/2 started January 4, 1995, UK GLP regs.

Study Description

Animals: Mouse, Crl: CD-1

Treatment: Drug was administered by daily s.c. injection into dorsal skin shoulder/thigh-rotate 4 sites. Duration of the experiment was 4 weeks.

Observations

The following parameters were examined as part of the study:

Clinical signs, morbidity and mortality, body weights, food consumption, necropsy (macroscopic examination), immunohistochemistry, and histopathology. Immunohistochemistry included sectioning the poles of the left kidneys of all animals and evaluation of COP-1, complement C3 and IgG antibody complexes.

Results

Note: The Experimental Results and Report were listed as "Not Available".

Conclusions

No conclusions could be made, as no results were reported.

2. COP-1 repeated dose subcutaneous toxicity to rats, stu[illegible] January 25, 1995, GLP.

Study Description

Animals: CD Sprague Dawley Rats

Treatment: Drug was administered by daily s.c. injections into supra-scapular region. Animals received 2, 10, 20 or 40 mg/kg/day of drug. The duration of the study was 4 weeks.

Observations: The following parameters were evaluated as part of the study: clinical signs, body weight, food and water consumption, clinical pathology, hematology, blood chemistry, macroscopic and microscopic pathology, organ weights. Histopathology was done mainly on animals from Groups 1 and 5, with the exception of kidneys, liver, lungs, and injection site tissue, which were processed and examined from animals of all groups. Also, processing and examination of all tissues was done for animals with obvious abnormalities and animals that died during the study.

Hematology included packed cell volume, hemoglobin, erythrocyte count, leukocyte count, neutrophils, lymphocytes, eosinophils, basophils, monocytes, normoblasts and platelets. Blood chemistries included urea nitrogen, fasting glucose, creatinine, alkaline phosphatase (ALPH), alanine aminotransferalse (ALT), aspartate

aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), protein, total bilirubin, sodium, potassium, chloride and calcium.

Results

Mortality
No deaths.

Clinical signs
The clinical signs and symptoms are summarized in the following table:

Dose (mg/kg/day) [a]	0	2	10	20	40
MALES					
No abnormalities detected	9	4	5	8	9
OBSERVATION					
Red ears	0	8	7	2	3
Swollen ears	1	0	0	0	0
Red skin	0	1	1	2	0
Swollen face	0	5	5	1	1
Periorbital staining	2	0	0	0	0
Swelling of limbs	0	0	0	1	0
Swollen nose	0	3	2	2	2
Wound	1	0	0	1	0
FEMALES					
No abnormalities detected					
OBSERVATION					
Hair loss on head	0	0	0	0	1
Red ears	0	4	4	1	2
Swollen face	0	3	3	0	3
Swollen nose	0	1	0	1	2
Wound	0	0	0	0	3
Abrasion	0	0	0	0	1

[a] There were 12 animals per group.

Reviewer's Comments:

The symptoms of red and swollen ears, swollen face, nose and limbs are mainly confined to animals treated with Copolymer-1 and are therefore most likely the result of drug treatment. The symptoms are probably the result of a drug allergic reaction as the result of the antigenicity of Copolymer-1 and are consistent with symptoms of a Type I hypersensitivity response.

Body weight and food intake
No effect on body weight or food consumption.

Hematology

A 5-6% decrease in packed cell volume, hemoglobin and erythrocyte counts was reported in both male and female animals. These effects appeared to be dose-related. No effects were seen on either white blood cell (WBC) number or neutrophil, lymphocyte, eosinophil or monocyte numbers.

Blood Chemistry

The response of the enzymes alkaline phosphatase (ALPH), alanine aminotransferase (ALT), and aspartate animotransferase (AST) differed between the sexes. ALPH was increased (42%@ HD) in the female high dose, with no effect in males. ALT was decreased in males (10%@ HD), and increased in females (45%@ HD). AST decreased in the male treatment group at 2 (14.7%) and 40 (20.5%) mg/kg/day. Urea concentrations were increased in female animals (15.3%). Phosphorus levels were increased in male rats at 10, 20 and 40 mg/kg/day (7, 2.2 and 10%, respectively).

Reviewer's Comments: The increased urea concentration in female rats could be a signal for effects of Cop-1 on the kidneys.

Organ weights

No effects.

Macroscopic findings

The only macroscopic findings of note were the following:

1. 2/12 HDM; accumulation of alveolar macrophages--multifocal.
2. 2/12 MDM and 2/12 HDM; hepatocytic pallor-centrilobular--slight.
3. Injection site lesions; data summarized in the following Table:

Group (12/group)	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
LESION subcutaneous inflammation-slight	4	1	3	2	0	7	7	6	3	1
Subcutaneous inflammation-moderate	6	7	6	4	3	3	4	4	6	3
Subcutaneous inflammation-marked	0	4	3	5	9	0	0	2	3	8
No abnormality detected	2	0	0	1	0	2	1	0	0	0

The number of animals responding to treatment with an increased "marked" severity of inflammatory reaction above Control was seen in both males and females.

Reviewer's Comments:

Copolymer-1 is antigenic, and this injection site inflammatory response could be due to Type III immune-complex mediated hypersensitivity. The formation of immune complexes can, with chronic exposure to the antigen (drug), result in circulating immune complex, and cause local (such as glomerulonephritis) or systemic immune complex disease. Therefore, while in this study the only symptoms of antigenicity appear to be injection site lesions, longer term studies may reveal more severe symptomology.

Summary and Conclusions

Four weeks of daily s.c. administration of Copolymer-1 to rats at 0, 10, 20 or 40 mg/kg/day resulted in minimal toxicity. The toxic symptomology probably relate mainly to the antigenicity of the drug. The clinical symptoms of red and swollen ears, swollen face, nose and limbs were confined to treated animals, and were most likely due to an allergic response to drug and are consistent with a Type I response. Lesions at the injection site could have been due to immune-complex formation (Type III hypersensitivity). Increased ALPH, AST and ALT could relate to a minimal effect on liver, as 4 animals (2MDM, 29HDM) demonstrated slight hepatocytic pallor. Increased urea concentration in female rats also suggest a minimal effect on kidney, which might be predicted for an antigenic drug. It is possible that effects on kidney could increase with a more chronic dosing regimen.

Overall, Copolymer-1 was fairly well tolerated at a s.c. dose up to 40 mg/kg/day in this 4 week study.

3. Subchronic intramuscular toxicity to rats of "COP-1", stu[illegible] December 1977, NOT GLP.

Study Description

Animals: Rat, CR

Treatment: Daily i.m. injection of Control (saline) or 250 mg/kg/day Copolymer-1 in saline for 3 months. Then s.c. injection of either Control (saline) or 200 mg/kg of Copolymer-1 in saline twice a week for an additional 3 months (total 6 month study). Throughout the study, drug was administered into the four legs of the animals.

Observations:

Mortality, clinical symptoms, necropsy, hematology, necropsy, histopathology, and bone marrow smears. Histopathology included brain, heart, thymus, lungs, intestines, liver, spleen, kidneys, adrenals, skeletal muscle, hypophysis and gonads. Bone marrow and blood smears were prepared for differential counts.

Results

Mortality: No deaths

Clinical symptoms: Edema of the injected areas of the four legs was apparent after 3 months of i.m. injection. The sponsor states that this subsided gradually with the implementation of the subcutaneous injection regimen for the last 3 months of the study.

Blood analysis: The sponsor concludes that there is no effect of Copolymer-1 on total WBC, RBC counts and other blood parameters.

Reviewer's Comment:

The sponsor mixed up the values for the means of blood analysis parameters (Table II, pg. 022 242) that is supposed to correspond to Table 1b (pg. 022 241), containing individual values for these same parameters. Due to this error in the submission, it is impossible to decipher the actual values with respect to correct treatment group (Male Controls, Female Controls, Male Copolymer-1, Female Copolymer-1). It is, therefore, impossible to determine from these data whether or not there is an effect of Copolymer-1 on total WBC, RBC counts, etc.

Bone marrow analysis:

Bone marrow differential counts showed a decrease in lymphocytes (M, 18%; F, 44%) and mast cells (M, 50%; F, 59%) with Copolymer-1 treatment when compared to Controls receiving saline injections (See Table VI below).

