Open Label Extension Study
natalizumab

PROTOCOL TITLE:	A prospective, non-interventional, multicenter, open label safety and efficacy study of intravenous natalizumab administered to patients with relapsing forms of multiple sclerosis who participated in STRATA.
PROTOCOL NUMBER:	BEL-TYS-14-10675
DATE:	Final Version, 11 August 2014
COORDINATING INVESTIGATOR:	Dr [redacted]
AFFILIATION:	[redacted]

SIGNATURE PAGE

Protocol BEL-TYS-14-10675 was approved by:

Date: .....

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Biogen Idec,
Cambridge, MA, USA

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2 ACRONYMS AND ABBREVIATIONS

CRO:	Clinical Research Organization
AE:	adverse event
SAE:	Serious Adverse Event
EDSS:	Expanded Disability Status Scale
EQ-5D:	EuroQol-5D
JCV:	JC Virus
MRI:	Magnetic resonance imaging
SDMT:	Symbol Digit Modalities

3 STUDY FLOW CHART

	Screening/Enrolment Phase Prior to treatment[2]	Treatment Phase					
		Wk 0 (Baseline)	Wk 24 (± 30 Days)	Wk 48 (± 30 Days)	Wk 72 (± 30 Days)	Unscheduled Possible relapse assesment	Wk 92 End of Study or Early Withdrawal
Informed Consent	X						
Elgibility	X						
Demographics	X						
Medical History/ Disease History	X						
Physical Examination	X		X	X	X		X
Vital Signs [3]	X		X	X	X		X
Pregnancy Test[5]	X						
JCV	X		X	X	X		X
EDSS	X		X	X	X		X
EQ-5D	X		X	X	X		X
SDMT	X		X	X	X		X
Neurological assessment	X		X	X	X		X
Brain MRI Scan[4]	X		X	X	X	X	
Relapse evaluation						X	
Pre-infusion Checklist[6]		X					X
Nataluzimab infusion		X[1]					X[7]
Monitoring /Recording of Adverse Events and Concomitant Medication	Monitor and record throughout the study						

1 First natalizumab infusion must occur within 4 weeks of Baseline/Enrolment Visit.
2 All pre-treatment evaulations must be performed and results reviewed prior to the first natalizumab injection.
3 Vitals signs: diastolic and systolic blood pressure, pulse rate, respiratory rate, body temperature. Subjects must remain in the same body position quietly for 5 minutes prior to having their pulse and blood pressure taken.
4 Brain scans to be read locally and compared for evidence of new lesions
5 Required for woman of childbearing potential. Follow-up testing throughout the study will be done at the discretion of the investigator.
6 Changes in the pre-infusion checklist will trigger suspension of the dose until approved by the treating physician. The pre-infusion checklist will need to be completed before every infusion.
7 Natalizumab infusion will not need to be given at an early withdrawal visit.

4 SUMMARY

Study Title: A prospective, non-interventional, multicenter, open label safety and efficacy study of intravenous natalizumab administered to patients with relapsing forms of multiple sclerosis who participated in STRATA

Objectives: The primary objective for this study is long-term safety (incidence and pattern of SAEs) in patients receiving natalizumab. The primary objective is to evaluate the safety of natalizumab in patients with Relapsing Forms of Multiple Sclerosis who were included in STRATA and did not meet reimbursement criteria upon termination of STRATA. Patients have been on treatment for at least 7-8 years and have very stable disease. In Belgium there is no option for these patients to continue with their treatment.

Data from the study will be used in negotiations with the Belgian authorities to find solutions for patients who participated in clinical trials and are not fulfilling local reimbursement criteria

The study will also evaluate the long-term effectiveness of natalizumab in delaying the progression of disability, reducing the frequency of relapses, and MRI activity during long-term treatment with natalizumab.

Quality of Life measurements and cognitive evaluation will be measured on a 6-monthly basis.

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Secondary objectives include long-term efficacy of natalizumab in delaying the progression of disability, reducing the frequency of relapses, MRI activity (for safety reasons) and explore quality of life and cognitive function in patients on treatment with natalizumab for more than 8 years.

- Disability progression as determined by EDSS (based on neurological examination, "physical EDSS") every six months
- MS disease activity as determined by the occurrence of clinical relapses (distribution of the total number of relapses over 2 years)
- JCV status
- Frequent MRI monitoring according to guidelines Belgian Study Group for MS
- Quality of life measurement by EQ-5D every six months

- Cognitive evaluation by SDMT every six months

Design: Prospective, non-interventional, multicenter, open label long-term safety study

Patient Population: Patients with RRMS who participated in STRATA, have stable disease for at least 7 years during STRATA, and do not meet reimbursement criteria for Tysabri® in Belgium, upon termination of the STRATA Study.

Treatment Groups: natalizumab

5 BACKGROUND AND RATIONALE

Natalizumab is a recombinant humanized anti-alpha 4 integrin antibody. Natalizumab is produced in a murine myeloma cell line (NS0) and binds to the alpha 4 subunit of human integrin, which is expressed at high levels on all circulating human leukocytes except polymorph nuclear leukocytes.

