PROTOCOL NUMBER: 218MS401

PHASE OF DEVELOPMENT: 4

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PROTOCOL TITLE: A Multicenter, Multinational, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Fampyra® When Used In Routine Medical Practice (LIBERATE)

DATE: 23 September 2013
Version 3
FINAL

Supersedes previous Version 2, dated 10 August 2012.

SIGNATURE PAGE

Protocol 218MS401 was approved by:

[redacted], MD

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Date

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TABLE OF CONTENTS

1. SPONSOR INFORMATION

Biogen Idec is the Sponsor of the study and is responsible for conducting the study.

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Primary contact for urgent medical issues:

All urgent medical queries should be referred directly to Biogen Idec according to standard commercial product reporting lines.

Medical issues directly related to the study should be referred to the relevant Quintiles clinical research associate.

Please refer to the Study Reference Manual for complete contact information.

2. LIST OF ABBREVIATIONS AND DEFINITIONS

AE	adverse event
CGI-I	Clinical Global Impression of Improvement
CRF	case report form
CRO	Contract Research Organization
EDSS	Expanded Disability Status Scale
ER	extended-release
IEC	Independent Ethics Committee
MS	multiple sclerosis
MSIS-29	Multiple Sclerosis Impact Scale-29 Items
PI	product information
PSUR	Periodic Safety Update Report
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SR	sustained-release
USA	United States of America
UTI	urinary tract infection

3. SYNOPSIS

This is a brief summary. For details refer to the body of the protocol.

Protocol Number:	218MS401
Protocol Title:	A Multicenter, Multinational, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Fampyra When Used In Routine Medical Practice (LIBERATE)
Version Number:	3
Name of Study Treatment:	Fampyra
Phase of Development:	4
Rationale for the Study:	Fampyra® represents a new class entity for the treatment of multiple sclerosis (MS); it is a K^+ channel blocker that at low concentrations has effects on action potential conduction selectively in demyelinated nerve fiber. It was recently approved in Europe (20 July 2011) and Australia (May 2011) as a treatment to improve walking in patients with MS. Due to the inherent constraints of clinical trials, the existing Fampyra safety database established during the development phase has its limitations in providing understanding of certain safety issues. For example, premarketing clinical trials were not powered to evaluate the incidence of rare adverse events (AEs), including seizure; the number of patients aged ≥65 years was limited; patients with pre-existing cardiovascular risk factors were excluded from the studies; and a 3.6% increase compared to placebo in the incidence of urinary tract symptoms was not fully characterized (with respect to if it was a result of infection or sensory overstimulation). The present study will be conducted in postmarketing routine practice setting. The study will expand the number and spectrum of patients treated with Fampyra to be observed to help further understand the safety profiles of Fampyra in subpopulations not fully studied during the development phase, and to increase our understanding of the specific safety issues described above. As such, this

observational study will assess the effectiveness of risk minimization measures, as specified in the risk management plan for Fampyra.

Study Objectives:

Primary:
The primary objective of the study is to collect additional safety data including the incidence rate of seizure and other specific AEs of interest from patients taking Fampyra in routine clinical practice.

Secondary:
The secondary objectives of the study are as follows:

- To characterize utilization patterns of Fampyra in routine clinical practice.
- To assess the effectiveness of risk minimization measures as described in the risk management plan of Fampyra.
- To assess the change over time in patient self-reported evaluation of the physical and psychological impact of MS while taking Fampyra.
- To assess the change over time in physician assessment of walking ability in patients taking Fampyra.

Study Design:

This is a prospective, noninterventional, multicenter, observational study of patients receiving Fampyra in a postmarketing routine clinical setting.

The decision to enroll a patient into this study will not be made until after the physician and patient have decided to begin Fampyra treatment.

Study Investigators will be neurologists who prescribe Fampyra. Investigators will not perform any medical procedures for this study that are outside of their routine practice, and should treat patients according to local marketing authorization and clinical practice.

Data will be collected at Enrollment (Baseline) and Follow-Up until 12 months after Enrollment (Baseline).

Patients who discontinue Fampyra will be encouraged to remain in the study, and reasons for discontinuation of Fampyra will be collected.

Data will be reviewed at regular intervals throughout the

	study period.
Study Location:	Approximately 300 sites in multiple countries outside the United States (US). Countries will be included based on the status of the marketing authorization and commercial availability of Fampyra.
Number of Planned Patients:	Approximately 5000 MS patients will be enrolled.
Study Population:	This study will be conducted in patients who have been prescribed Fampyra in routine clinical practice and in accordance with the terms of the local marketing authorization. Patients must meet the following eligibility criteria at the time of enrollment: 1. Patients have been newly prescribed Fampyra according to the terms of the marketing authorization, but who have not yet started the treatment. 2. Patients who are willing and able to provide written informed consent.
Treatment Supply:	Fampyra will not be supplied for this study. The neurologists (Investigators) will follow standard local procedures for prescribing commercial Fampyra.
Duration of Treatment and Follow-Up:	The planned duration of follow-up for each patient is approximately 1 year after the start of Fampyra treatment. All patients who discontinue Fampyra, regardless of the reasons and time of discontinuation, will be encouraged to remain in the study for the 1-year observation period, unless the patients withdraw consent to participate in the study.

Criteria for Evaluation:	• AEs reported by the Investigator of the following categories:
	  ○ all serious adverse events (SAEs) including seizures and spontaneous abortions
	  ○ all AEs leading to Fampyra dosage change or discontinuation
	  ○ all AEs experienced by the patient at the time of Fampyra overdose (overdose is defined in Section 11.1.3)
	  ○ all AEs of particular interest (refer to Section 11.2.2)
	
	All other non-serious AEs will not be collected as part of this study and should follow spontaneous postmarketing

reporting rules as per local regulations.