Reviewer's Comments:

The sponsor chooses to interpret these data by indicating that the Control animals (saline injection) have a higher number of lymphocytes than either Copolymer-1-treated or Normal (not receiving any injection) animals. They conclude that the number of lymphocytes in the Control (saline-injected) animals actually increased in relationship to Normal animals and Treated animals. However, I believe this to be an improper interpretation of these data.

In fact, the Normal (not injected) animal lymphocyte values fall between the values for Control (saline-injected) and Copolymer-treated animals, indicating that continued injection was not responsible for a general increase in lymphocyte number in either Treated or Control animals. And more importantly, the proper Controls for these experiments are the Control animals (placebo Controls) that also received injections (saline). Since both Controls and Treated animals received repeated injections, any difference due to injection "stress" is not a factor. When compared to the Control (saline injected) animals, there is a definite decrease in the number of lymphocytes and mast cells with treatment with Copolymer-1. This effect appears to be drug-related and of a magnitude (18-44%, M vs. F) that merits concern.

Furthermore, there was an increase in neutrophilic myelocytes (M, 13%; F, 39%) and neutrophilic granulocytes (M, 21%; F, 42%) (see Table 6 below).

Reviewer's Comments: The sponsor interprets these data as an increase in neutrophil production in bone marrow to compensate for the inflammatory response resulting from repeated injection of Copolymer-1. I concur with this interpretation.

Table VI. Bone marrow differential counts (%)--mean values

Treatment	Lymphocytes	Mast Cells	Neutrophilic myelocytes	Neutrophilic granulocytes
Control males	26.7	0.83	19.73	21.66
Cop-1 males	21.76	0.40	22.33	26.2
Control females	28.43	0.85	15.1	19.1
Cop-1 females	16.03	0.35	21.04	27.16
Normal males	23.66	0.33	21.83	17.16
Normal females	24.16	0.16	18.5	23.5

Peripheral blood analysis.

Data in Table VIII below show a small increase in peripheral blood lymphocytes in Copolymer-1 treated males (6%) and females (15%). The sponsor concludes that this increase is not biologically significant, and I concur.

Data from this same table demonstrates a more substantial decrease in peripheral blood neutrophilic granulocytes in Copolymer-1 treated males (42%) and females (26%). The sponsor concludes that this decrease in peripheral blood neutrophils is probably due to neutrophil participation in the inflammatory lesions at the injection sites. I would concur that this is probably the case, although this certainly doesn't rule out the potential for neutrophils to act at other inflammatory sites as well.

Table VIII. Averages of blood differential counts (as %).

Treatment	Lymphocytes	Neutrophilic granulocytes
Control I males	78.2	15.2
Cop-1 males	80.5	8.75
Control females	70.8	11.2
Cop-1 females	81.5	8.25
Normal males	81.0	10.66
Normal females	80.66	9.33

Histopathological exams

A description of histopathological findings was included, but no data to support this description were submitted. The only apparent drug-related histopathological finding reported was an alteration in the spleen. According to the sponsor, "Spleens of all treated animals showed changes in the ratio of red/white pulp." These changes were characterized by the sponsor as follows: "The red pulp was hyperplastic mainly due to excessive myeloid activity. The white pulp however, showed a narrowing of the corona areas of malpighian bodies and broadening of the perifollicular zone." According to the sponsor, "These changes in the spleen are a "physiological" reaction to the local inflammatory injury in the site of injection."

Reviewer's Comments:

Without data, pictures or a more detailed description, it is difficult to interpret these results. However, the effects as described in the spleen could be consistent with an antigen in the blood contacting the lymphocytes in the white pulp of the spleen and inducing an immune response. This could certainly be explained by the antigenicity of Copolymer-1.

Summary and Conclusions

Since this is not a GLP study, it's usefulness in supporting an NDA is negligible. A further confounding factor is the fact that animals were administered drug for 3 months i.m. and for an additional 3 months s.c. I.M. injection is one of the routes of administration that often results in the greatest immunogenicity of a given molecule. Furthermore, no SOPs for methodology for evaluating immune cells is bone marrow or peripheral blood were included, and therefore it is impossible to evaluate the validity of the sponsor's claims.

Irrespective of the fact that this is not a GLP study, it may be important to note the decrease (18%, M; 44%, F) in lymphocytes in the bone marrow of Copolymer-1 treated animals. A 44 % decrease could very well be a biologically significant effect. I disagree with the sponsor's contention that these effects are due to the stress of repeated injection for the reasons stated above.

The decrease in peripheral blood neutrophils could be explained by the inflammatory response at the injection sites. This is further supported by the increased neutrophilic myelocytes and granulocytes in the bone marrow. Unfortunately, in the absence of data, the reported histopathological effects in the spleen are impossible to interpret.

The effects on neutrophils and inflammatory effects at the injection sites are consistent with the administration of an antigenic drug.

4. COP-1: 26 week subcutaneous administration chronic toxicity study in the [redacted]. February 9, 1993, UK GLP regs.

Study Description

Animals: Rat/Charles River Crl:CD(SD)BR strain, 28 day old weanlings, housed 5/cage, 12-day acclimatization period before starting study.

Treatment: Rats (20/sex/group) were treated with Control (0.9% saline) or one of three doses of Copolymer-1 in saline (3, 10, 30 mg/kg/day). Rats were administered s.c. injections of 2 ml/kg constant dose volume of drug daily for 26 weeks into one of four sites (the left and right shoulder (sites 1 & 2) and above the left and right thigh (sites 3 & 4)). The injection sites were rotated daily whenever possible, commencing with the left shoulder.

Observations: The following parameters were examined during the study: morbidity and mortality, clinical observations, body weight, food consumption, ophthalmoscopy, hematology, anti-Cop-1 antibody determination (weeks 5, 13 and 26), clinical chemistry, immunotoxicological assessment, urine analysis, and pathology (necropsy, organ weights, macro and microscopic pathology evaluation).

Hematology included Hb conc., mean cell volume, packed cell volume, total and differential white blood cell count, platelet count, prothrombin time, and activated partial thromboplastin time.

Clinical chemistry included determination of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, sodium, chloride, inorganic phosphorus, urea, creatinine, albumin, total cholesterol, potassium, calcium, glucose, total bilirubin, total protein, albumin/globulin ratio, protein fractions (by electrophoresis).

Immunotoxicological assessment included obtaining blood samples from the remaining males and females in each main study group in Weeks 5, 13 and 26 and examination for the following: B lymphocytes, T lymphocytes, $CD4^+$ T lymphocytes, $CD8^+$ lymphocytes, $CD4^+/CD8^+$ T lymphocyte ratios, natural killer cells, anti-nuclear antibodies (ANA), anti-histone antibody analysis, and immunoglobulin G (IgG) and immunoglobulin M (IgM) anlysis.

Urine analysis inlcuded volume, specific gravity, protein, ketones, blood, reducing substances, pH, total bilirubin, urobilinogen and microscopy of deposits.

Organ weights included adrenals, brain, heart, kidneys, liver, ovaries, pituitary, prostate, spleen, testes, thyroids.

Histopathology included microscopic examination of all the tissues specified below in Control and High Dose group along with all tissues from animals that died or were killed in extremis:

adrenals, aorta, blood smear, bone marrow smear, brain, caecum, colon, duodenum, eyes, femur, Harderian gland, head, heart, ileum, injection sites, jejunum, kidneys, lachrymal gland, liver, lungs, lymph nodes, mammary gland, nasal turbinates, esophagus, optic nerves, ovaries, pancreas, peripheral nerves, Peyer patches,

pituitary, prostate, rectum, salivery glands, seminal vesicles, skeletal muscle, skin, spinal cord, spleen, sternum, stomach, testes, thymus, thyroids, tongue, trachea, urinary bladder, uterus, vagina, Zymbal's gland, all gross lesions.

Results

Mortality

Following is a summary table of animal deaths:

Group and sex	Animal number	Week of study	Reason for unscheduled death
1M	4	13	Eye damage during bleed
2M	39	20	Moribund removal
3M	52	27	Found dead
3M	58	14	Moribund removal
4F	158	19	Found dead
4F	159	26	Eye damaged during bleed.

