Clinical Study Protocol with Amendment 13
(including Statistical Analysis Plan)

Open Label Study to Evaluate the Safety of Copaxone® and to Monitor the Neurologic Course of Disease in Multiple Sclerosis Patients Treated with Copaxone®

Study Number GA-9004 (or 01-9004)

NCT00203021

Protocol with Amendment 13 Approval Date: 13 May 2016

TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

CLINICAL STUDY PROTOCOL

Study Title: **Open Label Study to Evaluate the Safety of Copaxone® and to Monitor the Neurologic Course of Disease in Multiple Sclerosis Patients Treated with Copaxone®**

Protocol No.: **01-9004**

Clinical Phase: **4**

Amendment No. 13: **Date: 13 May 2016**

[THIS VERSION SUPERSEDES ALL PREVIOUS VERSIONS]

Sponsor: **Teva Branded Pharmaceutical Products R&D, Inc.**

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Frazer, PA 19355

Clinical Trials Manager: [redacted]

This clinical study will be conducted in accordance with the Declaration of Helsinki and its updates, current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonisation); US Code of Federal Regulations (Title 21, CFR Part 11, 50, 54, 56 and 312); local country regulations and the sponsor's Standard Operating Procedures (SOPs)

PROTOCOL REVIEW & APPROVAL

Protocol 01-9004

Amended Protocol Following Amendment No. 13

[redacted]	[redacted]	13 May 2016 Date

TABLE OF CONTENTS

1. STUDY TITLE

Open Label Study to Evaluate the Safety of Copaxone® and to Monitor the Neurologic Course of Disease in Multiple Sclerosis Patients Treated with Copaxone®

2. INTRODUCTION

2.1. Background

Copaxone® injection is a clear, colorless to slightly yellow, sterile, nonpryrogenic solution for subcutaneous injection. Each 1.0 mL of solution contains 20 or 40 mg of glatiramer acetate and 40 mg mannitol, USP. Glatiramer acetate is the generic name used to designate the active ingredient of Copaxone®. It is composed of a mixture of acetate salts of synthetic polypeptides prepared from four naturally occurring amino acids L-glutamic acid, L-alanine, L-tyrosine, and L-lysine.

Copaxone® (glatiramer acetate for injection, formerly known as Copolymer 1 [COP-1]), was approved by the United States Food and Drug Administration (FDA) on 23 December 1996. It is the first non-interferon agent demonstrated to reduce the frequency of relapses in patients with relapsing-remitting multiple sclerosis (MS).

Glatiramer acetate was designed to treat MS specifically by selective immune modulation. Mechanism of action studies support the hypothesis that binding of glatiramer acetate to the MHC II groove may lead to 2 effects that positively moderate the pathogenesis of experimental allergic autoimmune encephalomyelitis (EAE) and MS: 1) glatiramer acetate induces specific suppressor T cells, and 2) glatiramer acetate inhibits specific effector T cells. Glatiramer acetate is believed to initiate its immunomodulatory effects at the site of subcutaneous injection, with subsequent systemic distribution of these locally activated T cells.

The evidence to support the safety and efficacy of Copaxone® is based primarily on 2 adequate and well controlled pivotal trials (Bronstein et al 1987; Johnson et al 1995). These trials were double-blind, randomized, placebo-controlled, long-term, fixed dose studies. In both studies, the objective was to assess the safety, tolerability, and therapeutic efficacy of 20 mg Copaxone® self-administered subcutaneously daily in patients with relapsing-remitting MS. Both studies were designed to last 24 months, and the double-blind period of the largest trial was extended up to 35 months.

In these previous studies of Copaxone® in MS patients, no clinically significant laboratory abnormalities were associated with Copaxone® therapy during nearly 3 years of dosing. The most commonly observed adverse experiences associated with the use of Copaxone® in the largest pivotal trial were local reactions at the site of injection. The most common of these local reactions were pain, erythema, and inflammation. The majority of injection site reactions were

reported as mild, and although common in patients treated with Copaxone®, were also observed in patients treated with placebo.

Some patients, including those assigned to placebo, reported symptoms consistent with the transient, self-limited, systemic reaction that may immediately follow subcutaneous injection, as originally described by Bornstein et al. This reaction was characterized by vasodilation (flushing) or chest tightness with palpitations, anxiety, and/or dyspnea (shortness of breath). These symptoms generally appeared within minutes of injection and lasted up to 15 minutes. In the largest pivotal trial, the component adverse experiences of these reactions were cited as the cause for discontinuation of 3% of those patients receiving Copaxone® and 1% of those receiving placebo. Most patients who had this reaction reported 1 episode. The maximum number of reported episodes per patient was 7 over a course of approximately 845 injections (<0.5%).

The 2 trials were similar with respect to the patient selection criteria, resulting in similar demographics and baseline disease characteristics between treatment groups across both studies. The population included in these studies reflected the characteristics of patients with relapsing-remitting MS.

In both trials, Copaxone® significantly reduced relapse rate. In the largest trial, Copaxone®-treated patients exhibited a statistically and clinically significant reduction in number of relapses over a period of 24 months. Copaxone®-treated patients with baseline Kurtzke Expanded Disability Status Scale (EDSS) scores of 0 to 6 showed a 29% reduction in the number of relapses compared with placebo-treated patients. Copaxone®-treated patients with baseline EDSS scores of 0 to 2 showed a 33% reduction in relapses compared with placebo-treated patients. The reduction in relapse rate after up to 35 months of treatment was even greater.

After up to 35 months of treatment, Copaxone® treatment resulted in a statistically and clinically significant increase in the proportion of relapse-free patients. While 33.6% of Copaxone®-treated patients remained relapse free, only 24.6% of placebo-treated patients did so.

In studies with Copaxone®, there has been no evidence that antibodies are produced which neutralize the activity of Copaxone®.

As of 30 November 2015, an estimated total of 8733 subjects have been exposed to glatiramer acetate, administered subcutaneously as part of the clinical development program, reflecting total of about 19,951 patient-years. The majority are relapsing remitting multiple sclerosis (RRMS) patients using the marketed formulation of Copaxone® 20 mg/mL on a daily basis.

An open-label, randomized, multi-center, parallel-arm study (MS-GA-303; GLACIER) was conducted to assess the safety and tolerability of Copaxone 40 mg/mL three times weekly (TIW) compared to 20 mg/mL daily subcutaneous injections in subjects with RRMS. A statistically significant ($p<0.0006$) reduction in the primary endpoint, injection related adverse event rate, in the Copaxone 40 mg/mL TIW group compared to the Copaxone 20 mg/mL daily group was revealed. Treatment with Copaxone at dosages of 20 mg/mL daily and Copaxone 40 mg/mL TIW was generally safe and well tolerated in patients with RRMS who had been treated continuously with Copaxone 20 mg/mL daily for a minimum of 6 months prior to screening, followed by 4 months of randomized treatment with Copaxone 20 mg/mL daily or Copaxone

40 mg/mL TIW (Core Phase), then followed by 4 months of treatment where patients were offered to continue on with the Copaxone 40 mg/mL TIW regimen (Extension Phase).

2.2. Rationale

Current treatment regimens for relapsing-remitting MS patients include physical and occupational therapies, and pharmaceutical intervention to alleviate the dysfunctions of the disease (e.g., spasticity, weakness, ataxia, etc.), the frequency of relapses, and to slow the accumulation of physical disability.

Acute relapses of neurologic impairment may be symptomatically treated with corticosteroids or adrenocorticotrophic hormone (ACTH). There is no evidence, however, to indicate that either of these agents alter the long-term course of MS.

Betaseron® (interferon beta-1b) is a general immunomodulator approved by the FDA and indicated for use in ambulatory patients with relapsing-remitting MS to reduce the frequency of relapses. However, many patients have difficulty tolerating this therapy, which may limit its utility. Also, 38% of Betaseron-treated patients developed neutralizing antibodies over time, that were associated with reduced efficacy (IFNB MS Study Group 1995).

Avonex® (Interferon beta-1a) is approved by the FDA and is indicated for use in the treatment of relapsing forms of MS to decrease the frequency of clinical exacerbations and to slow the accumulation of physical disability. During a clinical study, 24% of Avonex™-treated patients were found to have serum neutralizing activity at one or more time point. The significance of the appearance of serum neutralizing activity is unknown (Avonex Package Insert).

Tysabri® (natalizumab), a monoclonal antibody, was approved November 2004 by the FDA for patients with relapsing forms of MS. Tysabri® is given by monthly intravenous infusion in a doctor's office or medical center. Tysabri® was withdrawn February 2005 following 2 cases of progressive multifocal leukoencephalopathy (PML) in clinical trials and resumed marketing July 2006 following implementation of a restricted distribution program (Tysabri Package Insert).

Rebif® (interferon beta-1a) is approved by the FDA for treatment of patients with relapsing forms of MS. It is made up of the same amino acids as the interferon beta found in the human body. Rebif® is given three times a week subcutaneously (Rebif Package Insert).

Novantrone® (mitoxantrone) is an anthracenedione anti-neoplastic agent. Novantrone® was approved by the FDA for patients with secondary progressive MS, progressive-relapsing MS and worsening relapsing-remitting MS. Novantrone® is given by IV infusion once every 3 months for 24 months (Novantrone Package Insert).

Oral disease modifying treatments for relapsing-remitting MS include fingolimod (Gilenya®), teriflunomide (Aubagio®), and dimethyl fumarate (Tecfidera®); these are approved, in the US and will soon be approved in Europe.

Because of the potential loss of efficacy over time with interferon therapy, and the need to collect additional long-term safety data for Copaxone®, continuing evaluation of Copaxone® was

introduced in Amendment 11. In addition, an imaging sub-study was initiated in a previous Amendment (Amendment 10) to provide additional prospective nonconventional magnetic resonance imaging (MRI) data for Copaxone®.

A further amendment (Amendment 12) was added to the protocol to offer patients the Copaxone 40 mg TIW formulation while collecting safety and tolerability data that will be compared clinically, immunologically, and by MRI to the 20 mg daily dose of Copaxone. Since injection frequency affects long-term adherence to treatment, the sponsor is now seeking to gain more information about the injection experience of those patients who have been taking Copaxone 20 mg daily and are switched to Copaxone 40 mg/mL TIW. Overall, the study will continue to provide information regarding the safety of Copaxone administration for both the 20 mg daily injection as well as the 40 mg TIW injection in a large cohort of patients who have been on daily injections of Copaxone for an extended period of time.

This amendment (Amendment 13) will extend the study duration for an additional 2 years (until month 288). The longer duration of the study will help to better understand the long term safety of Copaxone, as the study includes a unique cohort of patients that have been followed continuously. Additionally, the longer duration will help to gain insight into the disease processes and activity in patients with 30+ years of disease. Finally, the extension will help understand the safety and efficacy of Copaxone 40 mg/mL TIW in comparison to Copaxone 20 mg daily in patients that have switched from a cross sectional and longitudinal perspective.

3. OBJECTIVES

This study will continue to provide information regarding the safety of administration of Copaxone® to a large number of patients. It will also provide information regarding the safety of Copaxone® administered for up to 26 years, or until the sponsor terminates the study, on approximately 60 patients who participated in the original double-blind study.

The objectives of this study are:

- To assess the long-term safety of Copaxone® in relapsing-remitting MS patients by the ongoing monitoring of
  - Clinical pathology (blood and urine)
  - Adverse reactions
- To evaluate the long-term neurologic course of the disease in the patients receiving Copaxone® by regular neurological examinations including:
  - Functional system evaluation
  - Kurtzke Expanded Disability Status score
  - Ambulation Index (AI)
- To evaluate the neurologic course of the disease in these patients by the monitoring of exacerbations.
- To evaluate the imaging course of the disease in these patients receiving Copaxone® by performing an MRI examination following 24 years of continuous Copaxone® therapy and comparing it to a previous scan obtained following 20 and 22 years of continuous Copaxone® therapy as well as to the neurologic course of the disease following 24 years of continuous therapy.

4. STUDY DESIGN AND DURATION

This open label study will evaluate the safety of Copaxone® and its effect on the neurologic course of patients with relapsing-remitting MS (Poser et al 1983). Copaxone® injection, a clear, colorless to slightly yellow, sterile, non-pyrogenic solution for subcutaneous injection will be given to patients to take either daily (20 mg dose) or TIW (40 mg dose). It is supplied as a single-use pre-filled syringe. Each 1.0 mL of solution contains 20 or 40 mg of glatiramer acetate and 40 mg of mannitol. Patients will be offered the opportunity to continue in this trial for an additional 2 years, extending to 2019 or until the sponsor terminates the study.

After all eligibility criteria for each patient have been met (see Section 6), treatment will continue for that patient. Patients will be evaluated every 3 months for safety and every 6 months for changes in neurological status.