Natalizumab binding blocks the interaction of α4β1integrin (also known as very late antigen-4 (VLA-4) on leukocytes with its counter receptor, vascular cell adhesion molecule-1 (VCAM-1), on endothelial cells of the blood-brain barrier. Disruption of these cell adhesion molecule interactions prevents trafficking of mononuclear leukocytes across the endothelium and into the parenchymal tissue. Increased leukocyte trafficking into the parenchyma of the brain is believed to play a role in the pathogenesis of multiple sclerosis (MS).

The α4 integrins bind additional ligands in tissues, including osteopontin and epitopes of fibronectin. A further mechanism of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibition of binding of α4-positive leukocytes with osteoponting and fibronection. Thus, natalizumab may act to suppress existing inflammatory activity present at the disease site (e.g. in brain macrophages/microglia/meningeal inflammatory foci), along with inhibition of further recruitment of innate and adaptive immune cells into inflamed tissues by interaction with VCAM-1.

Overview of Multiple Sclerosis

MS is an autoimmune disease characterized by inflammation, myelin destruction and axonal damage, with subsequent oligodendrocyte and neuronal loss in the central nervous system (CNS). It is the most common demyelinating disorder of CNS, affecting approximately 2.5 million people worldwide. In most cases, patients with relapsing-remitting MS (RRMS) experience discrete episodes of neurologic dysfunction (referred to as relapses, exacerbations or attacks), each lasting several days to several weeks, which occur intermittently over many years. Early in the course of this phase of the disease, these symptoms tend to subside completely after each attack; over time recovery from attacks tends to be incomplete, leading to the accumulation of functional disability. Approximately half of all patients will be unable to walk without assistance within 15 years of their initial diagnosis.

Natalizumab and precautions for use

Natalizumab has demonstrated a significant clinical effect, with a 68% reductions in relapse rate over 2 years relative to the placebo arm (Polman, 2006), but has been associated with cases of progressive multifocal leukoencephalopathy (PML).

PML, an opportunistic infection caused by the JC virus (JCV, human polyomavirus) that typically only occurs in patients who are immunocompromised, has occurred in patients who received natalizumab. In natalizumab-treated patients with PML, a reaction known as Immune Reconstitution Inflammatory Syndrome can occur after natalizumab is discontinued or removed (by plasma exchange). Clinically significant liver injury has been reported in

patients treated with natalizumab in the post-marketing setting and natalizumab may incrase the risk for certain infections by lowering the ability of the immune system to fight infections. Hypersensitivity reactions, although rare, have occurred in patients receiving natalizumab, including serious systemic reactions (e.g. anaphylactic/anaphylactoid reactions), which occurred at an incidence of <1%. Approximately 6% of subjects in clinical studies developed persistent antibodies to natalizumab that were associated with a decrease in the effectiveness of natalizumab.

Rationale for Dose

The proposed natalizumab dose regimen for this study is the current marketed regimen for the treatment of relapsing MS, i.e. 300 mg q4wk intravenously.

Rationale for this study

The purpose of this study is to evaluate the safety and efficacy of natalizumab in patients with Relapsing Forms of Multiple Sclerosis who were included in STRATA and did not meet reimbursement criteria upon termination of STRATA. Patients have been on treatment for at least 7-8 years and have very stable disease. In Belgium there is no other option for these patients to continue with their treatment. Data from the study will be used in negotiations with the Belgian authorities to find solutions for patients who participated in clinical trials and are not fulfilling local reimbursement criteria and therefore cannot continue with their treatment.

The study will also evaluate the long-term effectiveness of natalizumab in delaying the progression of disability, reducing the frequency of relapses, and MRI activity during long-term treatment with natalizumab.

Quality of Life measurements and cognitive evaluations will be measured on a 6-monthly basis.

6 METHODS

6.1 Study Objectives/Endpoints

6.1.1 Primary Objective

The primary objective for this study is long-term safety (incidence and pattern of SAEs) in patients receiving natalizumab.

6.1.2 Secondary Objective

Secondary objectives include long-term efficacy of natalizumab in delaying the progression of disability, reducing the frequency of relapses, MRI activity (for safety reasons) and explore quality of life and cognitive function in patients on treatment with natalizumab for more than 8 years.

6.1.3 Primary Endpoint

The primary endpoint of the open label study is the incidence of AEs and SAEs.

6.1.4 Secondary Endpoints

The secondary endpoints of the open label study are:

- Disability progression as determined by Expanded Disability Status Scale (EDSS) (based on neurological examination, "physical EDSS") every six months
- MS disease activity as determined by the occurrence of clinical relapses (distribution of the total number of relapses over 2 years)
- JCV status (anti-JCV antibody positive or negative according to the STRATIFY JCV® Test, Unilabs, Denmark)
- Frequent MRI monitoring according to guidelines Belgian Study Group for MS
- Quality of life measurement by EQ-5D every six months
- Cognitive evaluation by Symbol Digit Modalities Test (SDMT) every six months

6.2 Study Design

6.2.1 Overview

This Study is a phase 4 prospective, non-interventional, multicenter, open label study in subjects who have completed the STRATA protocol and meet the study entry criteria. It has been designed to assess the long-term safety and efficacy of natalizumab in subjects with Relapsing Forms of MS. Subjects previously participating in STRATA, who respond well to natalizumab and want to continue with treatment, and do not meet the reimbursement criteria for natalizumab in Belgium upon termination of the STRATA Study, will be enrolled.