The sponsor stated that there were no histopathological findings to suggest that these animal deaths were related to drug treatment.

Observations in animals in groups 3 and 4 included sores at the injection sites sufficiently serious to cause those sites to be abandoned. Also rough hair coat and stained fur were noted.

Body weight

There were no statistically significant differences in body weight, with the exception of an about a 10% increase in the body weight of the High Dose Females from weeks 0-4. This increase was statistically significant by the statistical dose-response test. Also, at all time points, the High Dose Male animals had slightly lower body weights (about 2-3%) than Control animals. While not statistically significant, since this slight decrease occurred at all time points, it could suggest some mild toxicity in this dosing group.

Food consumption

No effect.

Ophthalmoscopy

No effect.

Hematology

The sponsor states that there were no drug-related changes in hematological parameters.

Reviewer's Comments

Although not statistically significant due to the large variability in white blood cell (WBC counts), the data reflect a **consistent increase** in the number of WBC, lymphocytes, and neutrophils in the peripheral blood of High Dose Male and Female animals at all times examined with the exception of the High Dose Females at Week 4 (see following Table). These data are consistent with the rat data from the Non-GLP study reviewed above. In that study, the increase in peripheral blood lymphocytes corresponded with a decrease in bone marrow lymphocytes.

The data from these two studies, though by no means conclusive, do suggest that Copolymer-1 is affecting the immune system, possibly by decreasing the number of lymphocytes in the bone marrow while inducing a corresponding increase in peripheral blood lymphocytes. The mechanism for this effect, and whether or not it is tied to the immunogenicity of the drug, are unknown at this time. The major lymphocyte population in the bone marrow consists of B cells, which are the antibody-producing cells of the immune system.

Table: Effects of Copolymer-1 on total WBC, lymphocyte and neutrophil counts in rat peripheral blood in a 26 week study.

Group	% Increase in High Dose Group								
	Week 4			Week 13			Week 26		
	WBC	L	N	WBC	L	N	WBC	L	N
MALES	45	38	58	15.5	18.8	0	8.2	10.8	0
FEMALES	0*	0	0	0	7.5	0	29.0	23.0	62.5

* actually a 22% decrease. actually a 22% decrease.

These data are not consistent with those from the previous rat study, in that in that study the number of neutrophils in the peripheral blood decreased. The sponsor stated that this was probably due to the participation of peripheral blood neutrophils in the local injection site inflammatory responses seen in the treated animals. This discrepancy in effects on neutrophils could be explained partially by the fact that the previous rat study , was carried using both i.m. and s.c. injections (3 months of each) and by a difference in timing for collection of peripheral blood for analysis. (It is unclear when bloods were collected in study the Non-GLP study).

Anti-COP-1 antibody analysis

Antibodies to Copolymer-1 were determined, following 1, 3 and 6 months of s.c. treatment, by solid state radioimmunoassay using ^{125}I-labelled anti-rat IgG.

The sponsor stated that, "in general the level of anti-COP-1 antibodies peaked at Week 13 and declined at Week 26, except for Groups 2F and 3F, where the level peaked at Week 5. In all groups, the maximal number of responders was observed after 5 weeks and was lowest after 26 weeks."

Reviewer's Comments

Copolymer-1 proved to be a very antigenic drug in the rat in this study. Data indicate that the anti-Copolymer-1 antibody levels did peak at the 3 month time point, as did the number of responders (defined by the sponsor as any animal with an antibody titer two-times greater than the mean Control value for animals at that time point) (See Table 4 below).

Table 4. Summary: Anti-Copolymer-1 antibodies during 6-month study (at a 1:1000 dilution).

GROUP	COP 1 DOSE mg/kg	1 MONTH		3 MONTHS		6 MONTHS	
		Mean±(S.D.)	Responders	Mean±(S.D.)	Responders	Mean±(S.D.)	Responders
1M	0	95 (29)	0/10	116 (34)	0/10	107 (10)	0/10
2M	3	458 (303)	6/10	597 (843)	4/10	216 (195)	3/9
3M	10	682 (623)	6/10	2105 (2010)	6/10	633 (597)	6/9
4M	30	851 (755)	9/10	1850 (1112)	9/10	691 (572)	7/10
1F	0	123 (40)	0/10	112 (28)	0/10	107 (24)	0/10
2F	3	975 (740)	9/10	669 (916)	4/10	309 (342)	3/10
3F	10	505 (437)	4/10	320 (268)	3/10	131 (53)	1/10
4F	30	747 (801)	4/10	1532 (1700)	5/10	506 (569)	4/9

In examining the antibody titers of the animals that were reported to die during the study, it was interesting that the dead animals were ones who had expressed the highest antibody titers in their respective groups. Animal #52 in the males 10 mg/kg group died, and its anti-Copolymer-1 antibody titer was 2045 (1 month), 5495 (3 months) and 2046 (6 months), compared to corresponding treatment group means for this treatment group of 683, 2105 and 633 for the corresponding times. Animal #158 in the females 30 mg/kg group died, and its anti-Copolymer-1 antibody titer was 2078 (1 month) and 4255 (3 months) (dead at 6 months), compared to corresponding treatment group means of 747 and 1532 at the corresponding times.

A number of other animals were destroyed due to their moribund condition, but these were the two animals that were actually found dead. These data do not conclusively prove that animal deaths were somehow related to an exaggerated antigenic response to drug, but they do suggest that some correlation between antibody response and death may be present.

The fact that s.c. Copolymer-1 administration to rats resulted in antigenicity does not necessarily mean that a similar response will be found in man. This depends on how the immune system processes the antigen and presents it to the T and B lymphocyte populations. However, the fact is that the sponsor also looked for

anti-Copolymer-1 antibodies in patients treated with this drug by the s.c. route of administration, and a similar pattern of antibody production was reported.

The chronic administration of an antigenic drug to patients raises two major concerns. First, if the anti-drug antibody is neutralizing to the drug, then chronic administration of the drug may be impractical. Second, if the drug forms immune complexes with the antibody, then those immune complexes can deposit in various organs such as kidney, vasculature, or heart and result in the type of inflammatory tissue damage characteristic of serum sickness.

Clinical Chemistry

There were few changes in clinical chemistry values with drug treatment. The sponsor stated that there were no drug-related effects on the renal functions of the animals as assessed by urea, creatinine and electrolytes.

Reviewer's Comments

A review of the individual data revealed the following:

MALES
Week 4 HDM (high dose males) had 5% increase in creatinine.
Week 26 HDM had a 6% increase in urea and a 4% increase in creatinine.

FEMALES
Week 26 HDF (high dose females) had 12.6% increase in urea and 10% increase in creatinine.

The 5% increase in creatinine in HDM on Week 4 and the 10% increase in creatinine in HDF on Week 26 were statisticaly significant by dose-response statistics.

While these effects are admittedly small, they nevertheless do represent increases in parameters that are used as markers of altered kidney function.

There was no way to do an analysis of anti-Copolymer-1 antibody titer versus effects on urea or creatinine (kidney parameters) because a different group of animals was used for determination of antibody production than for determination of urea/creatinine levels.

Immunotoxicology assessment (as part of 26-week rat study by s.c. administration)

Immunohistochemical staining for complement C3, COP-1 and antibody in the glomeruli of Control and High Dose animals:

From the examination of anti-Copolymer-1 antibody titers in the Control and Test animals, it was determined that Copolymer-1, administered by the s.c. route, is antigenic. Administration of an antigenic drug can lead to formation of antigen-antibody complexes in the blood that can be deposited in various sites around the body, one of the most prevalent sites often being the glomeruli of the kidneys. Upon deposition of such antigen-antibody complexes in these tissues, the complement cascade is activated, and complement (including C3) acts to destroy the tissue where the antigen-antibody complexes are deposited. Therefore, with the knowledge that Copolymer-1 was antigenic, the sponsor responded appropriately by examining the glomeruli of animals treated with Copolymer-1 for deposition of Copolymer-1 drug, anti-COP-1 antibody, and the presence of C3 complement.