- Characteristics of Fampyra use in routine practice, including the following patient information:
  - demographics
  - medical history
  - underlying MS disease subtype
  - Expanded Disability Status Scale total score
  - previous (past 6 months) and current treatment, if any, for underlying MS disease
  - continuous concomitant procedures and medications, including herbals and nutraceuticals, (defined as a treatment administered regularly for 2 weeks or more)
  - reason for Fampyra use
  - dose and duration of Fampyra use
  - dosing deviations from the local Fampyra label, product information (PI), or prescription information (including incidence of overdoses)
  - reasons for change of dose or discontinuation of Fampyra treatment
  - date of neurological assessment of walking
- Physician's Clinical Global Impression of Improvement (CGI-I) of walking ability (Appendix A) [Guy 1976] assessed whenever a patient is seen by the neurologist
- Patient's assessment of physical and psychological impact of MS at each visit using the Multiple Sclerosis Impact Scale-29 Items (MSIS-29) [Appendix B] [Hobart 2001]

Statistical Methods:

Statistical analyses will be exploratory and descriptive in nature. Details of the analyses to be carried out will be included in the statistical analysis plan.

Patient Population

All patients who are enrolled in the study and receive at least 1 dose of Fampyra will be included in the safety population. All analyses will be presented for the safety population.

Baseline Patient Characteristics

Descriptive statistics (i.e., mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables. Counts and percentages will be provided for categorical variables.

Safety Analysis

Safety data will be coded using the current version of the Medical Dictionary for Regulatory Activities available at the time of study start.

Safety data will be analyzed to detect any potential new and unexpected safety signals and to further evaluate AEs of particular interest. All safety summaries will be presented for the safety population.

The number and percentage of patients with SAEs, AEs leading to Fampyra dosage change or discontinuation, and other reported events will be presented by System Organ Class and Preferred Term along with the relationship to Fampyra.

The incidence of SAEs and other events will be summarized for the safety population by age group (≥65 years and <65 years) and compared to published data and other sources.

In addition, the rates (number of events per patient-year of exposure) of AEs leading to discontinuation of Fampyra and SAEs (including seizures) will be calculated.

Drug Utilization

The pattern of Fampyra use (dose and duration) will be summarized descriptively. The underlying disease subtype, dosage change, or discontinuation will also be summarized. Additionally, dosing deviations from the local Fampyra label, PI, or prescription information (including incidence of overdoses) will be summarized.

Risk Minimization

The number and percentage of patients with a neurological assessment of walking within 14 days after the start of dosing with Fampyra will be presented to assess whether appropriate follow-up of effectiveness was performed.

Adherence to contraindications will be assessed by review and summaries of data (i.e., medical history, creatinine clearance at baseline, and concomitant medications). Summaries of AEs of particular interest will also be summarized by whether there was a relevant contraindication.

Other Observational Points

Summary statistics at each timepoint, as well as changes

	from baseline over time, will be presented for the MSIS-29 score for the physical and psychological impact of MS. Summary statistics over time will be presented for the Physician's CGI-I score for walking ability.
Interim Analysis:	No formal interim analyses are planned. Safety data will be analyzed at least annually once enrollment has begun. Summary reports will be submitted annually with Fampyra Periodic Safety Update Reports.
Sample Size Determination:	Approximately 5000 MS patients will be enrolled in the study and followed for approximately 1 year after the start of Fampyra treatment to collect at least 3308 patient-years of exposure to Fampyra based on a dropout rate of 34%. The sample size is calculated based on seizure rates in MS patients. A sample of 3308 patients would achieve 80% power to detect a doubling of seizure rates, assuming a background incidence rate of 0.003 per patient-year [Eriksson 2002] when the significance level is 0.05. Given this sample of 3308 patients and published background incidence on cardiovascular outcomes in MS patients (1% for arrhythmias and conduction disorders in patients aged 65 years or older [Fleming and Blake 1994], 0.1% for atrial fibrillation/flutter [Christiansen 2010]), the power to detect a doubling of events in 1 year of follow-up is 99% for any arrhythmias and conduction disorders and 46% for atrial fibrillation.
Study Stopping Rules:	Biogen Idec may terminate this study, after informing the Investigators, at any time. The Investigators will be notified by Biogen Idec if the study is placed on hold, completed, or closed.

4. SCHEDULES OF ASSESSMENTS FOR OBSERVATIONAL STUDY 218MS401

4.1. INVESTIGATOR SCHEDULE OF ASSESSMENTS FOR OBSERVATIONAL STUDY 218MS401

	Enrollment	Follow-Up[b]	
Assessments[a] Visit	Baseline[c]	Baseline Until Month 12 Study Completion	Early Treatment/Study Discontinuation[d]
Informed consent	✔		
Assess eligibility	✔		
Demographics	✔		
Creatinine clearance (if serum creatinine is available)	✔	✔	✔
Urine culture (if available)	✔	✔	✔
Review medical history	✔		
EDSS assessment	✔		
Previous (past 6 months) and current treatment (if any) for underlying MS disease	✔		
Continuous concomitant procedures and medications	✔	✔	✔
Fampyra treatment (start and stop date, dose, indication, and reason for use)[e]	✔ [d]	✔	✔
Safety (SAEs, AEs leading to Fampyra dosage change or discontinuation, AEs experienced by the patient at the time of Fampyra overdose, instances of overdose, and AEs of particular interest)		✔	✔
Neurological assessment of walking		✔ [f]	
Physician's CGI-I of walking ability		✔ [g]	✔

a. Refer to Section 10 for details of study procedures.
b. Sites can collect data at any timepoint between Baseline and Month 12 either by telephone contact (except for the assessment of CGI-I) or during routine local clinical practice site visits.
c. Baseline assessments must occur prior to the first dose of Fampyra.
d. Patient can continue on study even after terminating treatment. If a patient is discontinued from the study, then both the End of Treatment and End of Study case report forms (CRFs) should be completed. If the patient discontinued treatment early, but continued in the study, then the End of Treatment CRF should be completed as soon as possible after terminating treatment, and the End of Study CRF should be completed at the conclusion of the study.
e. Information on previous exposure to any formulations of fampridine (i.e., 4-AP) prior to Enrollment/Baseline should be recorded.
f. At intervals indicated by local marketing authorization and clinical practice.
g. If decline in walking ability is observed, physicians should consider an interruption to treatment in order to reassess the benefits of Fampyra. The re-evaluation should include withdrawal of Fampyra and performing the walking test. Fampyra should be discontinued if patients no longer receive walking benefit.