The Sponsor will provide natalizumab in this study.

6.2.2 Overall Study Duration and Follow-up

The study will consist of a screening/enrollment Visit, baseline visit and a 24 months treatment period.

At the Screening/Enrollment Visit, the subject will provide written informed consent to participate in the study. The subject's eligibility for the study will then be determined. Eligible Subjects will be enrolled into the study and undergo baseline assessments.

Eligible subjects will take natalizumab under this protocol for 24 months. After the Baseline/Enrollment Visit, clinic visits will occur at Month 6 (week 24), Month 12 (week 48), Month 18 (week 72) and Month 24 (week 96). The End of Treatment Visit is the Month 24 visit. Subjects who discontinue natalizumab early will complete the same assessments specified for the End of Treatment Visit.

No post-treatment follow-up is planned.

During this study anti-JCV antibody testing will be performed every 6 months.

6.2.3 End of Study

The end of Study is last Subject's last visit (Month 24 End of Treatment/Early Discontinuation Visit) for final collection of data for the primary objective.

6.3 Discontinuation of the Study

Biogen Idec, INC. may terminate this study, after consultation with the investigators, at any time. The Investigators will be notified by Biogen Idec or designee if the study is placed on hold, completed, or closed.

7 STUDY POPULATION

7.1 Number of Subjects

10 Subjects in 4 sites in Belgium are planned for enrollment.

7.2 Inclusion Criteria

To be eligible for entry into this study, candidates must meet **all** of the following eligibility criteria at the time of screening (unless otherwise specified):

1. Have the ability to understand the purpose and risks of the study and provide signed and dated informed consent and any authorizations required by local law in accordance with national and local subject privacy regulations.
2. Has participated in the STRATA Study, have stable disease and do not meet reimbursement criteria for natalizumab (Tysabri®) in Belgium, upon termination of the STRATA Study.
3. Are ≥18 years old.
4. Subjects of child bearing potential must practice effective contraception during the study and be able to continue contraception for 3 months after their last infusion.

7.3 Exclusion Criteria

Candidates will be excluded from study entry if **any** of the following exclusion criteria exist at the time of consent of the study:

1. Patients participating in STRATA who were in line with current Belgian reimbursement criteria when they started in one of the feeder studies (Affirm or Sentinel).
2. Subjects with any significant change in clinical status, that in the opinion of the Investigator, would make them unsuitable to participate in this study. The investigator must review the subject's medical fitness for participation and consider any diseases that would preclude treatment.
3. Subjects that are unwilling or unable to comply with study requirements, or are deemed unsuitable for study participation as determined by the Investigator.
4. Female Subjects who are considering becoming pregnant while in the study.
5. Female Subjects of childbearing potential and are not using the appropriate contraception as determined by the Investigator.
6. Female subjects who are currently pregnant or breastfeeding.
7. Any prescheduled elective procedure during the study period that, in the opinion of the Investigator, would interfere with study parameters.
8. Any other condition, clinical finding, or reason that, in the opinion of the Investigator, is determined to be unsuitable for enrollment into this study

8 STUDY MEDICATION, DESCRIPTION, AND ALLOCATION–IF APPLICABLE

Natalizumab will be stored in a secure location, preferably a locked refrigerator. The study drug may be dispensed only by his/her designee specifically authorized by the investigator. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is dispensed to a subject, it can be administered only to that subject.

Study drugs will not to be used beyond the initial expiration date on the drug packaging. Study site staff should refer to the local natalizumab product information for specific instruction on the handling and administration of natalizumab.

8.1 Natalizumab Stability & Storage

Natalizumab is a recombinant humanized IgG4k monoclonal antibody produced in murine myeloma cells. Natalizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to a4-integrin. The molecular weight of natalizumab is 149 kilodaltons. Natalizumab is supplied as a sterile, colorless, and clear to slightly opalescent concentrate for intravenous (IV) infusion. Each 15 mL dose contains 300 mg natalizumab; 123 mg sodium chloride, USP; 17.0 mg sodium phosphate, monobasic, monohydrate, USP; 7.24 mg sodium phosphate, dibasic, heptahydrate, USP; 3.0 mg polysorbate 80, USP/NF, in water for injection, USP at pH 6.1.

Administration Instructions
Infuse natalizumab 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP over approximately one hour. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.

Use of filtration devices during administration has not been evaluated. Other medications should not be injected into infusion set side ports or mixed with natalizumab.