Results

Copolymer-1 detection in the glomeruli of treated animals

By immunohistochemical staining, Copolymer-1 drug was demonstrated in the glomeruli of 3 of 20 High Dose (30 mg/kg) animals (animal #68M, 71M and 75M), with a fourth animal (78M) demonstrating "moderate staining" and therefore constituting a possible positive response as well. None of the Control Males showed any staining of the glomeruli. Therefore, it was found that the drug concentrated in the glomeruli of the kidneys of three or four treated animals at detectable levels by immunohistochemical staining techniques. It is possible that other animal glomeruli also contained drug, but in levels that were not detectable by these techniques. The sponsor chose to look only at the Control and High Dose animals.

Presence of C3 complement in the glomeruli of treated animals

PHARMACON carried out the portion of the study in which the kidneys were examined for the presence of C3 complement. The presence of this complement component is indicative of concurrent presence of antigen-antibody complex, as it is the presence of this complex that induces activation of the complement cascade. TEVA reports in this section of the NDA that positive immunohistochemical staining for C3 was found in the glomeruli basement membranes of the same three High Dose Male animals (68M, 71M and 75M) that were reported to show positive staining for Copolymer-1 drug in the glomeruli.

Reviewer's Comments:

Upon careful examination of the . . . report (see pg. 53 of this review, Study Results"), I discovered that, in fact, 7 of 20 HDM, 5 of 20 HDF, 3 of 20 Males from Group 3 (10 mg/kg/day) and 1 of 20 Females from Group 3 demonstrated positive staining for C3 complement, indicating quite a

high incidence of this phenomenon. Therefore, according to the data, it was fairly common to find animals in which immune complex had formed and deposited in the glomeruli of the kidneys in this study.

Presence of anti-Copolymer-1 antibodies in the glomeruli

No positive staining was reported for presence of anti-Copolymer-1 antibodies in the glomeruli of any of the Control or High Dose animals. The sponsor acknowledges the fact that antibodies are probably present in the glomeruli, but are undetectable due to insufficient sensitivity of the immunohistochemical staining technique used. It is reasonable to assume with presence of antigen (Copolymer-1) and complement C3 in the glomeruli that anti-Copolymer-1 antibodies are present.

Anti-Copolymer-1 antibody production in these animals

Two of these same three High Dose Male animals, #71M and 75M, also showed the highest levels of anti-COP-1 IgG in the radio-immuno assay at termination. The third animal, 68M, was not assessed for anti-Copolymer-1 IgG.

Summary of immunohistochemical evaluation results from TEVA report

At least three of the twenty High Dose Male animals treated with Copolymer-1 demonstrated positive staining for both Copolymer-1 and complement C3 in their glomeruli, while none of the Control animals demonstrated this staining. Two of these three animals were evaluated for the presence of anti-Copolymer-1 antibody in the peripheral blood, and were found to have the highest titers of those animals tested. Furthermore, a total of 7 of 20 HDM, 5 of 20 HDF, 3 of 20 Group 3 Males and 1 of 20 Group 3 Females demonstrated positive staining for C3 complement in the glomeruli of the kidneys. No anti-Copolymer-1 antibody was found in the glomeruli of any of the Control or High Dose animals, but this may be due to insufficient sensitivity of the assay.

Therefore, Copolymer-1 is antigenic in the rats, and this antigenicity does appear to result in the formation of immune complex (antigen-antibody complex) formation and deposition in the glomeruli of the kidneys. The deposition of immune complex in turn results in the presence of C3 complement. This is the mechanism by which immune complex disease, resulting in kidney damage, is mediated.

study results: HE study no 1028/18, June 3, 1994, Study sponsor (Note: the following aspects of the immunotoxicological analysis for Copolymer-1 were carried out and reported by and some of these results may be redundant from the TEVA report in the previous section of this review).

Lymphocyte subset analysis (CD5+, CD4+, CD8+, CD4+CD8+, and B lymphocytes), serum IgM and IgG levels, and anti-nuclear antibody levels.

Study objectives

To determine the potential effects of Copolymer-1 on the immune system by using the following parameters:

- assessment of lymphocyte subsets (T lymphocytes, B lymphocytes, CD4+, CD8+, and CD4+CD8+ lymphocytes), serum IgM and IgG levels, and anti-nuclear antibody levels.
- evaluation of the tissue deposition of immune complexes on kidney sections by immunohistochemistry.
- examination of lymphoid organs sections.

IgG and IgM levels

No treatment-related differences in IgG or IgM levels were found for the Treatment Animals compared to the Controls. However, **the sponsor only chose to look at the plasma Ig levels at week 5.**

Lymphocyte subset counts

No treatment-related differences in lymphocyte subset counts were observed in the Treatment Groups compared to Controls. However, **the sponsor only chose to look at the lymphocyte subset levels at week 5 of this 26-week study.**

Reviewer's Comment: While examining IgG/IgM levels at 5 weeks may be appropriate due to the well-characterized time schedule for antibody production in response to various antigens, this is not necessarily appropriate for examination of lymphocyte subset counts. There are a number of mechanisms by which lymphocyte subset counts could be altered, and there is no rational reason to expect such a change to be limited to Week 5 of a study. Data from the 6-month i.m./s.c. study in rats reported alterations in bone marrow lymphocyte number, peripheral blood neutrophil number and histopathological alterations in spleen after 6 months of treatment with Copolymer-1. Therefore, in this 26-week study, it would seem appropriate to examine lymphocyte subset counts at 26 weeks (about 6 months) as well rather than limit their examination of this parameter to 5 weeks. Therefore, with respect to lymphocyte subset data, the negative results may simply be due to the fact that the sponsor looked at a single time point.

Anti-nuclear antibody assays

The sponsor states in the IND that there was no significant increase in the total anti-nuclear antibodies assayed by immunofluorescence. They also state that there was no significant increase in anti-DNA (double strand) and anti-histone antibodies assayed by This is consistent with conclusion.

However, th data demonstrates a number of animals in which the plasma tested positive for anti-nuclear antibodies (see Table, Appendix 3 below):

Table, Appendix 3. Evaluation of total anti-nuclear antibodies (immunofluorescence)

MALES				FEMALES			
	Week 5	Week 13	Week 26		Week 5	Week 13	Week 26
Group 1 *				Group 1			
11	0	0	0	91	0	0	0
12	0	0	0	92	0	0	0
13	0	0	0	93	0	0	0
14	0	0	0	94	0	0	0
15	0 Cy**	0	0	95	0	0	0
16	0	0	0	96	0	0	0
17	0	0	0	97	0	0	0
18	0	0	0	98	0	0	0
19	0	0	0	99	0	0	0
20	0	0	0	100	0	0	0
Group 2				Group 2			
31	+++nu	0	0	111	0	0	0
32	0	0	0	112	0	0	0
33	+r	+r	+r	113	0	+nu	0
34	0	+r	0	114	0	0	0
35	0	0	0	115	0	0	0
36	0	++nu, '	0	116	0	0	0
37	0	0	0	117	0	0	0
38	0	0	0	118	0	0	0
39	0	0	NS	119	0	+r	0
40	0	0	0	120	0	0	0
Group 3				Group 3			
51	0	0	0	131	0	0	0
52	0	0	0	132	0	0	0
53	0	0	0	133	0	0	0
54	0	0	0	134	0	0	0
55	+hr	+r, '	0	135	0	0	+r
56	+r	0	0	136	0	0	0
57	0	0	+r	137	0	0	0
58	0	0	NS	138	0	0	0
59	0	0	0	139	0	0	0
60	0	+r	-r	140	0	0	0
Group 4				Group 4			
71	0	0	0	151	0	0	0
72	±ce	0	0	152	0	0	0
73	0	0	0	153	0	+r	0
74	0	0	0	154	0	0	0
75	0	0	0	155	0	0	0
76	0	0	0	156	0	0	0
77	0	0	0	157	0	0	0
78	0	0	0	158	Ce	0	NS
79	0	0	0	159	0	0	0
80	0	0	0	160	0	0	0

*Group 1=Control, Group 2=3 mg/kg/day, Group 3=10 mg/kg/day, Group 4=30 mg/kg/day.