Under Amendment 12, patients had the opportunity to continue participation in the optional MRI substudy, where an MRI examination was completed at the next scheduled treatment visit for Amendment 12 (following the 22 year scan) at month 252, the scheduled termination visit (month 264) or during an unscheduled visit after 24 years of continuous Copaxone® therapy.

The 9 university hospital centers in the United States which participated in the Double-Blind Study (Protocol 01-9001) are anticipated to collaborate in the conduct of the study extension.

5. MATERIALS AND SUPPLIES

5.1. Packaging

Copaxone® will be supplied in single dose pre-filled syringes. Patients will be given a three-month supply of study drug and injection supplies quarterly.

5.2. Labeling

Each outer packet will be labeled (Appendix H) by the investigational site according to federal regulations and include the following information:

- Study ID number
- Site number
- Lot number
- Expiration date
- Subject number
- Subject initials
- Date dispensed
- Visit month
- Storage instructions

A package insert will be in each box of study drug. The package insert includes dosing instruction.

5.3. Dispensing Information

Copaxone® will be dispensed to the patient every three months via overnight delivery service after each scheduled Coordinator Telephone visit and directly to the patient during the scheduled annual site visit. Starting with visits after July 2007, patients will return unused syringes to the study site annually during the site visit where they will be accounted for; unused vs. used syringes will be recorded on the appropriate case report form. The sponsor will handle the destruction of unused syringes.

All remaining study drug should be collected and stored by the investigator according to FDA regulations and returned to the sponsor for disposal.

5.4. Storage

Drug supplies must be kept in a secure, limited access refrigerator storage area. All pre-filled syringes must be kept at 2ºC to 8ºC (ie, in a refrigerator).

5.5. Distribution Site

Fisher Clinical Services (Allentown, PA) will serve as the US distribution center and will maintain a 3-month supply of study materials to ensure continuous dosing at all investigative sites. Additional information on supplies is contained in Section 9.3.

5.6. Injection Techniques

In November 2001, the Copaxone auto*ject*2® *for glass syringe* self-injection device was approved by the FDA and is currently available commercially for use with the Copaxone® pre-filled syringe. Patients in the study may continue to use the manual subcutaneous injection technique or may use the auto*ject*2® *for glass syringe.* For patients who elect to try the auto*ject*2® *for glass syringe*, an auto*ject*2® *for glass syringe*, along with directions on how to use it (Appendix G), will be provided and its use demonstrated by a member of the study staff. Patients may start or discontinue use of the auto*ject*2® *for glass syringe* at any time.

6. SELECTION OF PATIENTS

6.1. Inclusion Criteria

Patients must have previously met all the inclusion criteria in order to be eligible for the study extension.

- Patients must have participated (been randomized) in the Copaxone Double-Blind placebo controlled study (Protocol 01-9001).
- Gender: Patients may be male or female. Women of childbearing potential must practice an acceptable method of birth control.
- Patients must be psychologically and physically stable to participate in the trial as judged by the investigator.

Additionally:

- Patients must have completed the scheduled termination visit for Amendment 12 (month 264).
- Patients must sign an approved informed consent form (ICF) prior to continuing in the study extension or at the first visit in the extension (month 264 which corresponds to the termination visit of Amendment 12).

6.2. Exclusion Criteria

Any of the following conditions will exclude the patient from entering the study:

- Pregnancy or lactation.
- Medical or psychiatric conditions that affect the patient's ability to give informed consent or complete the study.
- Inability to self-administer subcutaneous medication or lack of another responsible individual to administer the study preparation daily (for Copaxone® 20 mg), or at minimum, 3 times a week (for Copaxone® 40 mg).
- Use of approved MS therapies including interferons, experimental MS therapies, or previous immunosuppressive therapy with cytotoxic chemotherapy (azathioprine, cyclophosphamide, or cyclosporine).

7. CONDUCT OF STUDY

7.1. Schedule of Activities and Evaluations

All procedures, tests, and examinations required for the study extension visits are listed on the Schedule of Activities Flow Chart found in Appendix A.

Screening visits through month 264 must have been completed to continue in the study extension. For the purposes of this amendment, the termination visit of Amendment 12 (month 264), will act as the screening visit for this amendment. Patients who have completed the termination visit and discontinued from the study under the Amendment 12 protocol may still continue in the extension study under Amendment 13; for these patients, the screening visit for Amendment 13 will be a separate visit to the termination visit of Amendment 12.

The study extension will involve 1 investigator visit (Section 7.1.3.2) annually supplemented by 3 nurse coordinator telephone visits (Section 7.1.3.1). This schedule will maintain contact with the patients on a quarterly basis, approximately every 90 days. The study extension period will end with the termination visit (Section 7.1.3.3 and Section 7.1.5) following 26 years of continuous Copaxone® therapy.

In addition to MRIs performed at month 240, the optional MRI sub-study will involve 2 MRIs for active study patients at the annual investigator visit (month 252) or at an unscheduled visit around the time of the investigator visits and at the final investigator visit for Amendment 12/screening visit for Amendment 13 (month 264).

The optional immunological sub-study will involve 2 blood samples, 1 taken during the screening visit for Amendment 12, and 1 at the next treatment visit at month 252. There will be no additional immunological assessments under Amendment 13.

7.1.1. Screening Visit for Amendment 13 (Month 264)

During screening for Amendment 13, the patient must be thoroughly informed about all aspects of the study extension, including the study visits and activities schedule. Written informed consent must be obtained.

At this visit, patients will be given the option of either continuing treatment with Copaxone 20 mg daily or switching to Copaxone 40 mg TIW. The choice of treatment will be recorded for each patient.

A checklist of the procedures to be performed during the screening visit follows.

- Eligibility checklist
- Signed informed consent for Amendment 13
- Record treatment (20 mg daily or 40 mg TIW)

- Complete neurological examination, including:
  - Functional Systems Status (FS) Evaluation (Appendix D)
  - Kurtzke Expanded Disability Status Score (EDSS) (Appendix C)
  - AI (Appendix E)
- Complete physical examination
- Laboratory studies as outlined in Section 7.7
  - Urinalysis
  - Hematology
  - Serum chemistries
- Adverse experiences
- Evidence of relapse
- Concomitant therapy
- Drug accountability

The visit procedures listed above may be completed as an unscheduled visit if the month 264 visit has already been completed.

7.1.2. Treatment Initiation

A patient found eligible for the study extension will continue Copaxone® therapy. Patients will be instructed again in preparation and self-administration of Copaxone®. Patients will be given all necessary supplies and a detailed instruction sheet, which will be reviewed with the patient at the visit. In addition, patients will be instructed to contact the study center if questions or problems arise.

7.1.3. Scheduled Treatment Visits

Checklists for the treatment visits for this amendment follow. All procedures, tests, and neurological examinations are listed.

7.1.3.1. Nurse Coordinator Telephone Visits

Months 267, 270, 273, 279, 282, and 285

- Visit checklist

- Adverse experiences
- Evidence of relapse
- Concomitant therapy
- Drug accountability

7.1.3.2. Investigator Visits

Month 276

- Visit checklist
- Neurological examination (FS, EDSS, and AI)
- Urinalysis
- Serum chemistries
- Hematology
- Adverse experiences
- Evidence of relapse
- Concomitant therapy
- Record treatment (20 mg daily or 40 mg TIW)
- Drug accountability

7.1.3.3. Termination Visit (Month 288)

- Visit checklist
- Complete physical examination
- Urinalysis
- Hematology
- Serum chemistries
- Neurological examination (FS, EDSS, and AI)
- Adverse experiences

- Evidence of relapse
- Concomitant therapy
- Drug accountability

7.1.4. Unscheduled Visits

An unscheduled visit can occur at any time during the study. The date of and reason for the visit and any data generated must be documented. Unscheduled visit forms should be placed in chronological order within the Case Report Form binder.

The patient should be seen and evaluated by the study staff. Unscheduled visits due to relapse will be indicated on the case report forms. The patients will be instructed to telephone their site immediately should any symptoms suggesting a relapse appear. The neurologist may evaluate the patients within 7 days of being informed if more information is required to confirm relapse information. Relapses will be classified as mild, moderate, or severe. A completed neurologic assessment will be performed including Functional Status Evaluation (Appendix D) and Kurtzke EDSS (Appendix C) by the neurologist. A decision will be made as to whether the change is considered a relapse as defined in Appendix B. Follow-up visits to monitor the course of the relapse will be made at the investigator's discretion in addition to assessment at the next monthly visit.

MRI procedures for patients who consent to participate in the MRI sub-study may be completed at an unscheduled visit rather than the month 264 termination visit.

7.1.5. Early Termination Visit

An early termination visit occurs whenever a patient discontinues treatment or the treatment protocol is terminated by either the sponsor or the FDA. An evaluation must take place within 4 weeks after the last dose of Copaxone®.

The checklist for the early termination visit follows. All procedures, tests, and examinations listed are the minimum required at each visit.

- Visit checklist
- Termination reason (see Section 7.2)
- Complete physical examination
- Neurologic examination (FS, EDSS, and AI)
- Urinalysis
- Hematology
- Serum chemistries

- Serum pregnancy test
- Adverse experiences
- Evidence of relapse
- Concomitant therapy
- Drug accountability

7.2. Premature Termination of Treatment

The reasons for premature termination of treatment follow. Teva Branded Pharmaceutical Products R&D, Inc. should be contacted before any patient is terminated from the study.

- Intolerable adverse effects.
- Patient's voluntary decision to discontinue treatment for any reason.
- Investigator's judgment that continued treatment is not in the best interest of the patient.
- Loss of patient to follow-up.
- Pregnancy.
- Gross noncompliance (i.e., use of less than 50% of prescribed doses in the preceding 3-month period).

7.3. Concomitant Therapy

- Symptomatic agents such as anti-cholinergic and spasmolytic drugs are permitted at clinically appropriate doses.
- Short-term treatment with corticosteroids will be allowed during acute relapses.
- Medications not allowed during this trial include:
  - Other investigational drugs.
  - Other approved MS drugs
  - Interferons.
  - Immunomodulator, cytotoxic, and immunosuppressive drugs (i.e., cyclophosphamide, cyclosporine, azathioprine, etc.)

  - Long term (>30 days) corticosteroids; overall dose of more than 2,000 mg oral prednisone; overall dose of more than 1,000 mg IV methylprednisolone per day for more than 7 days per treatment, with or without an appropriate tapering dose of an oral prednisone.

- All concomitant medications must be listed in the Case Report Form.

7.4. Assessment of Safety

Special attention will be given to detecting known adverse effects of Copaxone®. In the previous studies of Copaxone® in MS patients, no systemic laboratory abnormalities were observed during 2 years of dosing. Therefore, laboratory studies will be done at 6-month intervals and will consist of urinalysis, hematological evaluations, and a broad screen of blood chemistries (see Section 7.7).

Available data suggest that local reactions at the injection site have been reported more commonly in Copaxone®-treated than in placebo-treated patients. Soreness, itching, swelling, and redness were all reported. None of these reactions was persistent. The descriptions of such reactions will be recorded in the Case Report Form by the nurse coordinator. Appropriate observation will be continued until the patients return to baseline status.

In previous clinical studies, both Copaxone® and placebo-treated patients have occasionally experienced brief episodes of flushing, sweating, palpitations, a feeling of tightness in the chest, difficulty in breathing, and associated anxiety. The site should be contacted immediately and appropriate evaluation undertaken as clinically indicated. A complete description of the event should be placed in the Case Report Form.

The Medical Monitor can be consulted regarding suggested management of the above-mentioned adverse experiences.

Other adverse experiences have been reported during ongoing clinical trials with Copaxone®. A full accounting of adverse experiences is included in the package insert.

Any patient withdrawn from the study for drug-related side effects will be requested to continue to be observed by the physician as long as necessary until the patient's condition returns to the pre-reaction baseline.

7.5. Adverse Events

7.5.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent form should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug interactions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)

Hospitalization due to MS exacerbation should be recorded as an adverse event only if the presentation or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

7.5.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as that time period from signature on the informed consent form until the last study visit.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed to the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the serious adverse event form must be completed and the serious adverse event must be reported immediately (see Section 7.5.5.3). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring in a patient after the treatment of that patient has ended

should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in see Section 7.5.5.3.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open-ended question such as “Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe”. All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed to the CRF.

The relationship of each adverse event to study drug and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.5.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

7.5.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the study drug. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the study drug. • It does not reappear or worsen when the study drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the study drug. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the study drug, yet a drug relationship clearly exists. • It follows a known pattern of response to the study drug.

7.5.5. Serious Adverse Events

7.5.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- death
- a life-threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event

Hospitalizations scheduled before the patient signed the informed consent form will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study.

- Hospitalization for intravenous steroid treatment of a relapse will not be considered a serious adverse event unless it is a worsening of the condition beyond expected disease progression.

- persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)

- a congenital anomaly/birth defect

- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition

- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug-induced liver injury that meet Hy's law criteria, defined as **al**l of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3x the upper limit of normal (ULN)

- total bilirubin elevation of >2x ULN

- absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.5.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is considered an unexpected adverse event. The RSI for this study is the US prescribing information.

The sponsor's Global Patient Safety and Pharmacovigilance will determine the expectedness for all serious adverse events.

7.5.5.3. Reporting a Serious Adverse Event

7.5.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.5.5.1) that occur during the study period (including the protocol-defined follow-up period, described in Section 7.5.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. Any serious adverse event must be reported to the Teva Branded Pharmaceutical Products R&D, Inc., Local Safety Officer . Send by email using the Serious Adverse Event Form to the local safety officer (LSO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel for further instruction

The investigator does not need to actively monitor patients for adverse events once this study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the LSO . The LSO will forward the report to the sponsor's Global Patient Safety and Pharmacovigilance.

The following information should be provided to record the event accurately and completely:

- study number
- investigator and investigational center identification
- patient number
- onset date and detailed description of adverse event
- investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)

Additional information may include the following:

- age and sex of patient
- date of first dose of study drug
- date and amount of last administered dose of study drug
- action taken
- outcome, if known
- severity

- explanation of assessment of relatedness
- concomitant medication (including doses, routes of administration, and regimens) and treatment of the event
- pertinent laboratory or other diagnostic test data
- medical history
- results of dechallenge/rechallenge, if known
- for an adverse event resulting in death:
  - cause of death (whether or not the death was related to study drug)
  - autopsy findings (if available)

The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Additional information (follow-up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety and Pharmacovigilance will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.6).

7.5.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of Copaxone and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other measures may be required, including:

- altering existing research by modifying the protocol
- discontinuing or suspending the study
- altering the process of informed consent by modifying the existing consent form and informing all study participants of new findings
- modifying listings of expected toxicities to include adverse events newly identified as related to Copaxone

7.5.6. Protocol-Defined Adverse Events for Expedited Reporting

No protocol-defined adverse events for expedited reporting were identified for this study.

7.5.7. Overdose of Study Drug

Any dose of study drug (whether the investigational product, reference treatment, or placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

7.5.8. Protocol Deviations Because of an Adverse Event

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

7.6. Pregnancy

All pregnancies of women participating in the study and female partners of men participating in the study, if applicable that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.5.5.3).

Any female patient becoming pregnant during the study will discontinue treatment. All patients (or female partners of men participating in the study) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a serious adverse event.
- For an elective abortion due to developmental anomalies, report as a serious adverse event.
- For an elective abortion **not** due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.

7.7. Medication Error and Special Situations

Any administration of medication that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol or as a deviation, in the patients source documents, regardless of whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized on the CRF as "Non-Compliance to investigational medicinal product (IMP)".

Types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
3. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.
4. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
5. Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.
6. Occupational exposure: Exposure to a medicinal product, as a result of one's professional or non-professional occupation.

7.8. Laboratory Procedures

Blood samples and urine specimens must be obtained at the appropriate visits. Non-fasting samples may be obtained. Any laboratory samples which are outside the normal range must be assigned one of the following codes:

NS – Not Clinically Significant: A clinically meaningless departure from the normal range.

LE – Laboratory Error: Due to a poor sample, instrument error, etc. (the value is not valid).

PA – Patient Abnormality: Although the value is outside the normal range, the value is normal for that particular patient.

CS – Clinically Significant: A clinically meaningful departure from the normal range or a clinically meaningful change in the parameter. All clinically significant values during the study are adverse events and must be entered on the "Clinically Significant Lab Values" page of the Case Report Form.

7.8.1. Urinalysis

- Protein
- pH
- Specific gravity
- Glucose
- Microscopic examination of sediment

7.8.2. Hematologic Tests

- WBC
- RBC
- Differential white blood cells
- Platelet count
- Hemoglobin
- Hematocrit

7.8.3. Serum Chemistries

- BUN
- Creatinine
- Aspartate aminotransferase (AST) or SGOT
- SGPT (ALT)
- Alkaline phosphatase

- Bilirubin
- Phosphorous
- Total protein
- Albumin
- Calcium
- Cholesterol / triglycerides
- Glucose
- Serum electrolytes (Na^+, K^+, Cl^-, Bicarbonate)

7.9. Immunological Analyses

For patients who consent to the optional immunological analysis, blood samples will be collected at the Amendment 12 screening visit (month 240) and the investigator visit (month 252). There will be no additional immunological assessments under Amendment 13. Samples will be analyzed as follows:

8. STATISTICAL METHODS

Standard reporting and analysis procedures will be employed to present the safety profile of Copaxone® and its effect on the neurologic course of the disease.

8.1. Adverse Events

The total number and percent of patients reporting adverse events, across and by body system and event term, will be tabulated for all patients treated. The number of patients treated will serve as the denominator for incidence rate computation. Adverse events will also be summarized by maximum reported severity and relationship to treatment. Detailed data displays, narrative summaries, and copies of Case Report Forms will be provided for those patients who withdrew prematurely due to an adverse event or who dies.

8.2. Laboratory Tests

Summary statistics (number of patients, mean, standard deviation, minimum and maximum) will be displayed for the baseline value, the last value obtained during treatment, and the change from baseline to last observed value. Frequency distributions will be presented, by test, depicting the number of patients who had "clinically significant" changes from baseline in laboratory values, defined by criteria determined by the medical monitor. Scatterplots of each continuous-type lab test will be provided illustrating the graphical relationship between the baseline and endpoint values obtained for each patient by treatment group.

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1. Informed Consent

The principles of informed consent, as described in FDA Regulations, will be followed. A subject must give his/her written consent prior to entering the study. This consent will be witnessed and dated and retained by the Investigator as part of the study records. A copy of the consent will be given to the subject.

If the Experimental Subject's Bill of Rights is applicable, this form must also be prepared and signed by each subject and retained as part of the required study records. A copy of the Bill of Rights must be given to the subject. Some states (e.g., California, Oregon, Massachusetts) have additional requirements for the informed consent process; these must be adhered to as well if the clinical site is located in one of these states.

A copy of the proposed consent form must be submitted to the Institutional Review Board (IRB), together with the protocol, for approval. A copy of the IRB-approved consent form must be submitted to the study monitor prior to shipment of drug supplies to the investigator. Each subject's signed informed consent form (ICF) must be kept on file by the investigator for FDA inspection at any time.

9.2. Institutional Review

Any changes to the protocol, as well as a change of investigator, must also be approved by the IRB, and documentation of this approval provided to the study monitor. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the investigator and are subject to FDA inspection during or after completion of the study. Serious adverse events must also be reported to the IRB. See Section 7.5.5.3 for these requirements.

Periodic status reports must be submitted to the IRB at least yearly, as well as notification of completion of the study, and a final report within three months of study completion or termination. A copy of these reports must be sent to Teva Branded Pharmaceutical Products R&D, Inc.

The investigator must maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted. A copy of all site correspondence with the IRB should be sent to the study monitor at Teva Branded Pharmaceutical Products R&D, Inc or designee.

9.3. Drug Accountability

Each shipment of drug supplies to a center will contain an investigational drug invoice to assist the study staff in maintaining current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies. The invoice will identify for each shipment the lot number and the quantity of study drug and supplies contained in the shipment.

When a shipment is received, the investigator or the nurse coordinator must sign the "Shipment Receipt" form verifying the quantities received and retain this form in the study binder. The drug supply will be packaged and shipped to the centers in appropriate containers. If upon arrival at the investigational site the drug supply appears to be damaged, Teva Branded Pharmaceutical Products R&D, Inc. must be contacted immediately and the drug not used until authorized.

Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions (see Section 5.4). Only authorized personnel will have access to the drug. During the course of the study, the following information must be noted for accurate accountability: the identification code of the subject to whom drug is dispensed, the date(s), and the quantity of drug returned by the subject. Subjects should return all unused pre-filled syringes to the study center and the return noted in the ledger. These will be inventoried for patient compliance and drug accountability. These inventory records must be readily available for inspection by the study monitor and are open to FDA inspection at any time.

When unused pre-filled syringes are to be returned, the investigator or the nurse coordinator will record the returns on the Medication Dispensing CRF verifying the amount of unused pre-filled syringes returned by each study subject. In the event that unused pre-filled syringes are not returned by a subject for whatever reason, this must be explained and whatever attempts to have the syringes returned need to be documented.

Returned study supplies should not remain in the investigator's possession.

One copy of all inventory record sheets and the return statement will be retained by the investigator for his/her files; the inventory sheets will be included in the return shipment of drug supplies.

Upon completion of the study, all unused pre-filled syringes and the drug accountability information must be returned to the sponsor, Teva Branded Pharmaceutical Products R&D, Inc. or sponsor's designee. Teva Branded Pharmaceutical Products R&D, Inc. or designee will handle the destruction of unused syringes.

9.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- suspected contamination
- questionable stability (eg, color change, flaking, crumbling, etc)
- defective components
- missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)

- incorrect packaging, or incorrect or missing labeling/labels
- unexpected or unanticipated taste or odor, or both
- device not working correctly or appears defective in some manner

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

9.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will obtain the following information, as available:

- investigational center number and principal investigator name
- name, phone number, and address of the source of the complaint
- clinical protocol number
- patient identifier (patient study number) and corresponding visit numbers, if applicable
- product name and strength for open-label studies
- patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies
- product available for return Yes/No
- product was taken or used according to protocol Yes/No
- description or nature of complaint
- associated serious adverse event Yes/No
- clinical supplies unblinded (for blinded studies) Yes/No
- date and name of person receiving the complaint

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

9.4.2. Handling of Study Drug at the Investigational Center

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug.

If it is determined that the investigational center must return all study drug, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

9.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.5.5.3).

9.4.4. Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

9.5. Case Report Forms

Case Report Forms (CRF) for individual subjects will be provided by Teva Branded Pharmaceutical Products R&D, Inc. Each CRF page will be a three-part no carbon required (NCR) form, with copies for the study site and Teva Branded Pharmaceutical Products R&D, Inc. CRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the CRFs must be legible and complete. All forms should be filled out using a black ball point pen. Errors should be lined out, but not obliterated, and the correction inserted, initialed, and dated by the person making the correction. A CRF must be completed and signed by the investigator or subinvestigator listed on the FDA Form 1572, for each subject enrolled, including those subjects terminated from the study for any reason. The reason for termination must be noted on the Termination Visit CRF.

CRFs must be kept current to reflect subject status at each phase during the course of the study. Subjects are not to be identified on CRFs by name; appropriate coded identification and subject

initials must be used. The study staff must keep a separate log of subject names and addresses. This log is not subject to FDA inspection.

Because of the potential for errors, inaccuracies, and illegibility in transcribing data onto CRFs, originals of laboratory and other test results must be kept on file with the subject's CRF or clinic chart. CRFs and copies of test results must be available at all times for inspection by the study monitors and FDA.

Data collected from visit month 159 through the completion of the study will be recorded on electronic CRFs (eCRF). Paper CRFs may continue to be used in conjunction with the eCRFs, but will not be collected upon completion.

9.6. Study Administration

9.6.1. Continuation of Study

Prior to the continuation of the study, the following items must be received from the investigator:

- Letter of IRB approval.
- A signed copy of the protocol.
- A copy of the ICF approved by the IRB.
- The investigator's current curriculum vitae as well as the curriculum vitae of any subinvestigator(s).

9.6.2. Monitoring the Study

Regular monitoring of the study data at each site will be performed in accordance with FDA regulations (see 21 CFR 312 e.t. seq). Individual sites will be monitored periodically at the discretion of the sponsor to ascertain that data recording and protocol adherence are satisfactory. Additional monitoring will be performed by telephone, mail, or site visit as needed.

9.6.3. Interpretation of the Protocol

The procedures defined in the protocol and in the Case Report Forms will be carefully reviewed at the time of the extension to ensure standardized interpretation and implementation. In order to ensure validity of the data, with minimal exceptions, no deviations from the protocol may be made unless the issue is broad enough to warrant revisions of the protocol for all sites. Such changes must be approved by the study sponsor and communicated in writing to the FDA by the sponsor.

Such revisions must be submitted to and have approval in writing from the appropriate Institutional Review Board (IRB) prior to implementation.