Natalizumab concentrate is supplied as 300 mg natalizumab in a sterile, single-use vial free of preservatives. Each package contains a single-use vial.

Storage

Natalizumab single-use vials must be refrigerated between 2-8°C (36°-46°F) or stored according to instructions in the Package Inset. Do not use beyond the expiration date stamped on the carton and vial label. DO NOT SHAKE OR FREEZE. Protect from light.

If not used immediately, store the natalizumab solution for infusion at 2-8°C (36°-46°F). natalizumab solution for infusion must be administered within 8 hours of preparation.

8.2 Other Study Drug: Generic Name (Brand Name®)

Not Applicable.

8.3 Screening, Registration and Enrollment

Subjects must be consented before any baseline tests or assessments are performed. At the time of consent, the subject will be registered into the study. Participating study sites are required to document all registered candidates initially considered for enrollment in this study. If a subject is not enrolled in this study, the reasons will be documented in the subject's source documents and on the registration log.

Subjects will be enrolled at the Screening/Enrollment Visit, after all baseline assessments have been completed and after the Investigator has verified that they are eligible per criteria in section 7.2 and 7.3. Patients will be enrolled as soon as possible after the decision they can participate in the trial and their first infusion will take place within 4 weeks of enrolment.

No subject may begin study treatment prior to enrollment and assignment of a unique subject identification number. This unique identification number consists out of the site number (from [redacted] until [redacted]) and then a cumulative number [redacted]. For example site number [redacted] and patient number one will be [redacted], patient number 2 at this site will be [redacted]…

For this study 4 centers in Belgium will participate and 10 subjects will be enrolled.

8.4 Blinding Procedures

Not Applicable. This is an open-label study.

8.5 Drug Accountability

The study site must maintain accurate records demonstrating dates and amount of study drug received, to whom they are dispensed (subject-by-subject accounting), and accounts of any study drug accidentally or deliberately destroyed. Unless otherwise notified, the study sites must save all unused natalizumab vials for drug accountability. The investigator must return all unused vials of study drug to Biogen Idec pursuant to instructions (unless agreed otherwise by Biogen Idec and Elan Pharmaceuticals)." A written explanation must be provided for any discrepancies.

8.6 Treatment Schedule for Tysabri

All assessments associated with each study visit are to be completed before treatment is administered.

All subjects will receive open label natalizumab infusions q4wk for 96 weeks. The first infusion will take place within 4 weeks of enrolment.

8.7 Treatment Schedule for MS Relapse

An MS relapse will be defined as the onset of new or recurrent neurological symptoms lasting at least 24 hours, accompanied by new objective abnormalities on a neurological exam, and not explained solely by non-MS processes such as fever, infection, sever stress or drug toxicity. An unscheduled visit for investigation of a possible relapse and brain MRI should be performed before treatment of a protocol defined relapse. Treatment of a protocol defined relapse may proceed at the discretion of the Investigator according to local standards of care and will not affect the subject's eligibility to participate. New or recurrent neurological symptoms that occur less than 30 days following the onset of a protocol defined relapse should be considered as part of the same relapse. New or recurrent neurologic symptoms that evolve gradually over months should be considered disability progression, not an acute relapse, and should not be treated with a high-dose corticosteroids.

8.8 Discontinuation of Subjects from Investigational Treatment or from the Study

A subject must permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant.
- The subject withdraws consent
- The subject experiences a medical emergency that necessitates permanent discontinuation of the study treatment.
- At the discretion of the Investigator for medical reasons or for noncompliance.
- The subject experiences hypersensitivity reaction to the treatment.
- The subject is diagnosed with PML.

The reason for discontinuation must be recorded in the subject's CRF. Subjects who discontinue study treatment should withdraw from the study and are required to complete their Month 24/Early discontinuation Visit assessments..

8.9 Subject Withdrawal from the Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol
- The subject meets any of the criteria defined in section 7.7.1.

The reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

8.10 Treatment Compliance

Compliance with treatment and dosing is to be monitored and recorded by site staff.

8.11 Continuation of Treatment

Open-label treatment with natalizumab will continue for approximately 2 years.

8.12 Concomitant Therapy and Procedures

8.12.1 Concomitant Therapies

A concomitant therapy is any drug or substance administered from the time of the subject's written consent until the subject's last study visit.

8.12.2 Allowed Concomitant Therapy

Medication necessary for the treatment of AE s.
Medications used to treat the MS Symptoms such as spasticity, bladder impairment, pain or depression.
Short courses of high-dose corticosteroids per local standard of care as a rescue medication for exacerbations of MS disease.
Corticosteroids that are administered by non-systemic routes (e.g. topical, inhaled).
Pretreatment steroids or over-the-counter anti-inflammatory drugs at the time of natalizumab infusion are also allowed at the discretion of the Investigator.

8.12.3 Disallowed Concomitant therapy

- Combination with beta-interferons or glatiramer acetate or other disease modifying treatments for MS
- Other immunosuppressive and antineoplastic therapies

8.12.4 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g. surgery/biopsy, physical therapy) or diagnostic assessment (e.g. blood gas measurement, bacterial cultures) performed from the time the subject is enrolled in the study to the subject's last study visit, unless the subject is being followed for study related toxicity.