** Abbreviations: cy=cytoskeleton; nu=nucleolus; r=reticulate; hr=homogenous reticulate; ce=centriole; ' =mitotic spindle; ' =cytoplasmic granulations; 0=negative; ±=doubtful; +=positive (slight); ++= positive (moderate); ++++=positive (marked).

Reviewer's Comment:

The sponsor concludes that these data describing the presence of anti-nuclear antibodies in plasma are not significant. While I am under the impression that they used statistical methodology to determine significance, this is unclear in the submission.

The data in the above Table, taken from Appendix 3 (024 359 and 024 360) show that at least 4 of 10 Group 2 Males and 4 of 10 Group 3 Males demonstrated positive staining for anti-nuclear antibodies. 2 of 10 Group 2 Females and 1 each of 10 Group 3 and Group 4 Females also demonstrated positive staining. Therefore, a number of animals treated with Copolymer-1 did demonstrate the presence of anti-nuclear antibodies in their plasma. Since antinuclear antibodies are often associated with autoimmune disease such as systemic lupus erythematosis (SLE), these results could be interpreted to indicate the potential for this drug to induce autoimmunity, at least in this species of rat. This is not a surprising finding in light of the demonstrated antigenicity of the drug in rats.

Immunohistochemical staining of kidney sections

In the review of the study including immunohistochemical staining of kidney sections for C3 complement, it was reported that a minimal to slight reaction for C3 was associated with the basement membrane of the glomerulus in **7 of 20 High Dose (30 mg/kg/day) Male rats, 5 of 20 High Dose Female rats, 3 Male rats from Group 3 (10 mg/kg/day), and 1 Female rat from Group 3.**

concluded that "these deposits are considered to be probably related to treatment."

Reviewer's Comments:

These data indicate that in this 26 week rat study it was fairly common (35% of HDM; 25% of HDF) for the antigenicity of the drug to result in production of immune complex and deposition in the glomerulus of the kidneys.

Histopathology of lymphoid organs

There were apparently no changes observed in the lymphoid organs examined. Also there were no differences in the number of secondary follicles in the mesenteric lymph node and the proportion of thymic medulla between Control and High Dose treated rats.

Overall summary Immunotoxicology Data in the 26-week rat study

The repeated s.c. dosing of rats with Copolymer-1 for 26 weeks resulted in immunotoxicological effects that raise the level of concern for the chronic administration of Copolymer-1 proposed in this NDA. The drug was shown to be highly antigenic in rats, resulting in relatively high titers of anti-COP-1 antibody in all Treatment Groups. Glomeruli of the kidney of a number rats treated for 26 weeks stained positive for the presence of complement component C3. In at least three HDM animals, kidneys stained positive for both the presence of Copolymer-1 drug and C3 complement, and furthermore two of these animals produced the highest anti-COP-1 antibody titers. Finally, while the sponsor concluded that the data for presence of anti-nuclear antibodies was not significant, in fact, anti-nuclear antibodies were present in the plasmas of a number of Treated animals.

These data demonstrate that rats receiving repeated s.c. treatment with Copolymer-1, a highly antigenic drug, showed signs of immune complex deposition in the glomeruli of the kidneys and the production of anti-nuclear antibodies. While it is true that these effects did not lead to histopathological lesions in the kidneys of these animals, this could simply be due to the length of the study. Had this study been continued for more than 26 weeks, pathological lesions may have appeared. As previously stated, there was some evidence in this study for some minor effects on the kidney, in terms of increased urea and creatinine. Furthermore, the kidney is not the only potential site for immune complex deposition. This can also occur systemically, including vascular damage, heart lesions, and damage to other highly perfused organs. The Sponsor stated in their "Interpretation Section" that "The most probable explanation of these observations is that antibody-COP-1 complexes were formed, deposited in the glomerulus **(and other sites not intensively examined)**, and fixed complement."

Urine analysis

Only urine volume and specific gravity were examined. Urine volume increased in a dose-related fashion in male rats on Week 5 and decreased in a dose-related fashion in male rats on Week 25. No other effects were observed.

Organ weights

No effects of Copolymer-1 on organ weights were seen.

Macroscopic and Microscopic Pathology

The only finding of significance was the presence of injection site lesions, that could be explained by either Type III or Type IV hypersensitivity response at the injection site. This is due to the high level of circulating antibodies to Copolymer-1 as the result of the antigenicity of the drug.

Upon histopathological examination, it was determined that these lesions, which were more prominent at posterior injection sites, included myositis, fibrosis and cellulitis. The following Table 1, taken from the NDA, contains a list of injection site lesions by grade:

Table 1: Incidence of selected injection site lesions by grade.

Sex		Male				Female			
Group		1	2	3	4	1	2	3	4
Number		20	20	20	20	20	20	20	20
Injection site 1									
Fibrosis	Grade 1	4	0	2	6	1	6	2	4
	Grade 2	0	1	0	1	0	0	0	2
Injection site 2									
Fibrosis	Grade 1	4	2	0	3	5	2	2	3
	Grade 2	0	1	0	2	0	0	2	1
Injection site 3									
Myositis	Grade 1	1	2	1	6	2	3	2	5
	Grade 2	0	0	0	0	0	0	0	3
Cellulitis	Grade 2	0	0	1	0	0	0	0	1
	Grade 3	0	0	0	0	0	0	1	2
Fibrosis	Grade 1	7	5	2	3	2	11	8	2
	Grade 2	0	5	10	6	0	2	7	8
	Grade 3	0	0	2	10	0	0	0	9
	Grade 4	0	0	0	1	0	0	0	1
Injections site 4									
Myositis	Grade 1	0	1	8	2	0	2	5	7
	Grade 2	0	0	1	5	0	0	0	2
	Grade 3	0	0	0	0	0	0	0	1
Cellulitis	Grade 1	1	0	0	2	0	0	2	0
	Grade 2	0	2	1	2	0	0	1	0
	Grade 3	0	0	0	2	0	0	0	0
Fibrosis	Grade 1	9	9	6	0	5	10	6	4
	Grade 2	1	1	9	8	0	2	8	8
	Grade 3	0	0	1	10	0	0	0	8
	Grade 4	0	0	0	1	0	0	0	0

Key: Grade 1 = minimal; 2 = slight; 3 = moderate; 4 = moderately severe; 5 = severe (NB no findings graded 5)

The injection site lesions appeared macroscopically as sore areas and microscopically as treatment-related lesions resulting in slight to moderate myositis, cellulitis and fibrosis. The sponsor states that these changes noted at the injection site "...would prevent dose levels of above 30 mg/kg/day from being selected in longer term rodent studies."

Reviewer's Comments: Since the drug is antigenic in humans as well, one might expect similar injection site injury to that found in the rat. Since the drug is proposed for s.c. administration essentially for the life of the patient, one might predict that some discomfort from injection site inflammation would be experienced by patients as well.

Dose comparison with proposed human dose

No drug-related mortality was found with Copolymer-1 treatment at s.c. doses up to 30 mg/kg/day. The proposed human dose is 20 mg/day (0.4 mg/kg/day for 50 kg human; based on female). 30 mg/kg/day is about 75-fold higher than the proposed human dose by mg/kg, and about 10-fold higher on a mg/m^2 basis.

With respect to toxic effects, no NOEL was found for antigenicity or anti-nuclear antibody formation. The NOEL for immune complex deposition was 3 mg/kg/day, which is 7.5-fold greater than the proposed human dose (0.4 mg/kg/day) on a mg/kg basis and in the same dose range on a mg/m^2 basis.

5. COP-1 four week study in beagle dogs by subcutaneous injection, Study

September 29, 1988, GLP.

Study description

Animals: Beagle dogs

Treatment: Dogs (3/sex/group) were administered daily s.c. injections of study drug for 4 weeks. Animals received 0, 2, 10 or 20 mg/kg/day, injections distributed among three sites in the dorsal region of the dog.