4.2. PATIENT SCHEDULE OF ASSESSMENTS FOR OBSERVATIONAL STUDY 218MS401

	Enrollment	Follow-Up		
Assessment **Visit**	**Baseline[a]**	**At Regular Intervals[b]**	**Month 12: Study Completion**	**Early Treatment/Study Discontinuation**
MSIS-29	✔	✔	✔	✔

a. Baseline assessment must occur prior to the first dose of Fampyra.
b. To be completed up to 3 times prior to Study Completion.

5. INTRODUCTION

Fampyra® (fampridine-PR) is a prolonged-release formulation of the active drug substance 4-aminopyridine (4-AP; fampridine [International Nonproprietary Name]; dalfampridine [United States Adopted Name]). Fampridine is able to block certain voltage-gated K+ channels in neurons, particularly in demyelinated nerves. Blockade of repolarizing K+ currents can increase synaptic transmission throughout the nervous system by increasing the duration of the presynaptic action potential. Demyelinated nerves lose their ability to effectively conduct action potentials, and fampridine can help reverse this. This effect was demonstrated clinically in a proportion of multiple sclerosis (MS) patients who showed a significant improvement in motor function, specifically walking ability, with Fampyra treatment.

Fampridine-PR 10 mg every 12 hours or twice daily was approved in the United States (US) on 22 January 2010 as a treatment to improve walking in patients with MS under the brand name of Ampyra® (also known as dalfampridine-sustained-release [SR], fampridine-SR, dalfampridine-extended-release [ER], or fampridine-ER). It was also recently approved in Europe (20 July 2011) and Australia (May 2011) for the same indication under the brand name of Fampyra.

5.1. Profile of Previous Experience

Pharmacologically, the K^+ channel blocking properties of fampridine and its effects on action potential conduction in demyelinated nerve fiber preparations have been extensively characterized. At low concentrations that are relevant to clinical experience (in the range of 0.2 to 2 μM [18 to 180 ng/mL]), fampridine is able to block certain voltage-dependent K^+ channels in neurons. It is this characteristic that appears to explain the ability of the drug to restore conduction of action potentials in some critically demyelinated nerve fibers. At higher (millimolar) concentrations, fampridine affects other types of K^+ channels in both neural and non-neural tissues. Blockade of repolarizing K^+ currents may increase synaptic transmission throughout the nervous system by increasing the duration of the presynaptic action potential. A range of neurological effects consistent with increased excitability of nerve cells occurs with clinically relevant doses of fampridine.

Toxicology studies performed with fampridine included acute and repeated-dose toxicology studies, reproductive toxicity studies, genotoxicity studies, and carcinogenicity studies. Clinical signs evident after large, single, oral doses or repeated, lower, oral doses (and continuous intrathecal infusion in the dog) were similar in all species studied and were indicative of central nervous system activation (including tremors, convulsions, ataxia, dyspnea, dilated pupils, prostration, abnormal vocalization, increased respiration, excess salivation, gait abnormalities, and hyper- and hypo-excitability). These clinical signs are considered to represent exaggerated pharmacology of fampridine. It would appear that limiting toxicities would rule out any concerns regarding potential mutagenicity, carcinogenicity, or teratogenicity of fampridine.

During the Fampyra development program, more than 1900 subjects were exposed to fampridine in 57 clinical studies. The most frequent treatment-related adverse events (AEs) reported with fampridine in subjects with MS, as well as other populations, including subjects with spinal cord

injury, may be broadly categorized as excitatory effects in the nervous system, consistent with the K+ channel blocking activity of the compound in the nervous system. These AEs include dizziness, paresthesias, insomnia, balance disorders, anxiety, confusion, and seizure. In studies in MS patients, the following most frequent treatment-related AEs were also observed: urinary tract infection (UTI), asthenia, back pain, constipation, dyspepsia, and pharyngolaryngeal pain. At higher dose levels, more severe central nervous system AEs such as confusion and seizure have been seen. With the adoption of the 10 mg twice daily dose in extension studies, the rate of first seizure has been approximately 0.32 per 100 subject-years. This rate does not exceed the expected incidence of seizures in the MS population, particularly in the more advanced disease state with significant ambulatory disability [Eriksson 2002]. However, patients were excluded from these studies if they had a history of seizure or evidence of epileptiform activity on a screening electroencephalogram. Seizures have been seen in the postmarketing setting in the US, although confounding factors such as seizure history and use of concomitant medications that have been associated with a seizure risk may have contributed to the occurrence of seizures in some patients. No new safety signal has been detected as of March 2011.

Please refer to local Fampyra label, product information (PI), or prescription information, e.g., European Summary of Product Characteristics (SmPC) or Australian PI.

5.2. Study Rationale

Due to the inherent constraints of clinical trials, the existing Fampyra safety database established during the development phase has its limitations, for example, the number of patients aged ≥65 years was limited and patients with pre-existing cardiovascular risk factors were excluded from the studies. Therefore, understanding of safety issues in these patient subpopulations is limited. It is expected that these patients will be represented in this observational study to be conducted in postmarketing routine practice setting and will help understand the safety profiles in these subpopulations not yet fully studied during the development phase.

Specifically, premarketing clinical trials were not powered to evaluate the incidence of rare AEs, including seizure. This observational study is powered to detect a doubling in the incidence of seizures in the MS patient population to further assess if Fampyra treatment is associated with an increased seizure rate.