8.13 Recording Concomitant Medication

Concomitant Medication must be recorded in the subject's CRF.

9 STUDY SCHEMA

9.1 Tests and Evaluations

All tests and evaluations associated with each study visit are to be completed before treatment is administered.

All subjects will receive open label natalizumab infusions q4wk for 96 weeks. The first infusion will take place within 4 weeks of enrolment.

Prior to each infusion of natalizumab, subjects will complete a pre-infusion screening checklist. The study investigator, or designee, will review the outcomes of these assessments, compared to previous time points for neurological signs and/or symptoms that may suggest PML prior to administrating study treatment.

Subjects will remain in the clinic for 1 hour after the study treatment infusion to allow monitoring by the study site personnel for hypersensitivity reactions.

Please refer to the study flow chart.

9.2 Visits and Assessments

Regular clinical practice visits will occur every 6 months (+/- 1 month). The infusion will occur every month (+/- 1 week).

Clinical Efficacy Assesments:

The following clinical tests/assessments will be performed to assess the efficacy of natalizumab:

- Clinical relapses
- EDSS
- EQ-5D
- SDMT

Clinical Safety Assesments:

The following clinical assesments will be performed to assess the safety profile of natalizumab:

- Natalizumab preinfusion checklist (see appendix IV).
- Physical and neurological examinations
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure and respiratory rate
- Monitoring of AE s and SAE s (except for hospitalizations due to MS Relapses that are non-fatal)
- Monitoring of concomitant medications
- MRI

Laboratory Safety Assesments:

The following laboratory tests will be performed to assess the safety profile of natalizumab:

- anti-JCV antibodies (STRATIFY JVC® Test, Unilabs Denmark)

10 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS – DEFINITION & REPORTING

At the signing of the informed consent form, each subject will be given the names and telephone numbers of investigational site personnel for reporting adverse events and medical emergencies. Definitions and instructions for monitoring, recording, and reporting adverse events will be reviewed with investigational site personnel prior to enrollment.

10.1 Definitions

10.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) is any adverse event that is experienced by a subject who has received an investigational drug, but that does not necessarily have a causal relationship with the investigational drug.

10.1.2 Serious Adverse Events

In accordance with 21 Code of Federal Regulations (CFR) Part 312.32 and the recommendations of the International Conference on Harmonisation (ICH) [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45], any of the following adverse events are to be classified as a serious adverse event (SAE):

- An event that results in death.

- An event that, in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event). This does not include an event that, had it occurred in a more severe form, might have caused death.
- An outcome that results in a congenital anomaly/birth defect diagnosed in a child of a subject who participated in this study.
- An event that requires or prolongs in-patient hospitalization.
- An event that results in persistent or significant disability/incapacity.
- Other medically important events that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an in-patient hospitalization.).

If a serious adverse event is unresolved when a subject permanently discontinues the study, the subject will be followed until the event resolves or the clinical course is stabilized.

10.1.3 Adverse Event Recording/Reporting

All adverse events (including pre-dosing and treatment-emergent) should be recorded in the subject's record (or, if applicable, in the adverse event section of the CRF) regardless of severity or relationship to investigational drug.

10.1.4 Immediate Reporting of Serious Adverse Events

Any SAE required to be reported according to 21 Code of Federal Regulations (CFR) Part 312.32 and the recommendations of the International Conference on Harmonisation (ICH) [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45] that occurs regardless of whether or not the subject has undergone any study-related procedures or received investigational drug, through the completion of trial, will be reported to the FDA.

The Investigator will notify the local IRB/IEC per local requirements. The investigator may also notify Biogen Idec, INC of any major safety event AFTER the event is submitted to the FDA and the study IRB/IEC.

10.1.5 Safety Classifications

The following classifications should be considered when evaluating the relationship of adverse events and serious adverse events to investigational drug:

Relationship of Event to Investigational Drug	
Not related	An adverse event will be considered "not related" to the use of the investigational drug if there <u>is not a possibility</u> that the event has been caused by

Relationship of Event to Investigational Drug	
	the product under investigation. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (e.g., the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.
Related	An adverse event will be considered "related" to the use of the investigational drug if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to: a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.

Severity of Adverse Events and Serious Adverse Events

The following classifications should be considered when evaluating the severity of adverse events and serious adverse events:

Severity of Event	
Mild:	Symptoms(s) barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms(s) but may be given because of personality of subject.
Moderate:	Symptom(s) of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptom(s) may be needed.
Severe:	Symptom(s) cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with investigational drug; treatment for symptom(s) may be given and/or subject hospitalized.