Observations: Clinical signs, physical examinations (teeth and gums, mucous membranes and skin, ears, superficial lymph nodes, abdomen, external genitalia, chest, gait and stance, general behavior and appearance), food consumption, body weight, ophthalmoscopy, neurology (cranial nerve reflexes, segmental reflexes, postural reactions, general observations), clinical pathology, hematology (PCV, Hb, RBC, platelets, mean corpuscular volume, total leucocyte count, differentials, prothrombin time), blood chemistry (urea, blood creatinine, fasting glucose, CPK, LDH, ALT, AST, GGTP, ALPH, bilirubin, total protein, sodium, potassium, chloride, calcium, phosphorus), urinalysis, macroscopic pathology, organ weight, microscopic pathology (including auricular and ventricular sections of the heart, brain (cerebellum, cerebral cortex, thalamic nuclei, mid-brain and medulla), spinal cord (cervical, thoracic and lumbar) and abnormal and visible lesions, adrenals, aorta, bone, brain, caecum, colon, duodenum, epididymidis, eye; gall bladder, heart, ileum, injection sites, jejunum, kidneys, liver, lungs, lympn nodes, female mammary glands, esophagus, optic nerve, ovaries, pancreas, pituitary, prostate, rectum, salivary glands, sciatic nerve, skeletal muscle, skin, spleen, spinal cord, stomach, testes, thymus, thyroids, tongue, trachea, urinary bladder, uterus, vagina.

Results

Mortality

No deaths.

Clinical signs

Scratching of the injection site, certainly treatment related and seemingly dose-related.

Physical examinations

Swelling and hair loss at the injection site due to scratching was found for all treated animals. Other signs included dull coat, congested conjunctiva, oral papillomatosis and small bilateral testes.

Body weights

No effects.

Food consumption

No effects.

Ophthalmoscopy

Hyper-reflective points on the border between the Tapetum lucidum and negrum were observed in one male dog and one female out of 3 in the High Dose groups, respectively and in 2 of 3 males of the Intermediate Dose group when examined at 4 weeks. 2 of 3 HDM and 2 of 3 HDF also presented with congested bilateral eyes. It is not known whether or not these effects are drug related, but they did occur at the high dose.

Hematology

The **hematology data are uninterpretable** because the total WBC, neutrophil, lymphocyte and monocyte counts are decreased 36, 35, 35 and 95% in the High Dose Male animal group BEFORE the animals are treated with Copolymer-1. These values continue to be decreased when these same animals are examined after 2 and 4 weeks of treatment with Copolymer-1, but it is impossible to determine whether the decreases are due to drug treatment or to the fact that the animals in Group 4 had much lower values at the start of the experiment.

Blood chemistry

A small decline in sodium (1%) and phosphorus (26%) was found in HDF at 2 weeks of treatment. This effect disappeared at the 4 week time point. There was also an increase in gamma globulin in female animals receiving 10 or 20 mg/kg/day, which could reflect an increase in antibody production, possibly due to the antigenicity of the drug. The sponsor never examined the animals directly for anti-COP-1 antibody production.

Urinalysis

No effects.

Organ weights

No effects.

Macroscopic pathology

Injection site pathology only was reported, including subcutaneous congestion or hemorrhage (in Controls to same extent as Treated Animals), subcutaneous edema, and hair loss as shown in the following Table 1 (pg. 025 039 of NDA):

Text Table 1: Macroscopic lesions observed at the injection site:

Group and sex (3/sex/group)	1M	2M	3M	4M	1F	2F	3F	4F
LESIONS								
subcutaneous congestion or hemorrhages	2	1	2	3	2	0	2	3
subcutaneous edema	0	0	1	1	1	1	2	3
hair loss	0	0	0	1	0	0	0	1

Subcutaneous edema was observed at a higher incidence in the Treated Groups, while areas of hair loss, most probably resulting from itching and scratching, were observed in the high dosage group only.

Microscopic pathology

There was one of three Females at 10 mg/kg that presented with chronic cortical inflammation in both right and left kidney. It is unknown whether or not this was related to drug antigenicity.

The main microscopic pathological effects were again related to injection site wounds, as delineated in the following table:

Table 13: Summation of graded scores for micropathology at the injection site

	Group and sex							
	1M	2M	3M	4M	1F	2F	3F	4F
LESION								
recent hemorrhage	5*	3	12	6	4	1	7	8
chronic inflammation	4	7	17	15	3	7	19	15
acute inflammation	-	3	10	7	3	-	1	5
edema	-	4	25	14	2	7	20	15
mononuclear cell infiltrate	-	3	12	13	-	9	19	12
multinucleate giant cells*	-	-	8	1	-	3	4	3
hematoma	-	-	-	2	-	-	2	-
subcutaneous fibrosis	-	-	-	-	-	-	-	2

*The injection site effects were graded 0-4, and the values in this table reflect the addition of the grade for each lesion at the three sites for the three dogs in each sex group. The maximum possible score for scored criteria is 36.

These data indicate that there is a treatment relationship at the injection sites in all three treatment groups, in the criteria of recent hemorrhage, chronic and acute inflammation, edema, mononuclear cell infiltrate and the presence of multinucleate giant cells. The effect appears to be largely dose-related.

The presence of these injection site lesions is indicative of the fact that the drug was antigenic in the dogs as well.

Dose considerations

There was no NOEL with respect to injection site lesions. These occurred in all Treatment Groups. The only other toxicological finding, hyper-reflective points in the eyes, had a NOEL of 2 mg/kg/day, which is 5-fold higher than the human dose on a mg/kg basis and 2.5-fold greater on a mg/m^2 basis. The clinical significance of this finding is unknown. There were no animals deaths, so or LD_{50} was determined.

Overall summary

An increase in gamma globulin levels in the female animals receiving 10 or 20 mg/kg/day may suggest antibody production to the drug. The sponsor did not look specifically for anti-COP-1 antibodies in these animals.

Hyper-reflective points in the eye were observed in High Dose and Intermediate Dose animals. It is not known whether or not this effect is drug related, not is the clinical significance of this effect known.

The hematology data, which based on findings in the rat are important to this study, are uninterpretable because of unacceptably low values for blood cell counts in the Group 4 animals before treatment commenced.

The only other findings of significance in this study were the injection site lesions, which included hemorrhage, chronic inflammation, edema, mononuclear cell infiltrate, hematoma and subcutaneous fibrosis. These effects appeared to be both drug-related and dose-dependent. The presence of these injection site lesions suggests that the drug was antigenic in the dogs as well. The presence of mononuclear cell infiltrate and multinucleate giant cells is consistent with Type IV (delayed-type hypersensitivity) response.

These dog studies did not include an examination of the effects of Copolymer-1 administration on the cardiovascular system.

6. Subacute subcutaneous toxicity to beagle dogs of "COP-1", Study June, 1976, NOT GLP.

—and—

7. Subchronic subcutaneous toxicity to beagle dogs of "COP-1", Study , June, 1976, NOT GLP.

Study description

Five beagle dogs, ranging in weight from 8.5 to 16 kg, were administered daily s.c. injection of 10 mg/kg Copolymer-1 in saline for 90 days, with one male and one female being sacrificed after 36 days (hence #6 above, the so-called "Subacute" study). Batch #4, 5, 7 and 8 of Copolymer-1 were used.

Results

Clinical, necropsy and histological results were reported in narrative form only. The sponsor reported no clinical signs and no abnormal histopathological findings for brain, thymus, lungs, intestines, liver, spleen, kidneys, adrenals, pituitary, lymph nodes, testes and ovaries.

Reviewer's Comments: These studies are of no value in determining the toxicity of Copolymer-1 because they were not carried out under GLP guidelines and because insufficient information with respect to methodology or data were submitted to allow any scientific evaluation.

8. COP-1: 28 day subcutaneous sub-chronic toxicity study in the monkey, Study #1028/21-1050, May 24, 1993, UK GLP regs.

Study description

Animals

Cynomolgus monkeys, 1/sex/group. Males 2.25-2.5 kg, Females, 1.85-2.15 kg.

Treatment

Monkeys were administered s.c. injections of study drug into four different sites (left and right shoulder, sites 1 and 2, respectively; left and right lower back, sites 3 and 4, respectively). The injection sites were rotated sequentially on a daily basis. Drug was administered for 28 days.