9.6.4. Maintenance of Study Documentation and Supplies

It is the responsibility of the investigator and the study staff to maintain a comprehensive and centralized filing system of all relevant study documentation. A Regulatory Binder will be provided by Teva Branded Pharmaceutical Products R&D, Inc. for maintaining such documentation in a central location. Such documentation includes:

- Case Report Forms: Must be kept legible, accurate, and up-to-date.
- Patient Files: These substantiate the data entered in the CRFs with regard to lab data, patient histories, treatment regimens, etc.
- Patient Exclusion Record: Should reflect the reason any patient was screened for this study and excluded.
- Drug Dispensing Log: Should reflect the total amount of pre-filled syringes received and returned to the sponsor, and the amount distributed and returned by each patient. This information must agree with the information entered in the CRFs.
- ICFs: Must be available for each patient and be verified for proper documentation.
- Comments Page: This section of the CRF is to be utilized to explain any aspect of the study that is not easily entered on the routine CRFs, and would include such items as:
  - Protocol deviation(s).
  - Comments or explanations of unusual findings.
  - Any data or clarification of data not explicitly requested on the CRFs.
  - Description of details and duration of relapse(s).

Federal regulations require that all items listed under Initiation of Study (Section 9.6.1), Maintenance of Study Documentation and Supplies (Section 9.6.4), protocol amendments and their IRB approvals, revised FDA Form 1572 forms, correspondence, and any other documents pertaining to the conduct of the study, must be kept on file by the investigator until notified by the sponsor.

9.7. Patient Confidentiality

All participants are concerned for the individual patient's privacy and, therefore, all patient data will be identified only by a patient identification number and patient initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to the sponsor, it is required that the investigator permit the study monitor and/or FDA representative to review that portion of the patient's medical record that is directly related to the study. This shall include all study-relevant documentation including patient medical histories to verify eligibility, laboratory test result reports to verify transcription

accuracy, admission/discharge summaries for hospital admissions occurring while the patient is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the patient must be informed that his/her medical chart may be reviewed by the sponsor, the sponsor's authorized representative, or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the patient in writing before the patient is entered into the study.

10. DEFINITIONS AND EXPLANATIONS

10.1. Study Sponsors

Teva Branded Pharmaceutical Products R&D, Inc.

41 Moores Road

Frazer, PA 19355

10.2. Project Director

The Project Director will be responsible for the clinical aspects of the trial. This individual will also interact frequently with the study sponsors and be consulted for clinical interpretations regarding the study.

10.3. Principal Investigator

The Principal Investigator will be responsible for the clinical aspects of the trial at his/her site. He/she will assist with patient recruitment to the trial and will assure compliance with the clinical trial protocol.

10.4. Project Manager

The Project Manager will be responsible for the organizational aspects and day-to-day activities of the trial.

10.5. Medical Monitor

The Medical Monitor will review Serious Adverse Events.

10.6. Study Coordinator

Each site will appoint a study coordinator who will assist the investigator and his/her associates. The study coordinator will be responsible for patient scheduling and for completing and maintaining the Case Report Forms and all other patient records, including the consent form, in an orderly and confidential manner. The study coordinator will record local and systemic side effects. The study coordinator will also be responsible for collecting and forwarding clinical samples and requests to appropriate laboratories and obtaining and forwarding laboratory results.

10.7. Project CRA / Study Monitor

The study monitor/CRA for this trial will be provided by Teva Branded Pharmaceutical Products R&D, Inc. The study conduct will be monitored in accordance with GCP/ICH guidelines, applicable SOPs, and as per protocol.

11. REFERENCES

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INVESTIGATOR'S AGREEMENT

I have carefully read and understand the provisions of this protocol and am prepared to follow it in the conduct of this study.

Furthermore, I understand that this is a multi-center trial and that any changes in the protocol must be approved in writing by the sponsor prior to implementation.

_____ _____

Investigator's Signature Date

APPENDIX A. SCHEDULE OF ACTIVITIES AND EVALUATIONS

	Study Visit				
Procedures Performed	Screening Visit for Amendment 13 (Month 264)[a]	Unscheduled Visits as necessary for Protocol	Nurse Coordinator Telephone Visits[b]	Investigator Visits (Month 276)	Termination Visit (scheduled Month 288)
Study Extension Informed Consent	X				
Visit Checklist	X	X	X	X	X
Evidence of Relapse	X	X[c]	X	X	X
Physical Examination	X	X[c]			X
Urinalysis	X	X[c]		X	X
Hematology	X	X[c]		X	X
Serum Chemistries	X[d]	X[c,d]		X	X
Serum/Pregnancy Test (where appropriate)		X[c]			X[e]
Adverse Experiences	X	X[c]	X	X	X
Concomitant Therapy	X	X[c]	X	X	X
Medication History		X[c]			
Record Treatment	X			X	
Drug Accountability	X	X[c]	X	X	X
Neurological Assessments	X	X[c]		X	X
Termination Reason					X[e]
Optional MRI	X	X[c]			

[a] This will be the same visit as the termination visit for Amendment 12, except for patients who completed the termination visit of Amendment 12 but were not able to immediately enter Amendment 13; for these patients, the Amendment 13 visit will be distinct from the Amendment 12 termination visit.

[b] Months 267, 270, 273, 279, 282, and 285

[c] Optional as deemed necessary for the visit

[d] Serum creatinine should be obtained prior to an MRI scan

[e] For early termination only.

APPENDIX B. DEFINITION OF RELAPSE

The following: "relapse," "exacerbation," "attack," and "bout" are equivalent terms. The term "relapse" will be used throughout this protocol. A relapse is defined as the appearance of one or more new neurologic abnormalities or the reappearance of one or more previously observed neurologic abnormalities. This change in clinical state must last at least 48 hours and be immediately preceded by a relatively stable or improving neurologic state in the 30 days before deterioration. An event is counted as a relapse only when the patient's symptoms are accompanied by observed objective changes on the neurologic examination consistent with an increase of at least 0.5 on the EDSS (Appendix C) or one grade in the score for two or more of the seven functional systems (FS) (Appendix D) of Kurtzke or two grades in the score for one of the FS as compared to the previous evaluation. The patient must not be undergoing an acute metabolic change such as fever or other medical abnormality, and a change in bowel/bladder or in cognitive function must not be entirely responsible for the changes in EDSS or FS scores.

APPENDIX C. KURTZKE EXPANDED DISABILITY STATUS SCALE (EDSS) IN MULTIPLE SCLEROSIS

Note: EDSS steps below 5 refer to patients who are fully ambulatory and the precise step is defined by the Functional System (FS) score(s). EDSS steps from 5 up are defined by ability to ambulate, and usual equivalents in FS scores are provided. A mental function grade of 1 does not enter into FS scores for EDSS steps. EDSS should not change by 1.0 step unless there is a change in same direction of at least one step in at least one FS

0 = Normal neurologic exam (all grade 0 in Functional Systems (FS); Cerebral grade 1 acceptable).

1.0 = No disability, minimal signs in one FS (i.e., grade 1 excluding Cerebral grade 1).

1.5 = No disability, minimal signs in more than one FS (more than one grade 1 excluding Cerebral grade 1).

2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 = Moderate disability in one FS (one FS grade 3, others 0 or 1), or mild disability in three of four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3; or five FS grade 4 (others 0 or 1).

4.0 = Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combinations of lesser grades exceeding limits of previous steps.

4.5 = Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability, usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps. Able to walk without aid or rest some 300 meters.

5.0 = Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., unable to work full day without special provisions). (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0.)

5.5 = Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding those of step 4.0.)

6.0 = Intermittent or unilateral constant assistance (cane, crutch, or brace) required to walk about 100 meters without resting. (Usual FS equivalents are combinations with more than two FS grade 3+.)

6.5 = Constant bilateral assistance (canes, crutches, or braces) required to walk about 20 meters without resting. (Usual FS equivalents are combinations with more than FS grade 3+.)

7.0 = Unable to walk beyond about 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely, pyramidal grade 5 alone.)

7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair. (Usual FS equivalents are combinations with more than one FS grade 4+.)

8.0 = Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)

8.5 = Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions. (Usual FS equivalents are combinations, generally 4+ in several systems.)

9.0 = Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)

9.5 = Totally helpless bed patient; unable to communicate effectively or eat/swallow. (Usual FS equivalents are combinations, almost all grade 4+.)

10.0 = Death due to MS.

APPENDIX D. FUNCTIONAL SYSTEM SCALE STUDIES (FS)

Pyramidal Functions:

0 = Normal

1 = Abnormal signs without disability

2 = Minimal Disability

3 = Mild or moderate paraparesis, hemiparesis or severe monoparesis

4 = Marked paraparesis or hemiparesis or moderate quadriparesis or monoplegia

5 = Paraplegia, hemiplegia, or marked quadriparesis

6 = Quadriplegia

Cerebellar Functions:

0 = Normal

1 = Abnormal signs without disability

2 = Mild ataxia

3 = Moderate limb or truncal ataxia

4 = Severe ataxis in all limbs

5 = Unable to perform coordinated movements

Brain Stem Functions:

0 = Normal

1 = Signs only

2 = Moderate nystagmus or other mild disability

3 = Severe nystagmus, marked extraocular weakness or moderate diability of other cranial nerves

4 = Marked disarthria or other marked disability

5 = Inability to swallow or speak

Mental Functions:

0 = Normal

1 = Mood alteration only

2 = Mild decrease in mentation

3 = Moderate decrease in mentation

4 = Marked decrease in mentation

5 = Dementia and/or chronic depressed alertness

Other Functions:

0 = Normal

1 = Any other findings (specify below):

_____

Sensory Functions:

0 = Normal

1 = Vibration or figure writing decrease in 1 or 2 limbs

2 = Mild decrease in touch or pain or position sense and/or moderate decrease in vibration in 1 or 2 limbs; or vibratory decrease alone in 3 or 4 limbs

3 = Moderate decrease in touch or pain or position sense and/or essentially lost vibration in 1 or 2 limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in 3 or 4 limbs

4 = Marked decrease in touch or pain or proprioception alone or combined in 1 or 2 limbs; or moderate decrease in touch or pain and/or severe proprioceptive loss in more than 2 limbs

5 = Loss of sensation in 1 or 2 limbs; or moderate decrease in touch or pain and/or loss of proprioception below the head

6 = Sensation lost below the head

Bowel & Bladder Functions:

0 = Normal

1 = Mild urinary hesitancy, urgency, or retention

2 = Moderate hesitancy, urgency, retention of bowel or bladder or rare urinary incontinence

3 = Frequent urinary incontinence

4 = In need of almost constant catheterization but with adequate bowel function

5 = Loss of bladder function

6 = Loss of bowel and bladder function

Visual Functions:

0 = Normal

1 = Acuity better than 20/30 in the worse eye

2 = Acuity between 20/30 and 20/59 in worse eye

3 = Acuity between 20/60 and 20/99 in worse eye

4 = Acuity between 10/100 and 20/200 in worse eye or Grade 3 plus better eye 20/60 or less

5 = Acuity 20/200 or less in worse eye or Grade 4 plus better eye 20/60 or less

6 = Grade 5 plus better eye 20/60 or less

APPENDIX E. AMBULATION INDEX (AI)

0 = Asymptomatic; fully active.

1 = Walks normally but reports fatigue that interferes with athletic or other demanding activities.

2 = Abnormal gait or episodic imbalance; gait disorder is noticeable to family and friends. Able to walk 25 feet in 10 seconds or less.

3 = Walks independently, able to walk 25 feet in 20 seconds or less.

4 = Requires unilateral support (cane, single crutch) to walk; uses support more than 80% of the time. Walks 25 feet in 20 seconds or less.

5 = Requires bilateral support (canes, crutches, walker) and walks 25 feet in 20 seconds or less; or, requires unilateral support but walks 25 feet in greater than 20 seconds.

6 = Requires bilateral support and walks 25 feet in greater than 20 seconds. May use wheelchair on occasion*

7 = Walking limited to several steps with bilateral support; unable to walk 25 feet. May use wheelchair for most activities.

8 = Restricted to wheelchair; able to transfer independently.

9 = Restricted to wheelchair; unable to transfer independently.

***The use of a wheelchair may be determined by a patient's lifestyle and motivation. It is expected that patients in grade 7 will use a wheelchair more frequently than patients in grades 5 or 6. Assignment of a grade in the 5-7 range, however, is determined by the ability of a patient to walk a given distance, and not by the extent to which a patient uses a wheelchair.**

APPENDIX F. ADVERSE CLINICAL EVENT & ADVERSE LABORATORY REPORTING

The treating neurologist should review available information regarding toxicity, adverse clinical events, and adverse laboratories associated with the administration of Copaxone®.

An adverse clinical event is any adverse change in clinical status which occurs after the patient has been enrolled in the study regardless of relationship to the study drug. An adverse laboratory is any clinically significant laboratory parameter regardless of relationship to the study drug. Clinically significant laboratory parameters are either clinically meaningful departures from the normal of the parameter, or clinically meaningful changes in the parameter that are not expected as part of a disease process that existed in the patient prior to entry in the study. Every adverse clinical event and adverse laboratory must be recorded on the appropriate Case Report Forms.