10.2 Investigator Responsibilities

The Investigator will:

- Monitor and record all adverse events
- Determine the seriousness, causality, and severity of each adverse event
- Report all serious adverse events to the FDA according to the code of federal regulations
- Actively and persistently pursue follow-up of serious adverse events

- Notify Biogen Idec, INC. of any major safety event

10.3 Additional Procedures

10.3.1 Procedures for Handling Pregnancy

TYSABRI® (natalizumab) treatment will be immediately discontinued in the event of pregnancy in a subject enrolled in the study.

11 SUBJECT INFORMATION AND CONSENT

Prior to any testing under this protocol, including screening tests and evaluations, all subjects will sign an informed consent form that complies with the requirements of both 21 CFR Part 50 and HIPAA before entering the study. Or, a consent form that complies with the requirements of 21 CFR Part 50 and a separate HIPAA compliant authorization form for the use of and disclosure of the subject's protected health information (PHI) will be obtained from the subject in accordance with local practice and regulations.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the subject. A copy of the informed consent document signed and dated by the subject will be given to the subject. Confirmation of a subject's informed consent will also be documented in the subject's medical records prior to any testing under this protocol, including screening tests and evaluations.

11.1 Subject Data Protection

The subject will not be identified by name in any study reports, and these reports will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential.

12 ETHICAL REQUIREMENTS

The Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study according to local regulations.

12.1 Declaration of Helsinki

The Investigator must follow the recommendations contained in the Declaration of Helsinki, amended at the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, with Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002. See Appendix II in Section 15.2.

12.2 Ethics Committee

The Investigator must obtain written IRB approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Investigator makes any changes to the ICF, Biogen Idec must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen Idec. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen Idec.

It is the responsibility of the Principal Investigators to ensure that all aspects of institutional review are conducted in accordance with current governmental regulations.

Biogen Idec must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and Biogen Idec.

13 ADMINISTRATIVE PROCEDURES

13.1 Patient Enrollment

The Investigator must not enroll any subjects into the study prior to all prerequisite study document completion and agreement by the Investigator and Biogen Idec, INC.

Prior to performing any study-related activities under this protocol, written informed consent with the approved ICF must be obtained from the subject or the subject's legally authorized representative, as applicable, in accordance with local practice and regulations. Written informed consent must be obtained from all subjects participating in a clinical study conducted by Biogen Idec.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject. The subject must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the subject, must be given to the subject. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol.

Each consent form should contain an authorization allowing the Principal Investigator(s) and Biogen Idec to use and disclose PHI (i.e., subject-identifiable health information) in compliance with local law.

The signed consent form will be retained with the study records.

13.2 Study Site Initiation

The Investigator must not register any subjects prior to completion of a study initiation visit, conducted by Biogen Idec or designee. This initiation visit will include a detailed review of the protocol and study procedures.

13.3 Quality Assurance

During and/or after completion of the study, quality assurance officers named by Biogen Idec, INC. or the regulatory authorities may wish to perform on-site audits. The Investigator will be expected to cooperate with any audit and to provide assistance and documentation (including source data) as requested.

13.4 Monitoring of the study

The Principal Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories.

The Clinical Monitor(s) will call and visit the investigators at regular intervals during the course of the study and after the study has completed, as appropriate.

During these remote and on-site visits, CRFs and supporting documentation related to the study will be reviewed and any discrepancies or omissions will be resolved.

The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

13.5 Study Funding

Biogen Idec, INC. will financially support the work of the Investigator as it pertains to the conduct of this study. All financial details are provided in the separate contract between the Investigator and CRO.

14 FURTHER REQUIREMENTS AND GENERAL INFORMATION

14.1 External Service Organizations

A CRO, [redacted] will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, and management of SAE reports, and

datamanagement. Before subjects are registered at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

14.1.1 Data Capture

Subject Information will be captured and managed by study sites on case report forms (CRFs).

14.1.2 Central Laboratories for Laboratory Evaluations

Not applicable.

14.1.3 MRI Reading Center

Not applicable.

14.2 Study Committees

Not applicable.

14.2.1 Independent Assessment Panel

Not applicable.

14.2.2 Publication Policy

Investigators should refer to their Clinical Trial Agreement for details regarding the disclosure of study results.

14.3 Changes to Final Study Protocol

All protocol amendments must be submitted to the IRB/EC. Protocol modifications that impact subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the IRB/EC and submitted to the appropriate regulatory authorities (if applicable) before implementation of such modifications to the conduct of the study. In the event of a protocol modification, the subject consent form may also require modifications.

It is the responsibility of the PI to submit all revisions to the protocol to Biogen Idec, INC. before submitting to their IRB.

14.4 Record Retention

Appropriate legal guidelines regarding retention of records must be followed.

14.5 Reporting and Communication of Results

Investigators should refer to their Clinical Trial Agreement for details regarding the disclosure of study results.

14.6 Protocol Completion

The IRB/EC must be notified of completion or termination of the protocol. Within 3 months of protocol completion or termination, the investigator must provide a final clinical summary report to the IRB/EC. The principal investigator will maintain an accurate and complete record of all submissions made to the IRB/EC, including a list of all reports and documents submitted. A copy of these reports will be sent to Biogen Idec, INC. Adverse events, which are reported to regulatory authorities, must be submitted promptly to the IRB/EC.