One week prior to dosing, all monkeys randomized to receive Copolymer-1 were administered ^{125}I-radiolabelled Copolymer-1 at the intended dose of 20, 40 or 60 mg/kg for pharmacokinetic evaluation. Blood samples were taken at predose, 2, 5, 10, 20, and 30 minutes postdose and 1, 2, 4, 6, 8, 24 and 72 hours postdose.

Observations

Clinical condition and behavior, body weights, food consumption, ophthalmoscopy, electrocardiogram (prior to dosing and on Week 4 prior to dosing), hematology (Hb, MCV, RBC, differentials, platelets, reticulocytes, prothrombin times), clinical chemistry (AST, ALT, GGT, ALP, sodium, chloride, phorphorus, urea, creatinine, albumin, cholesterol, IgG, IgA, potassium, calcium, glucose, total bilirubin, total protein, IgM), Urine analysis (volume, pH, glucose, urobilinogen, blood, microscopy, specific gravity, protein, ketones, bilirubin), macropathology, organ weights (adrenals, brain, heart, kidneys, liver, ovaries, pituitary, spleen, testes and epididymides, thyroids), histology (adrenals, aorta, blood smear, brain, caecum, colon, duodenum, epididymides, ovaries, pancreas, peripheral nerves, pituitary, prostate, rectum, salivary gland, seminal vesicles, eyes, femur, gall bladder, heart, ileum, injection sites, jejunum, kidneys, lachrymal gland, liver, lung, lymph nodes, esophagus, all gross lesions, skeletal muscle, skin and mammary gland, spinal cord, spleen, sternum, stomach, testes, thymus, thyroids, tissue masses or tumors, tongue, trachea, urinary bladder, uterus, vagina). **Note: Although all of the above tissues were prepared for microscopic examination, only tissues from gross lesions from all animals were observed. Therefore, the sponsor chose not to examine the other tissues histologically.**

Results

Mortality and clinical signs

No deaths. The only clinical signs reported were minor sores at the injection site, and no specific data were presented for this observation.

Body weights

No effect.

Food consumption

Animal numbers 510 (Group 5F; 25%) and 509 (Group 4F; 20%) had slightly decreased food consumptions in Weeks 4. There were no other effects on food consumption. With only 1 animal/sex/group, data are hard to interpret.

Ophthalmoscopy

No effects.

Electrocardiology

The electrocardiology determination was not planned for optimal evaluation of the effects of Copolymer-1 administration on heart rate or ECG parameters, because ECG readings were taken at 4 Weeks, **before drug administration.** It would have been preferable to examine ECG parameters over time directly after drug administration.

At 4 weeks, the male animals demonstrated what appears to be a dose-related

decrease in heart rate. The High Dose Male animal demonstrated about a 15% decrease in heart rate at Week 4. With only 1 animal per group, statistical analysis is impossible. No effects on heart rate or other ECG parameters were seen in females.

Hematology

At 4 Weeks of treatment with Copolymer-1, High Dose male peripheral blood lymphocyte counts were down 59% with only a 14% decrease in total WBC counts. High Dose female total WBC counts were down 34%, Neutrophil counts down 24% and Lymphocyte counts down 50%. The sponsor states that "...since the Male Control values are similar to the Female Treated animal counts, that this effect is not real..."

Reviewer's Comments: It is true that it is inappropriate to place too much weight on results of a study that only includes a single animal per sex per group. However, I disagree with the premise that it is appropriate to compare the Female Treated Animal values with the Male Control Values. If one appropriately compares Male Treated to Male Control and Female Treated to Female Controls, then these decreases in WBC, lymphocyte and neutrophil counts are probably real, and decreases of this magnitude are more than likely biologically significant. I agree with the sponsor that these results raise the level of concern for effects of Copolymer-1 on immune cells and suggests that one must very carefully consider these data in the 52-week Monkey study to be reviewed in the next section.

Anti-Copolymer-1 antibody formation

All animals treated with Copolymer-1 in all treatment groups developed anti-COP-1 antibodies following a 4 week s.c. treatment, as shown in the following Table (from the ND/

Table:Development of anti-COP-1 antibodies following a 4-WK treatment with COP-1.

Sample No.	COP-1 dose (mg/kg)	plasma dilution 1:100	plasma dilution 1:250	plasma dilution 1:1000	plasma dilution 1:5000
MALES					
3501	0	3708	1971	861	402
3502	20	39061	35309	25293	8589
3503	40	39038	32847	19442	5440
3504	60	39663	33802	20880	5957
3505	60 (in 50% saline)	33511	28500	13404	4283
FEMALES					
3506	0	3521	2399	1311	934
3507	20	30322	20527	7686	2283
3508	40	31987	30039	14015	3791
3509	60	33412	26342	9856	2383
3510	60 (in 50% saline)	29913	19638	7841	1969

Results presented (in cpm) are from a solid-phase RIA utilizing COP-1 as the coating agent.

Reviewer's Comments: These data are consistent with data in the rat, in which all Treated Animals also developed antibodies to COP-1. As with the rat, there is also the possibility of immune complex formation and deposition in kidneys, cardiovascular system and other organ systems followed by development of inflammation. There is also the question of whether or not the antibodies formed as the result of Copolymer-1 are "neutralizing" antibodies. The sponsor does not appear to attempt to answer this question in this animal study.

Clinical chemistry
No effects.

Urine analysis
On Week 4 of treatment, urine volume dropped 57% in High Dose Male animal and 76% in the High Dose Female animal. Urine volume dropped somewhat in the other Treated animals as well. These data could suggest some effect of the drug on the kidney. However, in the animals tested 2 Weeks before commencement of treatment, the High Dose male had a decreased urine volume of 76% compared to Male Control, and the High Dose female animal's urine volume dropped 88%. Therefore, it is more likely that this decreased urine volume is not due to drug treatment.

Organ weights
High Dose Males had kidney weights that were increased from 19-24% and thyroid weights that were decreased by 49-66%. No such effects were seen in Female animals. The significance of these alterations in organ weight are unknown. However, the effects on kidney weights are of some interest in light of the antigenicity of the drug and potential effects of immune complex deposition.

Macroscopic/microscopic pathology
The Group 2 and 3 Males and Group 4 and 5 Females demonstrated injection site lesions. These lesions included dermatitis, cellulitis, myositis, and fibrosis with both macrophage and in some cases neutrophil infiltration. These lesions also included edema, hemorrhage and tissue necrosis.

The sponsor concluded the following: "Histopathological evaluation of the injection sites detected a chronic inflammatory response at 20 mg/kg/day and above. At 60 mg/kg/day this was accompanied in one animal by subcutaneous thickening and a gelatinous swelling. Therefore, in conclusion, although doses of up to 60 mg/kg/day of COP-1 appeared systemically well tolerated, changes at the injection site suggested that dose levels of less than 40 mg/kg/day should be considered for a subsequent 52 week study by the subcutaneous route."

Pharmacokinetics

Methodology

The pharmacokinetics of COP-1-related material was evaluated in male and female monkeys at dose levels of 20, 40 and 60 mg/kg by s.c. administration. A single dose was administered with a radiotracer (^{125}I)-COP-1 (Batch #00593-01). Blood samples were taken at predose, 2, 5, 10, 20, and 30 minutes postdose and 1, 2, 4, 6, 8, 24 and 72 hours postdose. In addition, the effect of changing the dose formulation from hyperosmotic (0.9% (w/v) saline) to isoosmotic (0.45% (w/v) saline) has been investigated at 60 mg/kg body weight.

Results

Results of the pharmacokinetics study with respect to total plasma radioactivity and TCA-precipitable ratioactivity (plasma protein-bound) are shown in the following Table 7.1 and 7.2, respectively:

Table 7.1 Total plasma radioactivity pharmacokinetic parameters following single subcutaneous doses of (^{125}I)-COP-1 to monkeys.