Furthermore, a 3.6% higher incidence of urinary tract symptoms (8.4% in placebo-treated patients versus 12.0% in Fampyra-treated patients) was observed based on data from 3 pooled premarketing placebo-controlled clinical trials; however, it is not fully understood if the event was a result of infection or sensory overstimulation. This study is also aimed to improve quantification of urinary tract symptoms as either culture-confirmed infection or culture-negative symptomatology.

6. STUDY OBJECTIVES AND OBSERVATIONAL POINTS

6.1. Objectives

6.1.1. Primary Objective

The primary objective of the study is to collect additional safety data including the incidence rate of seizure and other specific AEs of interest from patients taking Fampyra in routine clinical practice.

6.1.2. Secondary Objectives

The secondary objectives of this study are as follows:

- To characterize utilization patterns of Fampyra in routine clinical practice.
- To assess the effectiveness of risk minimization measures as described in the risk management plan for Fampyra.
- To assess the change over time in patient self-reported evaluation of the physical and psychological impact of MS while taking Fampyra.
- To assess the change over time in physician assessment of walking ability in patients taking Fampyra.

6.2. Observational Points

6.2.1. Primary Observational Point

AEs reported by the Investigator of the following categories:

- incidence of serious adverse events (SAEs)
- incidence of AEs leading to Fampyra dosage change or discontinuation
- incidence of AEs experienced by the patient at the time of Fampyra overdose (overdose is defined in Section 11.1.3)
- incidence of AEs of particular interest (refer to Section 11.2.2)

6.2.2. Secondary Observational Points

- Utilization patterns of Fampyra at participating sites, examined using the following variables:
  - demographics
  - medical history
  - underlying MS disease subtype
  - Expanded Disability Status Scale (EDSS) total score
  - previous (past 6 months) and current treatment, if any, for underlying MS disease
  - continuous concomitant procedures and medications, including herbals and nutraceuticals, (defined as a treatment administered regularly for 2 weeks or more)
  - reason for Fampyra use
  - dose and duration of Fampyra use
  - dosing deviations from the local Fampyra label, PI, or prescription information (e.g., European Union SmPC or Australian PI), including incidence of overdoses
  - reasons for dosage change or discontinuation of Fampyra treatment
  - date of neurological assessment of walking
- Physician's Clinical Global Impression of Improvement (CGI-I) of walking ability (Appendix A) [Guy 1976] assessed whenever a patient is seen by the neurologist
- Patient's assessment of physical and psychological impact of MS at each visit, using the Multiple Sclerosis Impact Scale-29 Items (MSIS-29) [Appendix B] [Hobart 2001]

7. STUDY DESIGN

7.1. Study Overview

This is a prospective, noninterventional, multicenter, observational study in patients who are beginning Fampyra treatment in the postmarketing setting. The decision to enroll a patient into this study will not be made until after the neurologist and patient have decided to begin Fampyra treatment and Fampyra has been prescribed.

The study will be conducted in postmarketing routine practice setting. The study will expand the number and spectrum of patients treated with Fampyra to be observed to help further understand the safety profiles of Fampyra in subpopulations not fully studied during the development phase, and to increase understanding of the specific safety issues described above. As such, this observational study will assess the effectiveness of risk minimization measures, as specified in the risk management plan for Fampyra.

Prescribing neurologists will be invited to participate in the study as Investigators. During the study, the Investigators should treat patients according to local clinical practice in line with the SmPC. Under the protocol, the Investigators are not required to perform any medical procedures that are outside of their normal clinical practice. Any cases of lack of efficacy or deterioration of a patient's health should be diagnosed and managed as per local guidelines.

Data will be collected at the Enrollment Visit (Baseline) and during the Follow-Up period (i.e., Baseline until approximately 1 year after Enrollment). Follow-Up visits should occur according to routine local clinical practice, with data collection possible at any timepoint during this period. A study site may consider a patient lost to follow-up after 3 failed documented contact attempts by the site staff (one of which must be a certified letter). Data to be collected for this noninterventional study are shown in Section 4.1 and Section 4.2. The study procedures are described in Section 10. All patient visits will be documented in the case report form (CRF).

7.2. Overall Study Duration and Follow-Up

The planned duration of observation for each patient is approximately 1 year. Patients who discontinue Fampyra, regardless of the reasons and time of discontinuation, will be encouraged to remain in the study for the full 1-year observation period, unless the patients withdraw consent to participate in the study.

7.3. Study Centers

Approximately 300 study centers will be initiated in multiple countries outside the US. Countries will be included based on the status of the marketing authorization and commercial availability of Fampyra.

The study will be proposed to neurologists based in secondary care settings or in private practice in the community as appropriate for individual countries.

7.4. End of Study

The end of study will be the last patient's last visit or telephone contact. Final statistical analysis will be performed once the database is locked.

8. PATIENT CHARACTERISTICS AND PRINCIPLES OF INCLUDING PATIENTS

8.1. Number and Characterization of Patients

Approximately 5000 MS patients who are prescribed Fampyra will be enrolled prior to initiation of their Fampyra treatment.

The decision to enroll a patient into the study will not be made until after the decision regarding therapy has been made and Fampyra has been prescribed.

8.2. Principles of Enrollment Into the Fampyra Observational Study

To be eligible to participate in this observational study, patients must fulfil the following eligibility criteria at the time of Enrollment:

1. Patients who have been newly prescribed Fampyra according to the terms of the marketing authorization, but who have not yet started treatment with Fampyra.
2. Patients who are willing and able to provide written informed consent.

8.3. Enrollment of Patients

The Investigators will be asked to invite eligible patients who are about to begin treatment with Fampyra to participate in the study.

Patients will be enrolled after the Investigator has verified that they are eligible per criteria in Section 8.2. At the Enrollment Visit, enrolled patients prescribed Fampyra will be assigned a unique patient identification number. This number will be used to track the patient throughout the study.

Any patient identification numbers that are assigned will not be reused even if the patient does not start Fampyra treatment.

An individual study patient may only be included once in the study. Patients who completed the study and patients who withdraw consent and/or complete the Early Treatment/Study Discontinuation Visit will not be eligible for re-enrollment.