All adverse clinical events and adverse laboratories must be evaluated for the following:

Is it serious?

What is its severity?

Is it due to the study drug?

A serious adverse clinical or laboratory adverse event is one that is fatal or life-threatening, permanently disabling, requires or prolongs hospitalization, or results in congenital anomaly, cancer, or drug overdose. **ALL serious adverse clinical events or serious adverse laboratories, whether related to the study drug or not, must be reported IMMEDIATELY to the** Teva Clinical department **by fax at [redacted], and within 10 working days to the Institutional Review Board.**

Any patient experiencing a serious clinical or laboratory adverse event should be immediately notified to the study sponsor, and a detailed history, physical examination, and laboratory determination should be performed at that time. Reports relative to the patient's subsequent status must be submitted to the Project CRA until the adverse event has subsided or until advised otherwise.

The intensity or severity of an adverse clinical or laboratory event is characterized as mild, moderate, or severe.

MILD events are usually transient, require no special treatment, and do not interfere with the patient's daily activities.

MODERATE events usually introduce a low level of inconvenience or concern to the patient and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

SEVERE events interrupt a patient's usual daily activity and traditionally require systemic drug therapy or other treatment.

The relationship to study drug in causing or contributing to the adverse clinical or laboratory event is characterized by the answer to the question "Due to study drug?"

The relationship to the study treatment is characterized as follows (Note: If applicable, more than one serious criterion for an individual SAE may be chosen):

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • it does not follow a reasonable temporal sequence from the administration of the test drug. • it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it does not follow a known pattern of response to the test drug. • it does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • it follows a reasonable temporal sequence from administration of the drug. • it cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • it disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • it follows a known pattern of response to the test drug.

If the Treating Neurologist classifies the association of the adverse clinical or laboratory event as No Reasonable Possibility (Not Related), he or she must also provide the rationale for the classification as:

a. Concurrent illness,

b. Progression/expression of disease state, and/or

c. Concurrent medication reaction.

APPENDIX G. AUTOJECT INSTRUCTIONS FOR USE

INSTRUCTIONS FOR USE

autoject® 2

for glass syringe

SAFETY PRECAUTIONS

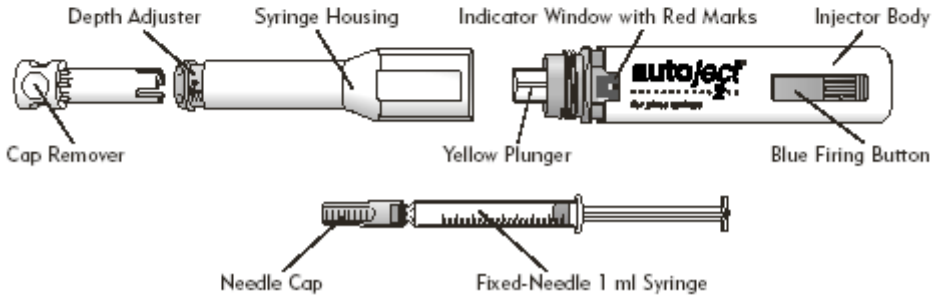
IMPORTANT: Do not operate the "autoject2 *for glass syringe*" without a syringe or with an empty syringe, as it may damage the syringe or the device. Point the "autoject2 *for glass syringe*" away from yourself and others while loading the syringe.

For single patient or individual use only. Rx only

For use with 1ml B-D Hypak Syringe with a 27G ½" fixed needle and Needle Cap.

The "autoject2 *for glass syringe*" is an automatic injection device for use with the 1ml B-D glass syringe for the subcutaneous injection of FDA approved drugs.

This insert contains the instructions for use of the "autoject2 *for glass syringe*". For instructions regarding the use of the drug, refer to the drug Patient Information Booklet provided with the drug product.



© OWEN MUMFORD

Manufactured by: Owen Mumford, Ltd., Brook Hill, Woodstock, Oxford, England.

autoject2 for glass syringe is a registered trademark of Owen Mumford, Ltd.
Rev 04/2003
AI/1391/11/0035/02

Step 1: Depth adjustment

Check with your physician to determine your correct needle depth adjustment, which must be made before the "auto*ject*2® *for glass syringe*" is loaded or used.

1. To set the depth of the needle penetration to 6mm (suggested for typical subcutaneous injection), first verify that the Cap Remover is fully attached to the Depth Adjuster (FIG 1). Screw the Depth Adjuster into the Syringe Housing, using the Cap Remover (FIG 2) until scale mark 6 is level with the end of the Syringe Housing (FIG 3). The lower the number shown on the Depth Adjuster, the shallower your penetration depth will be.

2. If your physician recommends a different injection depth, screw the Depth Adjuster further in for increased penetration depth, unscrew the Depth Adjuster further out for decreased penetration depth.

FIG 1

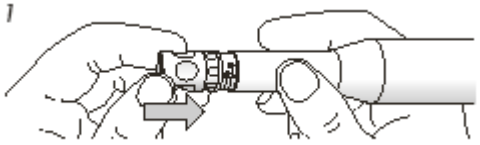


FIG 2

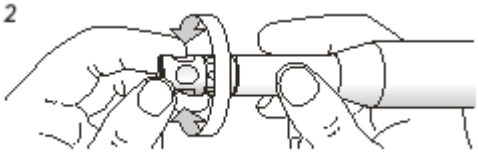
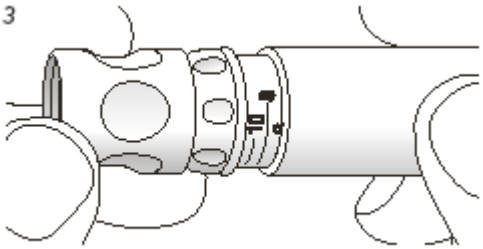


FIG 3



Step 2: Loading and using your "auto*ject*2® *for glass syringe*"

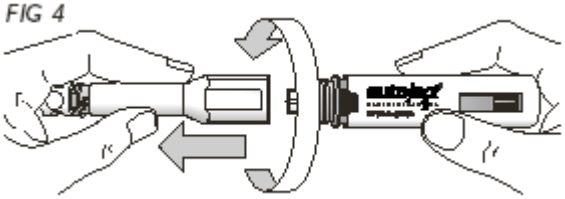
1. Prepare one dose of the drug:

Follow the instructions that come with the drug product.

2. Unscrewing the Syringe Housing:

Unscrew the Syringe Housing from the Injector Body (FIG 4).

FIG 4



3. Setting the automatic injection.

Hold the Injector Body with one hand, making sure you are **not** touching the blue Firing Button.

Hold the Syringe Housing with the Cap Remover attached with your other hand. Push the Syringe Housing squarely against the yellow part on the Injector Body as shown in FIG 5a.

Push it in completely until it locks into place (FIG 5b).

FIG 5a

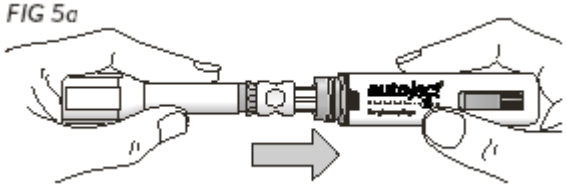
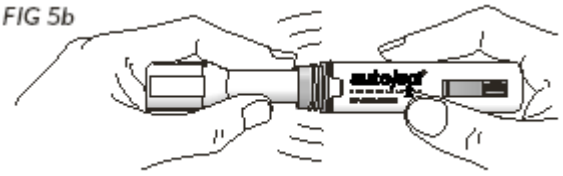


FIG 5b



4. Preparing the device for injection.

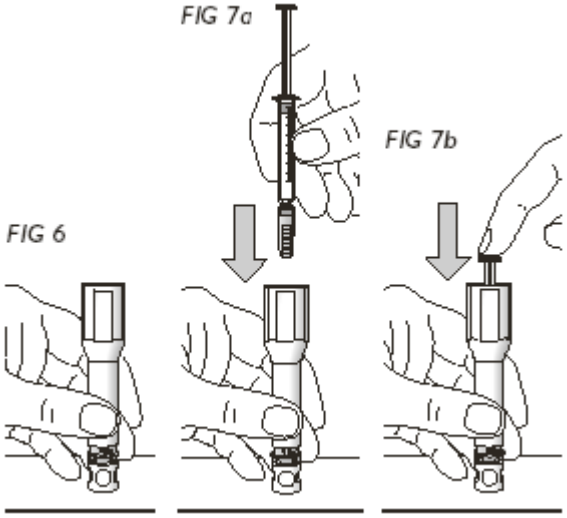
Make sure that the Cap Remover is inserted all the way into the Depth Adjuster. Place the Syringe Housing and Cap Remover onto a flat surface as shown in FIG 6.

Insert the syringe, needle end first into the Syringe Housing (FIG 7a) and push the syringe down firmly into the Syringe Housing until you feel the syringe click into place. (FIG 7b).

FIG 7a

FIG 7b

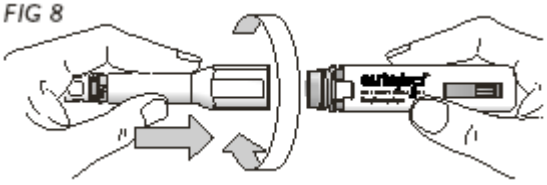
FIG 6



DO NOT USE IF SYRINGE IS CRACKED OR BROKEN.

Screw the Syringe Housing and the Injector Body together, taking care **not** to touch the blue firing button (FIG 8).

FIG 8



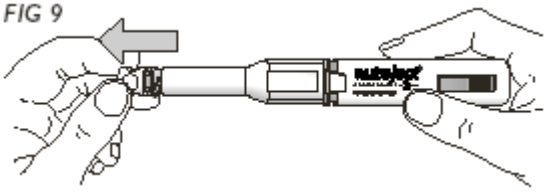
5. Selecting the injection site.

Select the injection site following advice from your health care professional.

When you are ready to perform the injection, hold the Injector Body with one hand.

Remove the Needle Cap by firmly pulling the Cap Remover directly away (without twisting it) from the Injector Body with the other hand (FIG 9).

FIG 9



Housing with the Needle Cap inside (FIG 10a).

The Cap Remover will come out of the Syringe Housing with the Needle Cap inside (FIG 10a).

Turn the Cap Remover upside down to release the Needle Cap (FIG 10b). The Needle Cap has two parts: a grey rubber inner part covered by a transparent plastic outer part. Make sure both parts of the Needle Cap are intact when the cap falls out of the Cap Remover. If both parts of the Needle Cap have not been removed, unscrew the Syringe Housing and Injector Body, remove the syringe and start over from instruction number 4 with a new syringe.

Dispose of the Needle Cap.

Save the Cap Remover for future use.

Check again that the Depth Adjuster is in the correct position.

Clean the injection site with a fresh alcohol prep and let it air dry for 60 seconds.

Making sure the Indicator Window is visible, place the "auto*ject*2® *for glass syringe*" perpendicular to the skin and apply slight pressure, so the Injector Body moves toward the Syringe Housing.

This releases the safety interlock so the Injection Button can be pressed (FIG 11).

FIG 10a

FIG 10b

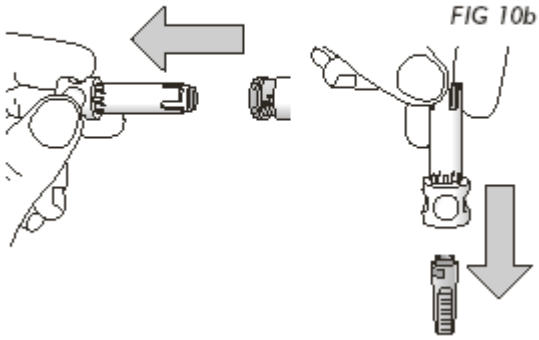
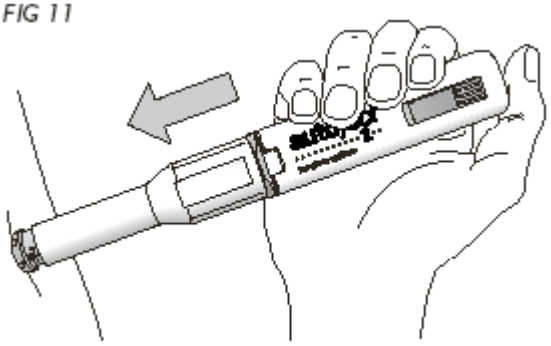
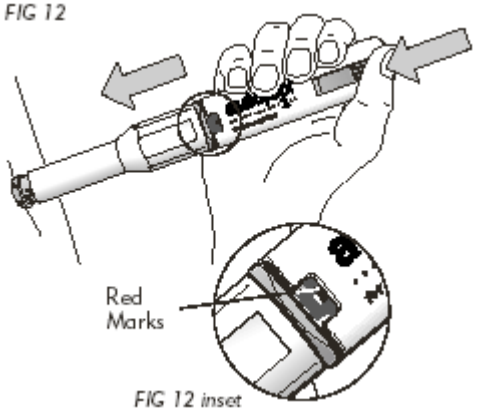


FIG 11



6. Injecting the drug. Press the blue Firing Button and watch the Indicator Window. Continue holding the device against the skin until the injection is complete (FIG 12). The syringe contents are injected automatically. Injection is complete when the Red Marks appear in the window and are stationary. (FIG 12 inset). This should take approximately 10 seconds. When your injection is complete, you may remove the device from the injection site. Always ensure that the full dose has been delivered from the syringe. **7. Removing and disposing of the syringe.** After use, unscrew the Syringe Housing from the Injector Body and separate the two, slowly. Hold the Syringe Housing above the open top area of a hard-walled container and invert the Syringe Housing, allowing the Syringe to fall out into the hard-walled container. **8. Cleaning your "auto*ject*2® *for glass syringe*".** After every use, the external components and the inside of the Syringe Housing of the "auto*ject*2® *for glass syringe*" should be cleaned by wiping with a clean damp cloth or an alcohol wipe. Do not immerse in water.	FIG 12  FIG 12 inset
9. Storing the "auto*ject*2® *for glass syringe*" safely. Reconnect the Syringe Housing and Injector Body. Re-insert the Cap Remover into the Depth Adjuster. Store your "auto*ject*2® *for glass syringe*" safely in the nylon wallet provided. In the unlikely event of "auto*ject*2® *for glass syringe*" failure, please return it to your supplier.	