Animal group	Dose level (mg/kg)	Formulation saline (%w/v)	Cmax (µg/ml)	Tmax (h)	AUC (0-24) (µg.h/ml)	$t_{1/2}$ (h)
M(2) F(2)	20 20	0.9 0.9	46.67 50.32	2.00 2.00	606.7 691.9	32.31 30.96
M(3) F(3)	40 40	0.9 0.9	96.39 78.01	4.00 2.00	1513.3 1103.2	30.81 37.80
M(4) F(4)	60 60	0.9 0.9	141.5 138.0	2.00 4.00	2323.8 2288.7	30.29 31.80
M(5) F(5)	60 60	0.45 0.45	133.9 132.8	2.00 2.00	1880.2 2004.1	34.28 31.03

Table 7.2 Total plasma TCA precipitable radioactivity pharmacokinetic parameters following single subcutaneous doses of (^{125}I)-COP-1 to Monkeys

Animal group	Dose level (mg/kg)	Formulation saline (%w/v)	Cmax (µg/ml)	Tmax (h)	AUC (0-24) (µg.h/ml)	$t_{1/2}$ (h)
M(2) F(2)	20 20	20 20	14.37 15.86	1.00 1.00	206.1 255.9	98.7 70.71
M(3) F(3)	40 40	0.9 0.9	20.78 20.81	1.00 1.00	466.7 420.3	86.19 112.1
M(4) F(4)	60 60	0.9 0.9	41.70 49.76	1.00 2.00	832.2 827.5	58.41 77.11
M(5) F(5)	60 60	0.45 0.45	46.13 38.50	0.50 2.00	761.2 752.2	70.50 66.26

Radio-labelled drug-related material exposure (AUC) increased in a linear fashion with dose. Within the limits of an experiment that only includes 1 animal/sex/group, there appears to be no difference in exposure with respect to sex of the animal. About 25-30% of the exposure (AUC_{0-24}) to total drug-related radioactivity appeared to represent TCA-precipitable radiolabel. TCA-precipitable radiolabel most likely represents a combination of intact Copolymer-1 drug, large degradation products, and some free radiolabelled amino acids that have been reincorporated into new TCA-precipitable plasma proteins as well as free radiolabelled iodide that has become bound to TCA-precipitable plasma proteins. No bioavailability was calculated for COP-1 by s.c. route.

Overall summary

Major findings in this toxicology study included possible decreased heart rate (15%) in HDM on Week 4. It is noted that this decrease was found even though ECG determinations were made before administering the drug on this day.

High Dose Male peripheral blood lymphocyte counts were decreased 59% (only 14% decrease in total WBC), while High Dose Females had total WBC counts down 34%, neutrophil counts down 24% and lymphocyte counts down 50%. These are probably biologically significant effects.

Anti-Copolyer-1 antibodies were formed in all Treated animals, with similar levels being produced irrespective of dose. Urine volume dropped 57% in High Dose Males and 76% in High Dose Females, although it is difficult to tell if this is drug-related, since these animals also had decreased urine volumes before commencement of treatment.

High Dose Males had increased kidney weights (19-24%) and thyroid weights that were decreased 49-66%. No such effects were seen in Females. Although the significant of these effects are unknown, effects on kidney are of special interest when the administered drug is antigenic and provides the potential for immune complex formation.

Pathology included injection site lesions, that presented with edema, hemorrhage and tissue necrosis.

Pharmacokinetics data demonstrated that the radioactive drug-related material exposure (AUC) increased in a linear manner with dose, with no sex differences. TCA-precipitable drug (plasma protein bound) made up about 25-30% of the total radioactive exposure.

Dosage considerations compared to proposed human dose

There were no animal deaths, so no LD_{50} was determined. With respect to toxicity, it is difficult to determine a NOEL in a study in which only a single animal per sex per group was utilized, because there are no statistical considerations to help delineate effect versus no effect. However, by common sense estimate upon examination of the data, the NOEL for decreased heart rate, decreased lymphocyte count (males), and injection site lesions appeared to be about 40 mg/kg/day (100-fold>proposed human dose by mg/kg; 33-fold> by mg/m^2). There was no NOEL for

decreased lymphocyte count (females) or decreased kidney weights, as these effects occurred in all Treatment Groups irrespective of dose.

9. COP-1: 52 week subcutaneous chronic toxicity study in the monkey, Study 1028/26-1050 , September, 1994.

Study Description

Animals

Cynomolgus monkey (Macaca fascicularis), 16 males (2.15-3.6 kg) and 16 females (2.0-2.4 kg).

Treatment

The monkeys were divided into four treatment groups, 4/sex/group. Each animal received Control (normal saline) or 3, 10 or 30 mg/kg/day Copolymer-1 as a single daily s.c. injection. Injections were initially administered into four different sites, the right and left upper and lower back. Due to thickening and fibrous swelling at the injection sites, the number of sites in the 10 and 30 mg/kg group was increased to seven, to include the left and right flanks of the abdomen and the area between the shoulders. The sites were rotated but not always in specific order. The study drug was administered daily for 52 weeks.

Observations

Clinical condition and behavior, body weight, food consumption, ophthalmoscopy, electrocardiography, hematology (Hb, MCV, RBC, differential and total WBC counts, platelets), clinical chemistry (AST, ALT, Gamma GT, Alk Phos, sodium, chloride, inorganic phosphorus, urea, creatinine, alph1 globulin, beta globulin,albumin, cholesterol, IgA, potassium, calcium, glucose, total bilirubin, total protein, alpha 2 globulin, gamma globulin, IgG, IgM), anti-Copolymer-1 antibodies, anti-nuclear antibodies, anti-histone and anti-single and double-stranded DNA antibodies, urine analysis (volume, specific gravity, protein, ketones, blood, creatinine, pH, glucose, total bilirubin, microscopy), organ weights (adrenals, brain, kidneys, liver, ovaries, pituitary, spleen, testes and epididymides, thyroids), histopathology (adrenals, aorta, blood smear, brain, caecum, colon, duodenum, epididymides, eyes, femur, gall bladder, heart, ileum, pancreas, peripheral nerves, Peyer's patches, pituitary, prostate, rectum, salivary glands, seminal vesicles, skeletal muscle, skin and mammary glands, spinal cord, spleen, injection sites, jejunum, kidneys, lachrymal gland, liver, lungs, lymph nodes, esophagus, ovaries, gross lesions, sternum, stomach, testes, thymus, thyroids, tissue masses or tumors, tongue, trachea, urinary bladder, uterus, vagina)—all tissues from all animals were examined.

Results

Mortality

Animal #636, a Group 3 (10 mg/kg/day) Female, was killed during Week 14 of the study. The animal exhibited poor food consumption and lost body weight. Although receiving electrolyte solutions orally, it did not recover and was killed for humane reasons.

Histologically, this animal revealed lymphoid and bone marrow atrophy and adrenal cortical hypertrophy. There were non-specific inflammatory lesions in the skin of the tail and paw and in the rectum. In three visceral organs (pancreas, ileum and colon) there was evidence of minor active focal fibrinoid arteritis (which the sponsor states probably arose due to "stress"). An inactive fibrosed arterial lesion (which the sponsor states was probably pre-existing in origin) was found in the heart. The sponsor states that, "No specific cause of the morbidity could be established." They further state that "The combination of non-specific inflammatory changes may have caused the debility."

Reviewer's Comments:

The toxicological results with respect to this animal may be consistent with a systemic inflammatory response as a cause of morbidity and death. The animal had active focal fibrinoid arteritis in three organs, pancreas, ileum and colon. A fourth, inactive lesion, was found in the heart.

Also in support of a systemic inflammatory response are the following toxicology results with respect to animal #636:

Hematology

Animal 636 had a neutrophil count 158% higher than Control and a lymphocyte count 71% below Control, and well out of line with the other three Female animals in this dosing group.

Antibody to double stranded DNA

During Week 4, animal #636 had an antibody titer for anti-double stranded DNA that was increased 138% over Control, and was almost two-fold greater than the other three Female animals in this dosing group. Results were also similar on Week 8.

Antibody to single stranded DNA

During Week 4, animal #636 had an antibody titer for anti-single stranded DNA that was increased 100% over Control, and was 1.5-fold higher than the other three animals in this dosing group.

Total IgG

Animal #636 responded to Copolymer-1 treatment with an IgG level 140% higher than Controls, and an IgG level 2-fold greater than the other three animals in the same dosing group.