9. TREATMENT OF PATIENTS

9.1. Fampyra Treatment

Fampyra is commercially available and is a prolonged-release tablet containing 10 mg active substance 4-AP and excipients.

Fampyra will not be supplied for this study. The Investigators will follow standard local procedures for prescribing commercial Fampyra. No reference therapies will be included in the study.

9.2. Fampyra Administration

The decision to administer commercially available Fampyra is the responsibility of the treating neurologist according to his/her medical judgment. The decision to treat a patient with Fampyra must be made prior to considering enrolling the patient into the study. Study neurologists (Investigators) are not required to perform any medical procedures that are outside of the local clinical practice or the prescribing information. Any cases of lack of efficacy or deterioration of a patient's health should be diagnosed and managed as per local PI. If decline in walking ability is observed, physicians should consider an interruption to treatment in order to reassess the benefits of Fampyra. The re-evaluation should include withdrawal of Fampyra and performing the walking test. Fampyra should be discontinued if patients no longer receive walking benefit.

9.3. Concomitant Therapies and Procedures

In addition to Fampyra, any other treatments or procedures that are considered necessary for the patient's welfare may be given at the discretion of the Investigator. Administration of continuous concomitant procedures and medications (including herbals and nutraceuticals) must be reported in the appropriate section of the CRF along with reasons for use. Continuous concomitant procedures and medications are defined as a treatment administered regularly for 2 weeks or more. The generic names for concomitant medications should be recorded, if possible. The total daily dose should be recorded in the CRF whenever possible.

9.4. Continuation of Fampyra Treatment

Following completion of the study, patients can continue to be treated with Fampyra according to normal clinical practice.

10. STUDY PROCEDURE

Following the decision to treat a patient with Fampyra, his/her suitability for enrollment into the study must be assessed according to the enrollment principles described in Section 8.2. Enrolled patients will undergo the assessments at Baseline and any timepoint during the Follow-Up period according to routine practice, as listed in Section 4.1 and Section 4.2 and defined below.

10.1. Enrollment (Baseline)

The Investigator will collect the following data at the Enrollment Visit (Baseline):

- assessment of eligibility for the Fampyra observational study
- informed consent for participating in the Fampyra observational study
- demographic data
- record creatinine clearance if serum creatinine is already available per normal practice (not specifically performed for the study)
- obtain urine culture (if available)
- medical history (in reference to the time prior to enrollment): assessment of clinically significant medical and surgical history and concomitant diseases (collected according to body system codes); known cardiovascular risk factors: the presence or absence of specific cardiovascular risk factors (e.g., conduction disorder, left-ventricular hypertrophy, coronary heart disease, hypertension, alcohol abuse, stress, smoking); MS disease classification
- assessment and recording of EDSS [Kurtzke 1983]
- previous (past 6 months) and current treatment (if any) for the underlying MS disease: use and duration including, but not limited to, disease-modifying, antineoplastic, or other immunosuppressive medications and systemic steroids
- continuous concomitant procedures and medications, including herbal preparations and nutraceuticals (defined as a treatment used regularly for ≥2 weeks)
- Fampyra treatment: dose, indication, reason for use, and start date (if started on the day of enrollment, otherwise record start date at the next visit). Information on previous exposure to any formulations of fampridine prior to Enrollment should be recorded.
- patient assessment of physical and psychological impact of MS using MSIS-29

10.2. Postenrollment Follow-Up

Data will be collected during the Follow-Up period: approximately 1 year after Enrollment. Follow-Up visits should occur according to clinical practice, with data collection possible at any timepoint during this period, either by telephone contact (except CGI-I) or during routine local clinical practice site visits. The following data will be collected during this period:

- record creatinine clearance if serum creatinine is already available per normal practice (not specifically performed for the study)
- obtain urine culture (if available)
- status of treatment with Fampyra: dose, start and stop date (if applicable), and date of dosage change or interruption, or date of discontinuation
- changes in continuous concomitant therapies
- SAEs, AEs leading to Fampyra dosage change or discontinuation, AEs experienced by the patient at the time of Fampyra overdose, instances of overdose, and AEs of particular interest (see Section 11.2.2)
- Physician's CGI-I of walking ability (needs to be assessed during clinical visit, not by telephone)

A neurological assessment of walking may be conducted, in line with the SmPC or other local prescribing information.

Additionally, MS patients will be asked to complete assessments of physical and psychological impact of MS using MSIS-29.

Throughout the study, female patients of childbearing potential should be asked about their pregnancy status and possible pregnancies/spontaneous abortions since their last consultation with their neurologist. See Section 11.2.5 for reporting pregnancies/spontaneous abortions.

Data will be collected as above for all patients, including those who are followed up after early discontinuation of Fampyra treatment (see Section 7.2).

10.3. Treatment/Study Discontinuation Visit

If a patient's participation in the Fampyra observational study is discontinued early, the Investigator must make every attempt to contact the patient in order to collect information specified in Early Treatment/Study Discontinuation Visit in Section 4.1 and Section 4.2. Patients can continue on study even after terminating treatment. If a patient is discontinued from the study, then both the End of Treatment and End of Study CRFs should be completed. If the patient discontinued treatment early, but continued in the study, then the End of Treatment CRF should be completed as soon as possible after terminating treatment, and the End of Study CRF should be completed at the conclusion of the study.

10.4. Lost to Follow-Up

A site may consider a patient lost to follow-up after 3 failed documented contact attempts, one of which must be a certified letter.

10.5. Replacements

Study patients who prematurely discontinue participation will not be replaced.

10.6. Patient Transfers

Study patients who change their place of residence may continue follow-up with a participating clinical site close to their new location, if one is available. This applies to both permanent moves and extended stays away from home such as college attendance or long-term job assignments that are expected to last for the remaining duration of follow-up.

10.7. Data Handling

Whenever possible, an electronic CRF will be used to store and transmit patient information. Access to electronic CRFs will be strictly password protected and limited to personnel directly participating in the study. The file structure and format for the CRF will be provided by Biogen Idec or their representative and should be handled in accordance with the instructions provided.