APPENDIX H. STUDY DRUG LABELING

STUDY DRUG LABELING – GA 20 mg/1 mL

Study Protocol 9004 - Teva Neuroscience, North Wales, PA 19454

Essential to **PRESS HARD** to record on copies

Site No._____ Lot No._____ Expiration Date_____

Subject No._____ Subject Initials_____

Date Dispensed _____/____/_____ Visit Month_____

dd mmm yyyy

Contents: Copaxone® 20 mg

30 single-use Prefilled Syringes. Subcutaneous Use Only.

KEEP REFRIGERATED between 2-8°C (36-46°F).

Return unused syringes.

Limited by Federal (U.S.) Law to Investigational Use Only. To be used by Qualified Investigator Only.

IND 27,998

Study Protocol 9004 - Teva Neuroscience, North Wales, PA 19454

Essential to **PRESS HARD** to record on copies

Site No._____Lot No._____Expiration Date_____

Subject No._____ Subject Initials_____

Date Dispensed _____/____/_____Visit Month_____

dd mmm yyyy

Contents: Copaxone® 20 mg

5 single-use Prefilled Syringes. Subcutaneous Use Only.

KEEP REFRIGERATED between 2-8°C (36-46°F).

Return unused syringes.

Limited by Federal (U.S.) Law to Investigational Use Only. To be used by Qualified Investigator Only.

IND 27,998

STUDY DRUG LABELING – GA 40 mg/1 mL

Study Protocol 9004 - Teva Neuroscience, North Wales, PA 19454

Essential to **PRESS HARD** to record on copies

Site No._____ Lot No._____ Expiration Date_____

Subject No._____ Subject Initials_____

Date Dispensed _____/____/_____ Visit Month_____

dd mmm yyyy

Contents: Copaxone® 40 mg

6 single-use Prefilled Syringes. Subcutaneous Use Only.

KEEP REFRIGERATED between 2-8°C (36-46°F).

Return unused syringes.

Limited by Federal (U.S.) Law to Investigational Use Only. To be used by Qualified Investigator Only.

IND 27,998

TEVA BRANDED PHARMACEUTICAL PRODUCTS R&D, INC.

PROTOCOL NUMBER: 01-9004

Open Label Study to Evaluate the Safety of Copaxone® and to Monitor the Neurologic Course of Disease in Multiple Sclerosis Patients Treated with Copaxone®

PROTOCOL AMENDMENT

Original Protocol: May 25, 1994
Amendment No. 1: March 2, 1998
Amendment No. 2: March 23, 1998
Amendment No. 3: October 19, 1999
Amendment No. 4: August 31, 2000
Amendment No. 5: September 14, 2001
Amendment No. 6: November 14, 2001
Amendment No. 7: April 10, 2002
Amendment No. 8: February 20, 2004
Amendment No. 9: January 15, 2007
Amendment No. 10: January 11, 2012
Amendment No. 11: July 31, 2012
Amendment No. 12: July 18, 2014
Amendment No. 13: 13 May 2016

This clinical study will be conducted in accordance with the Declaration of Helsinki and its updates, current Good Clinical Practice (GCP), the provisions of ICH (International Conference on Harmonisation); US Code of Federal Regulations (Title 21, CFR Part 11, 50, 54, 56 and 312); local country regulations and the sponsor's Standard Operating Procedures (SOPs)

CONFIDENTIAL

PROTOCOL AMENDMENT REVIEW AND APPROVAL

[redacted]	[redacted]	13 May 2016 Date

TABLE OF CONTENTS

1. RATIONALE

The purpose of this amendment is to add an additional 2 years to the study duration, to allow collection of additional long term safety data for Copaxone, and to help understand the safety and efficacy of 40 mg Copaxone three times weekly (TIW) compared to 20 mg daily injection in patients that have switched, from a cross sectional and longitudinal perspective.

The termination visit for Amendment 12 will serve as the screening visit for Amendment 13 (month 264).

A scheduled treatment visit will occur 12 months after the screening/initiation visit for Amendment 13 (month 276). The tests/procedures/neurological visits will be the same as per Amendment 12, with the exception of the magnetic resonance imaging (MRI) and immunological procedures.

Nurse Coordinator telephone visits will occur as per Amendment 12 between the screening visit, scheduled treatment visits, and the termination visit.

The termination visit will be 24 months following the screening visit for Amendment 13 (month 288). The tests/procedures/neurological examinations will be the same as Amendment 12 at this visit, with the exception of the MRI and immunological procedures.

This amendment also details the list of tests for the immunological analyses (as previously described in an administrative letter), although no additional immunological testing will be performed under Amendment 13.

New sections on overdose of study drug and clinical product complaints have been added, in accordance with the most current Teva protocol requirements.

2. FORMAT OF CHANGES

The corrections in **bold** and ~~strikethrough~~ refer to the section in the 9004 Protocol following Global Amendment No. 12 dated July 18, 2014. The changes have also been implemented in the schedule of activities and evaluations (Appendix A).

2.1. Section 2.1. Background

*Change to read (changes in **bold** and ~~strikethrough~~):*

As of 30 November 2015, an estimated total of 8733 subjects have been exposed to glatiramer acetate, administered subcutaneously as part of the clinical development program, reflecting total of about 19,951 patient-years. The majority are relapsing remitting multiple sclerosis (RRMS) patients using the marketed formulation of Copaxone® 20 mg/mL on a daily basis.

An open-label, randomized, multi-center, parallel-arm study (MS-GA-303; GLACIER) was conducted to assess the safety and tolerability of Copaxone 40 mg/mL three times weekly (TIW; compared to 20 mg/mL daily subcutaneous injections in subjects with RRMS. A statistically significant (p<0.0006) reduction in the primary endpoint, injection related adverse event rate, in the Copaxone 40 mg/mL TIW group compared to the Copaxone 20 mg/mL daily group was revealed. Treatment with Copaxone at dosages of 20 mg/mL daily and Copaxone 40 mg/mL TIW was generally safe and well tolerated in patients with RRMS who had been treated continuously with Copaxone 20 mg/mL daily for a minimum of 6 months prior to screening, followed by 4 months of randomized treatment with Copaxone 20 mg/mL daily or Copaxone 40 mg/mL TIW (Core Phase), then followed by 4 months of treatment where patients were offered to continue on with the Copaxone 40 mg/mL TIW regimen (Extension Phase).

2.2. Section 2.2. Rationale

*Change to read (changes in **bold** and ~~strikethrough~~):*

Because of the potential loss of efficacy over time with interferon therapy, and the need to collect additional long-term safety data for Copaxone®, continuing evaluation of Copaxone® was introduced in Amendment 11. In addition, an imaging sub-study was initiated in a previous Amendment (Amendment 10) ~~that will be continued and~~ **to** provide additional prospective nonconventional **magnetic resonance imaging (**MRI**)** data for Copaxone®.

A further amendment (Amendment 12) ~~has been~~ **was** added to the protocol to offer patients the Copaxone 40 mg ~~three times weekly (~~TIW~~)~~ formulation while collecting safety and tolerability data that will be compared clinically, immunologically, and by MRI to the 20 mg daily dose of Copaxone. Since injection frequency affects long-term adherence to treatment, the sponsor is now seeking to gain more information about the injection experience of those patients who have been taking Copaxone 20 mg daily and are switched to Copaxone 40 mg/mL TIW. Overall, the study will continue to provide information regarding the safety of Copaxone administration for both the 20 mg daily injection as well as the 40 mg TIW injection in a large cohort of patients who have been on daily injections of Copaxone for an extended period of time.

This amendment (Amendment 13) will extend the study duration for an additional 2 years (until month 288). The longer duration of the study will help to better understand the long term safety of Copaxone, as the study includes a unique cohort of patients that have been followed continuously. Additionally, the longer duration will help to gain insight into the disease processes and activity in patients with 30+ years of disease. Finally, the extension will help understand the safety and efficacy of Copaxone 40 mg/mL TIW in comparison to Copaxone 20 mg daily in patients that have switched from a cross sectional and longitudinal perspective.

2.3. Section 3. OBJECTIVES

*Change to read (changes in **bold** and ~~strikethrough~~):*

It will also provide information regarding the safety of Copaxone® administered for up to ~~24~~ **26** years, or until the sponsor terminates the study, on approximately ~~70~~ **60** patients who participated in the original double-blind study.

2.4. Section 4. STUDY DESIGN AND DURATION

*Change to read (changes in **bold** and ~~strikethrough~~):*

Patients will be offered the opportunity to continue in this trial for an additional 2 years, extending to ~~2017~~ **2019** or until the sponsor terminates the study.

...

~~Current, active~~ **Under Amendment 12**, patients ~~will also have~~ **had** the opportunity to continue participation in the optional MRI substudy, where an MRI examination ~~will be~~ **was** completed at the next scheduled treatment visit for Amendment 12 (following the 22 year scan) at month 252, the scheduled termination visit (month 264) or during an unscheduled visit after 24 years of continuous Copaxone® therapy.

2.5. Section 6.1. Inclusion Criteria

*Change to read (changes in **bold** and ~~strikethrough~~):*

Additionally:

- Patients must have completed the scheduled termination visit for Amendment ~~11~~ **12** (month ~~240~~ **264**).
- Patients must sign an approved informed consent form (ICF) prior to continuing in the study extension or at the first visit in the extension (month ~~240~~ **264** which corresponds to the termination visit of Amendment ~~11~~ **12**).
- ~~For participation in the optional MRI sub-study, patients must sign an approved ICF prior to any MRI procedures taking place.~~
- ~~For participation in the optional immunological sub-study, patients must sign an approved ICF prior to any blood being taken.~~

2.6. Section 7.1. Schedule of Activities and Evaluations

*Change to read (changes in **bold** and ~~strikethrough~~):*

Screening visits through month ~~240~~ **264** must have been completed to continue in the study extension. For the purposes of this amendment, the termination visit of Amendment ~~11~~ **12** (month ~~240~~ **264**), will act as the screening visit for this amendment. Patients who have completed the termination visit and discontinued from the study under the Amendment ~~11~~ **12** protocol may still continue in the extension study under Amendment ~~12~~ **13**; for these patients,

the screening visit for Amendment ~~12~~ **13** will be a separate visit to the termination visit of Amendment ~~11~~ **12**.

The study extension will involve 1 investigator visit (Section 7.1.3.2) annually supplemented by 3 nurse coordinator telephone visits (Section 7.1.3.1). This schedule will maintain contact with the patients on a quarterly basis, approximately every 90 days. The study extension period will end with the termination visit (Section 7.1.3.3 and Section 7.1.5) following ~~24~~ **26** years of continuous Copaxone® therapy.

In addition to MRIs performed at month 240, the optional MRI sub-study will involve 2 MRIs for active study patients at the annual investigator visit (month 252) or at an unscheduled visit around the time of the investigator visits and at the final investigator visit **for Amendment 12/screening visit for Amendment 13** (month 264).

The optional immunological sub-study will involve 2 blood samples, 1 taken during the screening visit for Amendment 12, and 1 at the next treatment visit at month 252. **There will be no additional immunological assessments under Amendment 13**.

2.7. Section 7.1.1. Screening Visit for Amendment ~~12~~ 13 (Month ~~240~~ 264)

*Change to read (changes in **bold** and ~~strikethrough~~):*

During screening for Amendment ~~12~~ **13**, the patient must be thoroughly informed about all aspects of the study extension, including the study visits and activities schedule

...