15 REFERENCES

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APPENDIX I: SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, entitled "A prospective, non-interventional, multicenter, open label safety and efficacy study of intravenous natalizumab administered to patients with relapsing forms of multiple sclerosis who participated in STRATA" and agree to conduct the study as detailed herein and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

_____

Investigational Site (Print)

16 APPENDIX II: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be

recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

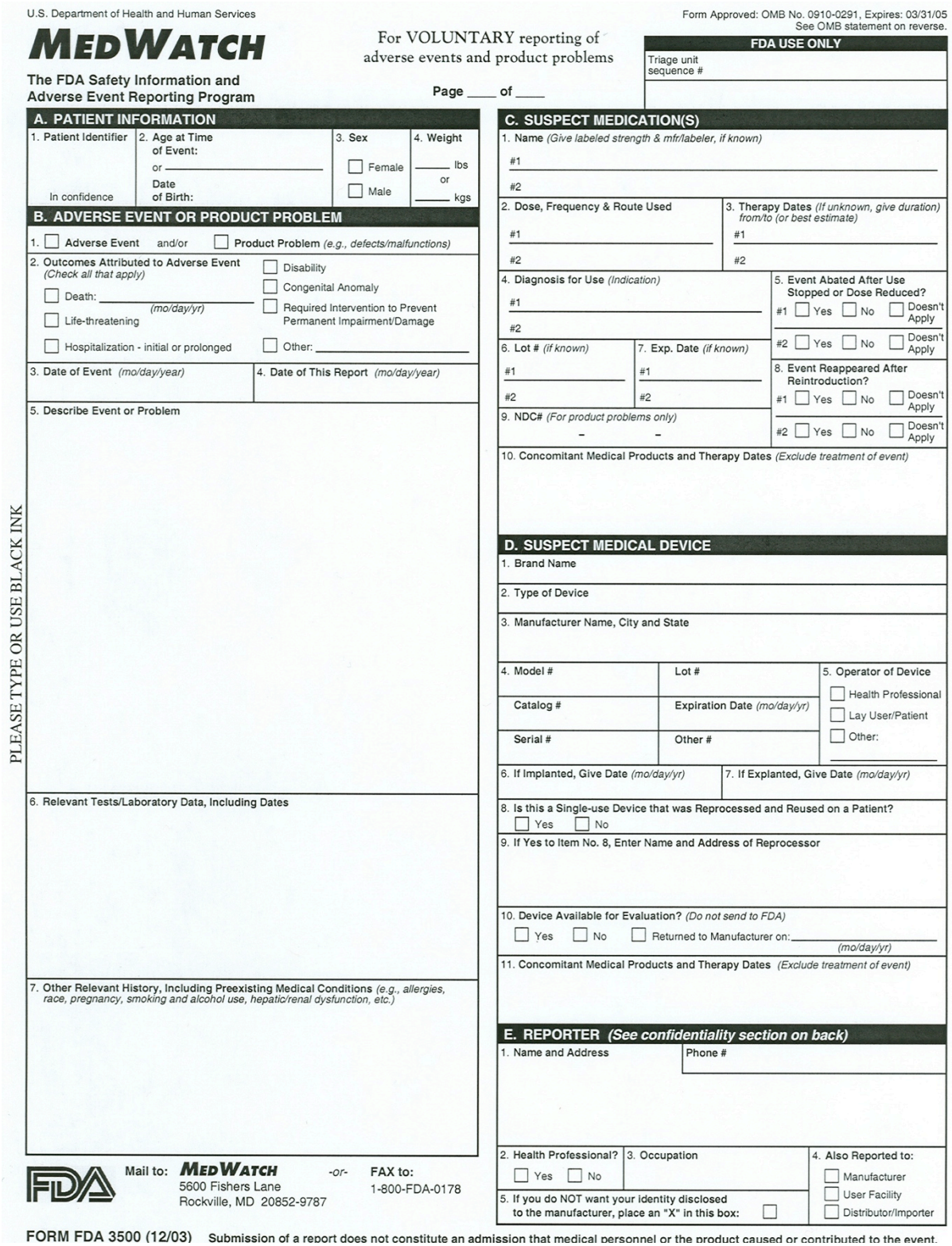
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

17 APPENDIX III: MEDWATCH SERIOUS ADVERSE EVENT REPORTING – FORM 3500



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

FDA USE ONLY
Triage unit sequence #

PLEASE TYPE OR USE BLACK INK

A. PATIENT INFORMATION

1. Patient Identifier — In confidence
2. Age at Time of Event: or Date of Birth:
3. Sex — ☐ Female ☐ Male
4. Weight — ____ lbs or ____ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem *(e.g., defects/malfunctions)*
2. Outcomes Attributed to Adverse Event *(Check all that apply)*
   ☐ Death: _____ *(mo/day/yr)*
   ☐ Life-threatening
   ☐ Hospitalization - initial or prolonged
   ☐ Disability
   ☐ Congenital Anomaly
   ☐ Required Intervention to Prevent Permanent Impairment/Damage
   ☐ Other: _____
3. Date of Event *(mo/day/year)*
4. Date of This Report *(mo/day/year)*
5. Describe Event or Problem
6. Relevant Tests/Laboratory Data, Including Dates
7. Other Relevant History, Including Preexisting Medical Conditions *(e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)*