The CRF must be completed as soon as possible after any patient evaluation or communication. If data need to be changed due to erroneous input or for other reasons, an electronic audit will track these changes. The CRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

The CRF must be reviewed, signed (electronically, if appropriate), and dated by the Investigator.

11. SAFETY DEFINITIONS, MONITORING, AND REPORTING

Throughout the course of the study, every effort must be made to remain alert to possible SAEs, AEs leading to dosage change or discontinuation of Fampyra, AEs experienced by the patient at the time of Fampyra overdose, instances of overdose (even without an AE), and AEs of particular interest (see Section 11.2.2).

11.1. Definitions

11.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

11.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- results in death
- in the view of the Investigator, places the patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event that, in the opinion of the Investigator, may jeopardize the patient 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 inpatient hospitalization.)

For the purpose of this study, all seizures and spontaneous abortions will be considered SAEs.

11.1.3. Overdose

An overdose is any dose of Fampyra given to a patient or taken by a patient that exceeds the dose described in the local Fampyra label, PI, or prescription information. All incidences of overdose, with or without any symptoms or signs, will be recorded. Symptoms or signs experienced by the patient at the time of overdose will be reported as AEs (see AE categories to be reported in Section 11.2.2).

11.2. Monitoring and Recording Events

11.2.1. Serious Adverse Events

Regardless of whether the patient continues on Fampyra treatment or not, any SAE experienced by an enrolled patient between the time of the first dose of Fampyra and Study Completion (approximately 1 year after the first dose) or Early Study Discontinuation Visit is to be recorded on the SAE form, regardless of the severity of the event or its relationship to Fampyra treatment. For reporting timelines and procedures, see Section 11.2.4.

11.2.2. Adverse Events

The Investigators should review all AEs and record the following events in the CRF:

- SAEs (including all seizures and spontaneous abortions)
- AEs leading to Fampyra dosage change or discontinuation
- AEs experienced by the patient at the time of Fampyra overdose
- AEs of particular interest
  - symptoms of UTI, including results of urine culture where possible
  - depression and suicide attempt
  - cardiac disorders
  - severe infections other than UTI
  - anxiety
  - events suggestive of central nervous system stimulation (insomnia, dizziness, paresthesia, balance disorder, dyskinesia, falls, anxiety, sleep disorder, agitation, psychosis, hallucinations, tremor, trigeminal neuralgia, neuralgia, dysesthesia, sensory disturbance, muscle spasms, muscle twitching, and irritability)
  - clinically significant hematologic abnormalities

All other non-serious AEs will not be collected as part of this study and should follow spontaneous postmarketing reporting rules as per local regulations.

11.2.3. All Events

Regardless of whether the patient continues on Fampyra or not, any AE as defined in Section 11.2.2 experienced by a patient between the time of first dose of Fampyra and Study Completion or Early Study Discontinuation Visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment.

All events must be assessed to determine the following:

- whether the event meets the criteria for an SAE as defined in Section 11.1.2
- the relationship of the event to Fampyra treatment as defined in Section 11.3.1
- the outcome of the event

11.2.4. Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Quintiles as soon as possible, within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

Any Serious Event that occurs between the time of first dose of Fampyra and Study Completion or Early Study Discontinuation Visit must be reported to Quintiles as soon as possible, within 24 hours of the study site staff becoming aware of the event.

A report ***must be submitted*** to Quintiles regardless of the following:

- the severity of the SAE; and
- the relationship of the event to Fampyra treatment.

To report initial or follow-up information on a Serious Event, the SAE form must be faxed to the local Quintiles office. The fax number is provided in the Study Reference Manual.

11.2.5. Reporting Pregnancy and Coordination With the Pregnancy Registry

Throughout the study, female patients of childbearing potential should be asked about their pregnancy status and possible pregnancies/spontaneous abortions since their last consultation with their neurologist.

If female patients become pregnant at any time during the Fampyra observational study period, the Investigator or site staff must report the pregnancy to Quintiles as soon as possible and provide follow-up report(s) of pregnancy outcomes.

A Fampyra pregnancy registry is being conducted independently of the Fampyra observational study, and all pregnant women taking Fampyra (regardless of participation in any studies) will be offered participation in the Fampyra pregnancy registry. Pregnant women may be dually enrolled into Fampyra observational study and the pregnancy registry.

Please note that congenital abnormalities/birth defects in the offspring of male or female patients should be reported as an SAE if conception occurred during the Fampyra treatment period.

11.3. Classification of Events

11.3.1. Relationship of Events to Fampyra Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the Fampyra treatment:

Relationship of Event to Fampyra Treatment	
Not related	An AE will be considered "not related" to the use of Fampyra if there is not a possibility that the event has been caused by Fampyra. 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 AE (e.g., the event occurred before administration of the drug), or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of Fampyra if there is a possibility that the event may have been caused by Fampyra. Factors that point toward this assessment include, but are not limited to, a positive rechallenge, 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 AE, or a lack of an alternative explanation for the AE.

12. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

12.1. Statistical Analysis Plan

Statistical analyses will be exploratory and descriptive in nature. Details of the analyses to be carried out will be included in the statistical analysis plan.

12.2. Patient Population

All patients who are enrolled into the study and receive at least 1 dose of Fampyra will be included in the safety population and used for all analyses.

12.3. Baseline Patient Characteristics

Descriptive statistics (i.e., mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables. Counts and percentages will be provided for categorical variables.

12.4. Safety Analysis

Safety information recorded will be coded using the most recent version of the Medical Dictionary for Regulatory Activities available at the time of study start.

Safety data will be analyzed to detect any potential new and unexpected safety signals and to further evaluate any AEs of particular interest (Section 11.2.2). All safety summaries will be presented for the safety population.