A checklist of the procedures to be performed during the screening visit follows.

- Eligibility checklist
- Signed informed consent for Amendment ~~12~~ **13**

...

- ~~MRI (for patients who have consented to participate in the MRI sub-study)~~
- ~~Blood collection (for patients who have consented to participate in the immunological analysis under Amendment 12 protocol)~~

The visit procedures listed above may be completed as an unscheduled visit if the month ~~240~~ **264** visit has already been completed. ~~The MRI scan performed for the month 240 visit will suffice for the screening visit of amendment 12.~~

2.8. Section 7.1.3.1. Nurse Coordinator Telephone Visits

*Change to read (changes in **bold** and ~~strikethrough~~):*

Months ~~243, 246, 249, 255, 258, 261~~ **267, 270, 273, 279, 282, and 285**

2.9. Section 7.1.3.2. Investigator Visits

*Change to read (changes in **bold** and ~~strikethrough~~):*

Month ~~252~~ **276**

...

- ~~MRI (for patients who have consented to participate in the MRI sub-study.)~~
- ~~Blood collection (for patients who have consented to participate in the immunological analysis under Amendment 12 protocol)~~

2.10. Section 7.1.3.3. Termination Visit (Month ~~264~~ 288)

*Change to read (changes in **bold** and ~~strikethrough~~):*

- ~~MRI (for patients who have consented to participate in the MRI sub-study)~~

2.11. Section 7.1.4. Unscheduled Visits

*Change to read (changes in **bold** and ~~strikethrough~~):*

MRI procedures for patients who consent to participate in the MRI sub-study may be completed at an unscheduled visit rather than the month ~~252 and~~ 264 termination visit.

2.12. Section 7.1.5. Early Termination Visit

*Change to read (changes in **bold** and ~~strikethrough~~):*

- ~~MRI (for patients who have consented to participate in the MRI sub-study)~~

2.13. Section 7.4. ~~Evaluation~~ Assessment of Safety

*Change to read (changes in **bold** and ~~strikethrough~~):*

Section 7.4. ~~Evaluation~~ **Assessment** of Safety

2.14. Section 7.4. Assessment of Safety

*Subsections removed. Change to read (changes in **bold** and ~~strikethrough~~):*

~~7.4.1. Serious Adverse Event Reporting~~

~~7.4.1.1. Definition~~

~~According to FDA guidelines, a Serious Adverse Event (SAE) is defined as any undesirable event experienced by a patient that suggests a significant hazard, contraindication, side effect, or precaution whether or not considered drug-related by the investigator. A serious adverse event is defined as an event that is:~~

- ~~Fatal or life threatening (in the opinion of the investigator, the patient was at immediate risk of death from the adverse event);~~
- ~~Permanent, persistent or significant disability/incapacity;~~
- ~~Requires or prolongs in-patient hospitalization (except for hospitalization due to MS exacerbation);~~
- ~~A congenital anomaly or birth defect;~~
- ~~Important medical events requiring medical or surgical intervention to prevent an outcome listed above;~~

~~An unexpected adverse reaction is defined as any undesirable event experienced by the patient that was not documented in the package insert.~~

~~7.4.1.2. Reporting~~

~~Any serious adverse event occurring during this study must be reported immediately (within 24 hours) to the Teva Clinical Department at Teva Pharmaceuticals, Inc., by fax using the Serious Adverse Event Report form. The SAE reporting requirements are outlined in Section 9.5. Any serious adverse event occurring after completion of the study must be reported if the investigator becomes aware of it.~~

~~7.4.1.3. Patient Follow-Up~~

~~Patients who have a SAE should be followed clinically until all parameters (including laboratory) have either returned to normal or are otherwise explained.~~

~~7.4.1.4. Minor Adverse Event~~

~~Any adverse event that does not meet the definition of a SAE is considered by the FDA to be a minor adverse event. These events should be recorded by the investigator and/or nurse coordinator on the "Adverse Experience" page in the Case Report Form. All events should be entered whether or not the event is considered study drug related.~~

2.15. Section 7.5. Adverse Events

(New section, including subsections as presented below)

7.5.1. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

In this study, any adverse event occurring after the clinical study patient has signed the informed consent form should be recorded and reported as an adverse event.

An adverse event can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study, or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- **intercurrent illnesses**
- **physical injuries**
- **events possibly related to concomitant medication**
- **significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions**
- **drug interactions**
- **events occurring during diagnostic procedures or during any washout phase of this study**
- **laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, require medical treatment or further diagnostic work-up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events.)**

Hospitalization due to MS exacerbation should be recorded as an adverse event only if the presentation or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

7.5.2. Recording and Reporting of Adverse Events

For recording of adverse events, the study period is defined for each patient as that time period from signature on the informed consent form until the last study visit.

All adverse events that occur during the defined study period must be recorded on the source documentation and transcribed to the CRF, regardless of the severity of the event or judged relationship to the study drug. For serious adverse events, the serious adverse event form must be completed and the serious adverse event must be reported immediately (see Section 7.5.5.3). The investigator does not need to actively monitor patients for adverse events once the study has ended. Serious adverse events occurring in a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them, following the procedures described in see Section 7.5.5.3.

At each contact with the patient, the investigator or designee must question the patient about adverse events by asking an open ended question such as "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe". All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, on the serious adverse event form.

The clinical course of each adverse event will be monitored at suitable intervals until resolved, stabilized, or returned to baseline; or until the patient is referred for continued care to a health care professional; or until a determination of a cause unrelated to the study drug or study procedure is made.

The onset and end dates, duration (in case of adverse event duration of less than 24 hours), action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation and transcribed to the CRF.

The relationship of each adverse event to study drug and study procedures, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

7.5.3. Severity of an Adverse Event

The severity of each adverse event must be recorded as 1 of the choices on the following scale:

Mild: No limitation of usual activities

Moderate: Some limitation of usual activities

Severe: Inability to carry out usual activities

.5.4. Relationship of an Adverse Event to the Study Drug

The relationship of an adverse event to the study drug is characterized as follows:

Term	Definition	Clarification
No reasonable possibility (not related)	**This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.**	**The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply:** • **It does not follow a reasonable temporal sequence from the administration of the study drug.** • **It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.** • **It does not follow a known pattern of response to the study drug.** • **It does not reappear or worsen when the study drug is re-administered.**
Reasonable possibility (related)	**This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty.**	**The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply:** • **It follows a reasonable temporal sequence from administration of the study drug.** • **It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.** • **It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the study drug, yet a drug relationship clearly exists.** • **It follows a known pattern of response to the study drug.**

7.5.5. Serious Adverse Events

7.5.5.1. Definition of a Serious Adverse Event

A serious adverse event is an adverse event occurring at any dose that results in any of the following outcomes or actions:

- **death**
- **a life threatening adverse event (ie, the patient was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death**

- **inpatient hospitalization or prolongation of existing hospitalization, which means that hospital inpatient admission or prolongation of hospital stay were required for treatment of an adverse event, or that they occurred as a consequence of the event**

  Hospitalizations scheduled before the patient signed the informed consent form will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study.

- **Hospitalization for intravenous steroid treatment of a relapse will not be considered a serious adverse event unless it is a worsening of the condition beyond expected disease progression.**

- **persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)**

- **a congenital anomaly/birth defect**

- **an important medical event that may not result in death, be life threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition**

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

All occurrences of possible drug induced liver injury that meet Hy's law criteria, defined as all of the below, must be reported by the investigator to the sponsor as a serious adverse event:

- **alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation of >3x the upper limit of normal (ULN)**

- **total bilirubin elevation of >2x ULN**

- **absence of initial findings of cholestasis (ie, no substantial increase of alkaline phosphatase [ALP])**

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a nonserious adverse event.

7.5.5.2. Expectedness

A serious adverse event that is not included in the Adverse Reaction section of the relevant reference safety information (RSI) by its specificity, severity, outcome, or frequency is

considered an unexpected adverse event. The RSI for this study is the US prescribing information.

The sponsor's Global Patient Safety and Pharmacovigilance will determine the expectedness for all serious adverse events.

7.5.5.3. Reporting a Serious Adverse Event

7.5.5.3.1. Investigator Responsibility

To satisfy regulatory requirements, all serious adverse events (as described in Section 7.5.5.1) that occur during the study period (including the protocol defined follow up period, described in Section 7.5.2), regardless of judged relationship to treatment with the study drug, must be reported to the sponsor by the investigator. The event must be reported within 24 hours of when the investigator learns about it. Completing the serious adverse event form and reporting the event must not be delayed, even if not all the information is available. Any serious adverse event must be reported to the Teva Branded Pharmaceutical Products R&D, Inc., Local Safety Officer . Send by email using the Serious Adverse Event Form to the local safety officer (LSO). The email address will be provided in the serious adverse event report form. In the event of difficulty transmitting the form, contact the sponsor's study personnel for further instruction

The investigator does not need to actively monitor patients for adverse events once this study has ended. Serious adverse events occurring to a patient after the treatment of that patient has ended should be reported to the sponsor if the investigator becomes aware of them.

The serious adverse event form should be sent to the LSO . The LSO will forward the report to the sponsor's Global Patient Safety and Pharmacovigilance.

The following information should be provided to record the event accurately and completely:

- **study number**
- **investigator and investigational center identification**
- **patient number**
- **onset date and detailed description of adverse event**
- **investigator's assessment of the relationship of the adverse event to the study drug (no reasonable possibility, reasonable possibility)**

Additional information may include the following:

- **age and sex of patient**

- **date of first dose of study drug**
- **date and amount of last administered dose of study drug**
- **action taken**
- **outcome, if known**
- **severity**
- **explanation of assessment of relatedness**
- **concomitant medication (including doses, routes of administration, and regimens) and treatment of the event**
- **pertinent laboratory or other diagnostic test data**
- **medical history**
- **results of dechallenge/rechallenge, if known**
- **for an adverse event resulting in death:**
  - **cause of death (whether or not the death was related to study drug)**
  - **autopsy findings (if available)**

The investigator must ensure that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Additional information (follow up) about any serious adverse event unavailable at the initial reporting should be forwarded by the investigator within 24 hours of when it becomes known to the same address as the initial report.

For all countries, the sponsor's Global Patient Safety and Pharmacovigilance will distribute the Council for International Organizations of Medical Sciences (CIOMS) form/Extensible Markup Language (XML) file to the LSO/CRO for submission to the competent authorities, IEC/IRBs, and investigators, according to regulations. The investigator is responsible for ensuring that the IEC/IRB is also informed of the event, in accordance with national and local regulations.

Note: Although pregnancy is not a serious adverse event, the process for reporting a pregnancy is the same as that for reporting a serious adverse event, but using the pregnancy form (see Section 7.6).

7.5.5.3.2. Sponsor Responsibility

If a serious unexpected adverse event is believed to be related to the study drug or study procedures, the sponsor will take appropriate steps to notify all investigators participating in sponsored clinical studies of Copaxone and the appropriate competent authorities (and IEC/IRB, as appropriate).

In addition to notifying the investigators and competent authorities (and IEC/IRB, as appropriate), other measures may be required, including:

- **altering existing research by modifying the protocol**
- **discontinuing or suspending the study**
- **altering the process of informed consent by modifying the existing consent form and informing all study participants of new findings**
- **modifying listings of expected toxicities to include adverse events newly identified as related to Copaxone**

Section 7.5.6. Protocol Defined Adverse Events for Expedited Reporting

No protocol defined adverse events for expedited reporting were identified for this study.

2.16. Section 7.5.7. Overdose of Study Drug

(New section)

Any dose of study drug (whether the investigational product, reference treatment, or placebo), whether taken intentionally or unintentionally, in excess of that prescribed must be immediately reported to the sponsor.

2.17. Section 7.5.8. Protocol Deviations Because of an Adverse Event

(New section)

If a patient experiences an adverse event or medical emergency, deviations from the protocol may be allowed on a case-by-case basis. To ensure patient safety, after the event has stabilized or treatment has been administered (or both), the investigator or other physician in attendance must contact the physician identified in the Clinical Study Personnel Contact Information section of this protocol as soon as possible to discuss the situation. The investigator, in consultation with the sponsor, will decide whether the patient should continue to participate in the study.