C. SUSPECT MEDICATION(S)

1. Name *(Give labeled strength & mfr/labeler, if known)*
   #1
   #2
2. Dose, Frequency & Route Used
   #1
   #2
3. Therapy Dates *(If unknown, give duration)* from/to (or best estimate)
   #1
   #2
4. Diagnosis for Use *(Indication)*
   #1
   #2
5. Event Abated After Use Stopped or Dose Reduced?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
6. Lot # *(if known)*
   #1
   #2
7. Exp. Date *(if known)*
   #1
   #2
8. Event Reappeared After Reintroduction?
   #1 ☐ Yes ☐ No ☐ Doesn't Apply
   #2 ☐ Yes ☐ No ☐ Doesn't Apply
9. NDC# *(For product problems only)*
   – –
10. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

D. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Type of Device
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date *(mo/day/yr)* / Serial # / Other #
5. Operator of Device
   ☐ Health Professional
   ☐ Lay User/Patient
   ☐ Other: _____
6. If Implanted, Give Date *(mo/day/yr)*
7. If Explanted, Give Date *(mo/day/yr)*
8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   ☐ Yes ☐ No
9. If Yes to Item No. 8, Enter Name and Address of Reprocessor
10. Device Available for Evaluation? *(Do not send to FDA)*
    ☐ Yes ☐ No ☐ Returned to Manufacturer on: _____ *(mo/day/yr)*
11. Concomitant Medical Products and Therapy Dates *(Exclude treatment of event)*

E. REPORTER ***(See confidentiality section on back)***

1. Name and Address
   Phone #
2. Health Professional? ☐ Yes ☐ No
3. Occupation
4. Also Reported to:
   ☐ Manufacturer
   ☐ User Facility
   ☐ Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box: ☐

FDA

Mail to: MEDWATCH 5600 Fishers Lane Rockville, MD 20852-9787 -or- FAX to: 1-800-FDA-0178

FORM FDA 3500 (12/03) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report adverse experiences with:

- Medications *(drugs or biologics)*
- Medical devices *(including in-vitro diagnostics)*
- Special nutritional products *(dietary supplements, medical foods, infant formulas)*
- Cosmetics
- Medication errors

Report product problems - quality, performance or safety concerns such as:

- Suspected counterfeit product
- Suspected contamination
- Questionable stability
- Defective components
- Poor packaging or labeling
- Therapeutic failures

Report SERIOUS adverse events. An event is serious when the patient outcome is:

-Fold Here-

- Death
- Life-threatening *(real risk of dying)*
- Hospitalization *(initial or prolonged)*
- Disability *(significant, persistent or permanent)*
- Congenital anomaly
- Required intervention to prevent permanent impairment or damage

Report even if:

- You're not certain the product caused the event
- You don't have all the details

How to report:

- Just fill in the sections that apply to your report
- Use section C for all products except medical devices
- Attach additional blank pages if needed
- Use a separate form for each patient
- Report either to FDA or the manufacturer *(or both)*

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise.

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

-Fold Here-

Important numbers:

- 1-800-FDA-0178 -- To FAX report
- 1-800-FDA-1088 -- To report by phone or for more information
- 1-800-822-7967 -- For a VAERS form for vaccines

To Report via the Internet:

http://www.fda.gov/medwatch/report.htm

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
MedWatch; HFD-410
5600 Fishers Lane
Rockville, MD 20857

Please DO NOT RETURN this form to this address.

OMB statement:
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FORM FDA 3500 (12/03) (Back) **Please Use Address Provided Below -- Fold in Thirds, Tape and Mail**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

19 APPENDIX IV: NATALIZUMAB PREINFUSION SAFETY CHECKLIST

1. Over the past month, have you had any new or worsening medical problems (such as a new or sudden change in your thinking, eyesight, balance, strength, or other problems) that have persisted over several days?
   - ❑ Yes
   - ❑ No

2. Do you have a medical condition that can weaken your immune system, such as human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS), leukemia or lymphoma, or an organ transplant that may suggest that your body is not able to fight infections well?
   - ❑ Yes
   - ❑ No

3. In the past month, have you taken medicines to treat cancer or multiple sclerosis (MS) or any other medicines that weaken your immune system?
   - ❑ Yes
   - ❑ No

4. In the past month, other than for the treatment of a recent relapse, have you taken any of the following medicines: Solu-Medrol®, methylprednisolone, Decadron®, dexamethasone, Depo-Medrol®, prednisone, or other steroid medicines?
   - ❑ Yes
   - ❑ No

If the patient answered YES to question 1, 2, 3, or 4, DO NOT INFUSE until approved by the treating physician.