The number and percentage of patients with SAEs, AEs leading to Fampyra dosage change or discontinuation, and other reported events will be presented by System Organ Class and Preferred Term along with the relationship to Fampyra. The incidence of AEs experienced by the patient at the time of Fampyra overdose and AEs of particular interest will also be summarized by System Organ Class and Preferred Term.

The incidence of SAEs and other events will be summarized for the safety population by age group (≥65 years and <65 years) and compared to published data and other sources.

In addition, the rates (number of events per person-year of exposure) of AEs leading to discontinuation of Fampyra, SAEs, and AEs of particular interest (e.g., seizures) will be calculated.

Drug Utilization

The pattern of Fampyra use (dose and duration) will be summarized descriptively. The underlying disease subtype, dosage change, or discontinuation will also be summarized. Additionally, dosing deviations from the local Fampyra label, PI, or prescription information (including incidence of overdoses) will be summarized.

Risk Minimization

The number and percentage of patients with a neurological assessment of walking within 14 days after the start of dosing with Fampyra will be presented to assess whether appropriate follow-up of effectiveness was performed.

Adherence to contraindications will be assessed by review and summaries of data (i.e., medical history, creatinine clearance at baseline and concomitant medications). Summaries of AEs of particular interest will also be summarized by whether there was a relevant contraindication.

12.5. Other Observational Points

Summary statistics at each timepoint, as well as changes from baseline over time, will be presented for the MSIS-29 physical and psychological scores for measuring patient impression of impact of MS. Summary statistics over time will be presented for the Physician's CGI-I score for walking ability.

12.6. Interim Analyses

No formal interim analyses are planned. Safety data will be analyzed at least annually once enrollment has begun. Summary reports will be submitted annually with Fampyra Periodic Safety Update Reports (PSURs). Early identification of any potential safety signals to elderly patients will be evaluated by reviewing adverse drug reactions for patients aged 65 years or older. These data will be reviewed as they are received on the safety database and will be further assessed in the periodic (i.e., monthly) signal review and as part of the PSUR.

12.7. Sample Size Considerations

12.7.1. Patient Sample Requirement

This study is exploratory in nature, and no confirmatory statistical testing will be performed.

Seizures

In a cohort study of MS patients with a known background incidence rate of seizures of 0.003 per patient-year [Eriksson 2002], a sample of 3308 patients has 80% power to detect a doubling of the seizure rate when the significance level is 0.05.

Cardiac Conduction Disorders

Information on cardiac conduction disorders in the MS population is limited, but the prevalence rate of arrhythmias and conduction disorders in MS patients aged 65 years and older was reported in a study to be 1% [Fleming and Blake 1994]. If this rate is used as background incidence, a sample of 3308 patients has 99% power to detect an incidence of 2% of arrhythmias and conduction disorders over 1 year of follow-up.

The most recent publication on cardiovascular outcomes in MS patients was used to determine the background rate of atrial fibrillation [Christiansen 2010] (0.1% for atrial fibrillation/flutter). A sample size of 3308 patients has 46% power to detect a 2-fold increase in atrial fibrillation over 1 year of follow-up.

Background rates are not readily available for the other events based on the safety profile in the clinical development program; thus, power calculations are not feasible.

Based on the assumption that approximately 34% of patients will drop out or discontinue treatment, at least 5000 MS patients will be enrolled to ensure 3308 evaluable patients treated for 1 year. The maximum number of patients to be enrolled can be adjusted on an ongoing basis to reflect the dropout rate.

13. ETHICAL REQUIREMENTS

Biogen Idec and the Investigators agree to comply with this protocol and to conduct the Fampyra observational study in accordance with Good Pharmacoepidemiology Practices, local national laws and regulations applicable to noninterventional studies, and Volume 9A of The Rules Governing Medicinal Products in the European Union (in European Economic Area countries). The patient's privacy, physical and mental integrity, and his/her personality and confidentiality will be strictly respected in accordance with the World Medical Association Declaration of Helsinki.

13.1. Ethics Committee

As regulations for observational studies differ among participating countries, Competent Authorities and Independent Ethics Committees (IECs) will be consulted as dictated by local country regulations.

If an IEC vote is required per local regulations, the Investigator/institution must have written and dated approval/favorable opinion from the IEC for the study protocol/amendment(s), written data consent form, and any data consent form updates before initiating a study. The IEC approval must identify the protocol version as well as the documents reviewed.

13.2. Patient Information and Consent

Prior to any data collection under this protocol, the patient, in accordance with local practice and regulations, must sign a written informed consent. Information about the Fampyra observational study will be explained to the patient. Data will be collected during the year of observation. A copy of the informed consent form, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must be documented in the patient's medical record prior to any data collection under this protocol. The approved informed consent form must not be altered without the prior agreement of the relevant ethics committee and Biogen Idec.

In order to ensure patient confidentiality, patients will be assigned a unique identifying number. The transmitted data sets use this identifying number plus partial date of birth but are otherwise anonymous.

In any presentations or in publications of the Fampyra observational study results, the patients' identities will remain anonymous and confidential. Biogen Idec, its designee(s), and various government health agencies may inspect the records of the Fampyra observational study. Every effort will be made to keep the patients' personal medical data confidential.

13.3. Registration of Study and Disclosure of Study Results

Biogen Idec will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

14. ADMINISTRATIVE PROCEDURES

14.1. Quality Assurance

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

14.2. Monitoring of the Study

Biogen Idec or designee representatives may conduct onsite visits to the study facilities for the purpose of monitoring various aspects of the study. The Investigator must agree to Sponsor-authorized personnel having direct access to the patient (or associated) files for the purpose of verifying entries made in the CRF, and assist with their activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigators or study staff.

The site must complete the CRFs in a timely manner and on an ongoing basis to allow regular review by the study team.

14.3. Confidentiality

All information obtained during the conduct of the study with respect to the patient's state of health will be regarded as confidential. The Investigator must ensure that each patient's anonymity is maintained. On CRFs and other documents submitted to Biogen Idec or the Contract Research Organization (CRO), patients must not be identified by name. Instead, patients will only be known by the unique patient number allocated to them in order to ensure confidentiality on all study documentation. Patients will retain this unique number throughout the study. The Investigators will keep a separate log of these codes. For disclosure of any confidential information, an agreement will be obtained in writing.