2.18. Section 7.6. Pregnancy

*Change to read (changes in **bold** and ~~strikethrough~~):*

Section ~~7.5~~.**7.6.** Pregnancy

~~All pregnancies (pregnancies of women participating in the study and partners of men participating in the study) that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the investigator must provide the Teva Clinical Department with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event (see Section 7.4.1).~~

~~Any patient becoming pregnant during the study will be withdrawn. All patients (or partners) who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy will be reported as an adverse event or serious adverse event, as appropriate.~~

~~If the pregnancy does not continue to term, 1 of the following actions will be taken:~~

- ~~For a spontaneous abortion, report as a serious adverse event.~~
- ~~For an elective abortion due to developmental anomalies, report as a serious adverse event.~~
- ~~For an elective abortion **not** due to developmental anomalies, report only on the pregnancy form.~~

All pregnancies of women participating in the study and female partners of men participating in the study, if applicable that occur during the study, or within 14 days of completion of the study, are to be reported immediately to the physician identified in the Clinical Study Personnel Contact Information section of this protocol, and the investigator must provide the LSO with the pregnancy form. The process for reporting a pregnancy is the same as that for reporting a serious adverse event but using the pregnancy form (see Section 7.5.5.3).

Any female patient becoming pregnant during the study will discontinue treatment. All patients (or female partners of men participating in the study) who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the investigator becomes aware of after withdrawal from the study will be reported as an adverse event or serious adverse event, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- **For a spontaneous abortion, report as a serious adverse event.**

- **For an elective abortion due to developmental anomalies, report as a serious adverse event.**

- **For an elective abortion not due to developmental anomalies, report on the pregnancy form; do not report as an adverse event.**

2.19. Section 7.7. Medication Error and Special Situations

(New section)

Any administration of medication that is not in accordance with the study protocol should be reported on the CRF either as a violation, if it meets the violation criteria specified in the protocol or as a deviation, in the patients source documents, regardless of whether an adverse event occurs as a result. All instances of incorrect medication administration should be categorized on the CRF as "Non-Compliance to investigational medicinal product (IMP)".

Types of medication errors and special situations:

1. **Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.**

2. **Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.**

3. **Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.**

4. **Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.**

5. **Off-label use: Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.**

6. **Occupational exposure: Exposure to a medicinal product, as a result of one's professional or non-professional occupation.**

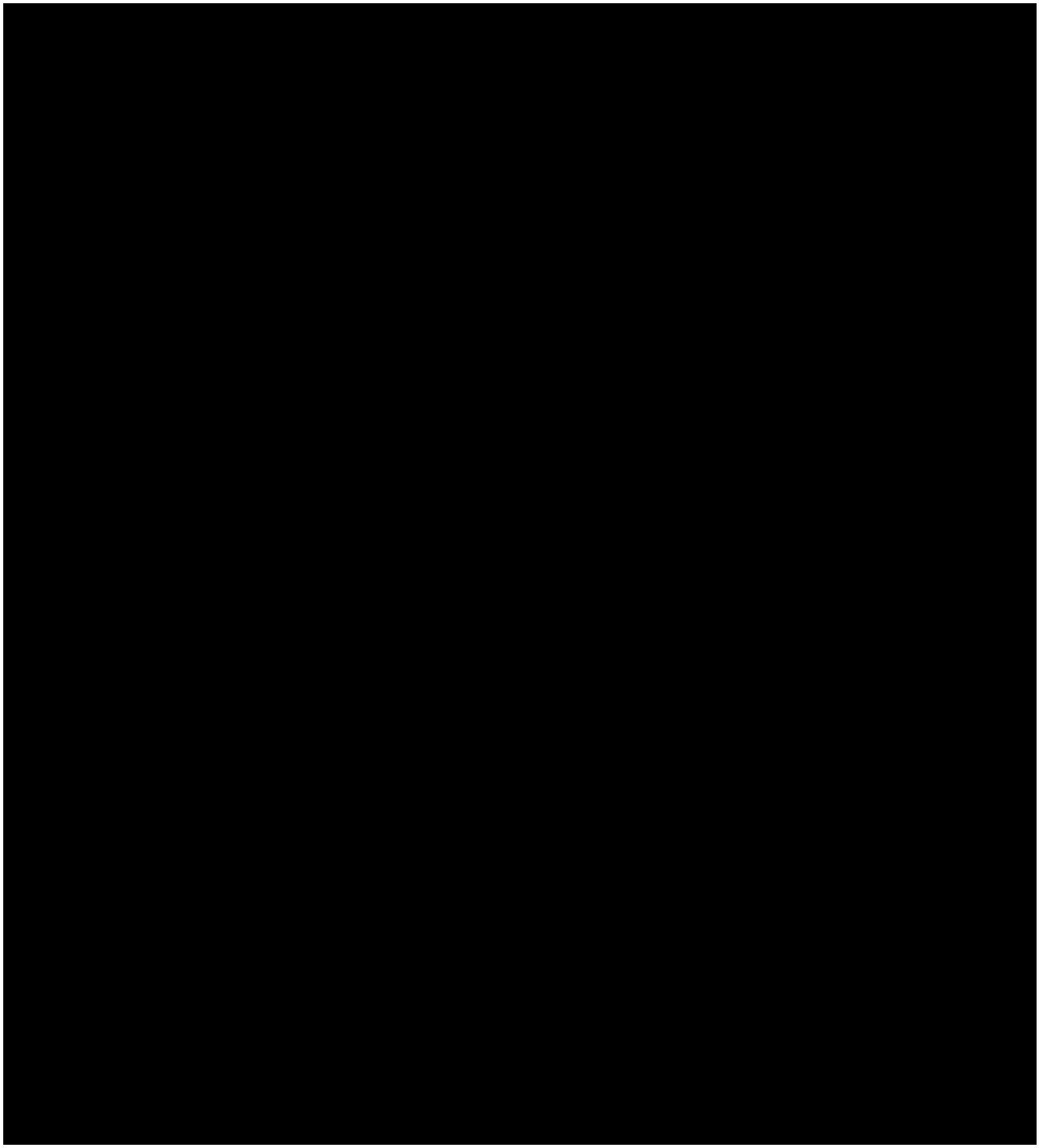
2.20. Section 7.9. Immunological Analyses

*Change to read (changes in **bold** and ~~strikethrough~~):*

Section ~~7.7.~~ **7.9** Immunological Analyses

For patients who consent to the optional immunological analysis, blood samples will be collected at the Amendment 12 screening visit (month 240) and the investigator visit (month 252). **There**

will be no additional immunological assessments under Amendment 13. Samples will be analyzed as follows:



2.21. Section 8.1. Adverse Events

*Change to read (changes in **bold** and ~~strikethrough~~):*

The total number and percent of patients reporting adverse events, across and by ~~COSTART~~ body system and event term, will be tabulated for all patients treated. The number of patients treated will serve as the denominator for incidence rate computation. Adverse events will also be summarized by maximum reported severity and relationship to treatment. Detailed data displays, narrative summaries, and copies of Case Report Forms will be provided for those patients who withdrew prematurely due to an adverse event or who dies.

2.22. Section 9.4. Clinical Product Complaints

(New section)

9.4. Clinical Product Complaints

A clinical product complaint is defined as a problem or potential problem with the physical quality or characteristics of clinical drug supplies or clinical device supplies used in a clinical research study sponsored by Teva. Examples of a product complaint include but are not limited to:

- **suspected contamination**
- **questionable stability (eg, color change, flaking, crumbling, etc)**
- **defective components**
- **missing or extra units (eg, primary container is received at the investigational center with more or less than the designated number of units inside)**
- **incorrect packaging, or incorrect or missing labeling/labels**
- **unexpected or unanticipated taste or odor, or both**
- **device not working correctly or appears defective in some manner**

Each investigational center will be responsible for reporting a possible clinical product complaint by completing the product complaint form provided by Teva and emailing it to [redacted] within 48 hours of becoming aware of the issue.

For complaints involving a device or other retrievable item, it is required that the device (or item) be sent back to the sponsor for investigative testing whenever possible. For complaints involving a drug product, all relevant samples (eg, the remainder of the patient's drug supply) should be sent back to the sponsor for investigative testing whenever possible.

9.4.1. Product Complaint Information Needed from the Investigational Center

In the event that the product complaint form cannot be completed, the investigator will obtain the following information, as available:

- **investigational center number and principal investigator name**
- **name, phone number, and address of the source of the complaint**
- **clinical protocol number**
- **patient identifier (patient study number) and corresponding visit numbers, if applicable**
- **product name and strength for open-label studies**
- **patient number, bottle, and kit numbers (if applicable) for double-blind or open-label studies**
- **product available for return Yes/No**
- **product was taken or used according to protocol Yes/No**
- **description or nature of complaint**
- **associated serious adverse event Yes/No**
- **clinical supplies unblinded (for blinded studies) Yes/No**
- **date and name of person receiving the complaint**

Note: Reporting a product complaint must not be delayed even if not all the required information can be obtained immediately. Known information must be reported immediately. The sponsor will collaborate with the investigator to obtain any outstanding information.

9.4.2. Handling of Study Drug at the Investigational Center

The investigator is responsible for retaining the product in question in a location separate from the investigator's clinical study supplies. The sponsor may request that the investigator return the product for further evaluation and/or analysis. If this is necessary, the clinical study monitor or designee will provide the information needed for returning the study drug.

If it is determined that the investigational center must return all study drug, the sponsor will provide the information needed to handle the return.

The integrity of the randomization code and corresponding blinded clinical supplies will be maintained whenever possible. A serious adverse event or the potential for a product

quality problem existing beyond the scope of the complaint may be a reason to unblind the clinical supplies for an affected patient.

9.4.3. Adverse Events or Serious Adverse Events Associated with a Product Complaint

If there is an adverse event or serious adverse event due to product complaint, the protocol should be followed for recording and reporting (Section 7.5.5.3).

9.4.4. Documenting a Product Complaint

The investigator will record in the source documentation a description of the product complaint, and any actions taken to resolve the complaint and to preserve the safety of the patient. Once the complaint has been investigated by the sponsor and the investigator, if necessary, an event closure letter may be sent to the investigational center where the complaint originated or to all investigational centers using the product.

2.23. Section 9.5. Adverse Event Reporting

(Section deleted)

~~Section 9.5. Adverse Event Reporting~~

~~Any Serious or Unexpected Adverse Event as defined in Section 7.4.1, whether deemed study drug-related or not, must be reported to the Teva Clinical Department at Teva Branded Pharmaceutical Products R&D, Inc. within 24 hours of when the investigator learns about it or, if the event occurs on a weekend or national holiday, on the next working day, by fax using the Serious Adverse Event Report form.~~

~~The investigator should be prepared to supply the Teva Clinical Department with the following information:~~

- ~~Investigator name and center number~~
- ~~Patient ID number and initials~~
- ~~Patient demographics (age, sex, etc.)~~
- ~~Clinical event~~
  - ~~Description~~
  - ~~Date of onset~~
  - ~~Severity~~
  - ~~Treatment (including hospitalization)~~
  - ~~Relationship to study drug (investigator's judgment)~~

~~– Action taken regarding study drug~~

~~If the adverse event was fatal, the following information is needed:~~

- ~~Cause of death (whether or not the death was related to study drug)~~
- ~~Autopsy findings (if available)~~

~~Patients who have had an SAE should be followed clinically until all parameters (including laboratory) have either returned to normal or are otherwise explained. Any Serious or Unexpected Adverse Event (including all deaths) must also be reported to the IRB within ten working days and documentation of this report sent to Teva Branded Pharmaceutical Products R&D, Inc.~~

~~The investigator should provide a follow-up report within 1 working day of receiving any additional clinical information on the SAE and/or when all parameters including laboratory have returned to normal or are otherwise explained.~~

~~All adverse events, whether serious or not, must also be recorded in the appropriate section of the Case Report Form. The report should include, wherever possible, a description of the adverse event, date of onset, duration, severity, seriousness, action taken, relationship to the study drug, and outcome of the event. Appendix F contains instructions and definitions of the terminology used for reporting SAEs.~~

2.24. Section 10.1. Study Sponsors

*Change to read (changes in **bold** and ~~strikethrough~~):*

Teva **Branded** Pharmaceuticals~~.~~ **Products R&D**, Inc.

Other sections affected by this change:

TITLE PAGE

Section 7.2. Premature Termination of Treatment

Section 7.4.1.2. Reporting

Section 9.2. Institutional Review

Section 9.3. Drug Accountability

Section 9.5. Adverse Event Reporting

Section 9.6. Case Report Forms

Section 9.7.4. Maintenance of Study Documentation and Supplies

Section 10.7. Project CRA / Study Monitor

INVESTIGATOR'S AGREEMENT

I have carefully read the foregoing protocol amendment and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and amendments according to the current GCP guidelines and will attempt to complete the study within the time designated.

I will provide copies of the protocol and amendments, and all other information submitted by the Sponsor relating to pre-clinical and prior clinical experience, to all personnel for whom I am responsible that participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all subject information (case report forms, shipment and drug return forms and all other information collected during the study) in accordance with the current GCP and local regulations.

Site Principal Investigator's name	Teva Representative's name
Signature	Signature
Date (DDMmmYYYY)	Date (DDMmmYYYY)
Institution	