Documents that are not for submission to Biogen Idec or the CRO (e.g., consent forms) will be maintained by the Investigators in strict confidence, except to the extent necessary to allow monitoring by Biogen Idec and the CRO, and auditing by Competent Authorities. Patient identity will remain confidential in all publications related to the study.

14.4. Study Funding

Biogen Idec is the Sponsor of the study and is funding the study. All financial details are provided in the separate contract(s) between the institution, Investigator, and Biogen Idec.

14.5. Publications

Details are included in the clinical trial agreement for this study.

15. FURTHER REQUIREMENTS AND GENERAL INFORMATION

Biogen Idec or designee will be responsible for all administrative aspects of this study including, but not limited to, study initiation, monitoring, management of AEs, and data management.

15.1. External Contract Organizations

15.1.1. Contract Research Organization

Quintiles (CRO) will be responsible for administrative aspects of the study including, but not limited to, study initiation, monitoring, management of SAE reports, and data management. Before patients are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

15.1.2. Electronic Data Capture

Study data will be captured and managed by study sites on electronic CRFs by a web-based electronic data capture tool, which will be formally reviewed and approved by Biogen Idec and Quintiles.

15.2. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and Regulatory Authorities if required by local law. Protocol modifications that affect patient safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

15.3. Study Report Signatory

A final study report will be completed after study end. The final study report will be prepared regardless of whether the study is completed or prematurely terminated. Biogen Idec will provide all Investigators with a summary of the final results. The final study report will be submitted to the regulatory authorities in accordance with applicable regulatory requirements.

16. REFERENCES

Christiansen CF, Christensen S, Farkas DK, et al. Risk of arterial cardiovascular diseases in patients with multiple sclerosis: a population-based cohort study. Neuroepidemiology. 2010;35(4):267-74.

Eriksson M, Ben-Menachem E, Andersen O. Epileptic seizures, cranial neuralgias and paroxysmal symptoms in remitting and progressive multiple sclerosis. Mult Scler. 2002;8(6):495-9.

Fleming ST, Blake RL. Patterns of comorbidity in elderly patients with multiple sclerosis. J Clin Epidemiol. 1994;47(10):1127-32.

Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: U.S. Department of Health, Education, and Welfare; 1976.

Hobart J, Lamping D, Fitzpatrick R, et al. The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. Brain. 2001;124(Pt 5):962-73.

Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444-52.

17. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter, Multinational, Observational Study to Collect Information on Safety and to Document the Drug Utilization of Fampyra When Used in Routine Medical Practice," Version 3, and agree to conduct the study according to the protocol and the applicable International Conference on Harmonisation guidelines and Good Clinical Practice regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

APPENDIX A. PHYSICIAN'S CLINICAL GLOBAL IMPRESSION-IMPROVEMENT (CGI-I) SCALE ON WALKING ABILITY

The Clinical Global Impression-Improvement (CGI-I) scale is a 7-point scale that requires the clinician to rate the improvement or worsening of the overall walking ability of the patient relative to a baseline state at the beginning of Fampyra treatment as follows.

How much has the patient's overall walking ability improved or worsened relative to a baseline status at the beginning of Fampyra treatment?

1 = very much improved

2 = much improved

3 = minimally improved

4 = no change

5 = minimally worse

6 = much worse

7 = very much worse

Adopted and modified based on CGI [Guy 1976].

APPENDIX B. THE MULTIPLE SCLEROSIS IMPACT SCALE (MSIS-29)

MS IMPACT SCALE (MSIS-29)
US English translation of the MSIS-29 v1

- The following questions ask for your views about the impact of MS on your day-to-day life **during the past two weeks**
- For each statement, please **circle** the **one** number that **best** describes your situation
- Please answer **all** questions

In the past two weeks, how much has your MS limited your ability to …	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4	5
2. Grip things tightly (e.g. turning on faucets)?	1	2	3	4	5
3. Carry things?	1	2	3	4	5

In the past two weeks, how much have you been bothered by …	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
4. Problems with your balance?	1	2	3	4	5
5. Difficulties moving around indoors?	1	2	3	4	5
6. Being clumsy?	1	2	3	4	5
7. Stiffness?	1	2	3	4	5
8. Feelings of heaviness in your arms or legs?	1	2	3	4	5
9. Tremors in your arms or legs?	1	2	3	4	5
10. Spasms in your arms or legs?	1	2	3	4	5
11. Your body not doing what you want it to do?	1	2	3	4	5
12. Having to depend on others to do things for you?	1	2	3	4	5

Please make sure that you have answered all the questions before going on to the next page. **1**

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In the past two weeks, how much have you been bothered by …	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
13. Limitations in your social and leisure activities at home?	1	2	3	4	5
14. Being stuck at home more than you would like to be?	1	2	3	4	5
15. Difficulties using your hands in everyday tasks?	1	2	3	4	5
16. Having to cut down on the amount of time you spent on work or other daily activities?	1	2	3	4	5
17. Problems using transportation (e.g. car, bus, train, taxi, etc.)?	1	2	3	4	5
18. Taking longer to do things?	1	2	3	4	5
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4	5
20. Needing to go to the bathroom urgently?	1	2	3	4	5
21. Feeling unwell?	1	2	3	4	5
22. Problems sleeping?	1	2	3	4	5
23. Feeling mentally fatigued?	1	2	3	4	5
24. Worries related to your MS?	1	2	3	4	5
25. Feeling anxious or tense?	1	2	3	4	5
26. Feeling irritable, impatient, or short tempered?	1	2	3	4	5
27. Problems concentrating?	1	2	3	4	5
28. Lack of confidence?	1	2	3	4	5
29. Feeling depressed?	1	2	3	4	5

Please make sure that you have circled ONE number for EACH question. 2

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[Hobart 2001]