Title page:

PROTOCOL NUMBER: SVUHneuro002

PHASE OF DEVELOPMENT: 4

PROTOCOL TITLE:
A double blind, randomized, placebo controlled, crossover study of the effectiveness of oral fampridine in improving upper limb function in progressive multiple sclerosis.

VERSION: 2.1

DATE: 3rd February 2013

Department of Neurology,
St. Vincent's University Hospital,
Elm Park,
Dublin 4,
Ireland

2.0 APPLICATION DETAILS

2.1 STUDY TITLE

A double blind, randomized, placebo controlled, crossover study of the effectiveness of oral fampridine in improving upper limb function in progressive multiple sclerosis.

2.2 REFERENCE NUMBERS

Protocol identification (code or reference number): SVUHneuro002
EudraCT number: 2011-002561-38
Date and version number: Version2.1/Feb2013

2.3 APPLICANT DETAILS

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2.4 SIGNATURES

Sponsor's Signature…….Date……
Sponsor: Dr Peter Doran, Scientific Director, Clinical Research Centre, University College Dublin

Principle Investigator……..Date……
Principle Investigator: Christopher McGuigan, St. Vincent's University Hospital, Dublin

2.5 OTHER RELEVANT INFORMATION

3.0 CONFIDENTIALITY STATEMENT

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigative team, regulatory authorities, and members of the Research Ethics Committee.

4.0 TABLE OF CONTENTS

5.0 DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Protocol Version 2.1	03.02.2013	1.Defined walking speed removed from inclusion criteria 2. Additional questionnaire on upper limb function added (AMSQ).
Protocol Version 2.0	28.03.2012	Formatted IMB specification
Original Protocol	02.01.2012	Not applicable

6.0 SYNOPSIS

Title of study	A double blind, randomized, placebo controlled, crossover study of the effectiveness of oral fampridine in improving upper limb function in progressive multiple sclerosis.
Name of sponsor/company	St. Vincent's University Hospital, Dublin
Phase of development	IV
Objectives	Primary Aims: To assess the effect of treatment with fampridine in patients with secondary progressive MS (SPMS) or primary progressive MS (PPMS) with upper limb dysfunction (as defined by a 9-HPT time of between 15-90 seconds) and Kurtzke EDSS scores in the range 4.0-7.0 on upper limb function assessed by the nine-hole peg test (9-HPT) and the Jebson Taylor Hand Function Test (JTT). Secondary aims: To assess the effect of treatment with fampridine on walking mobility assessed by the Timed 25 foot Walk (T25FW) and the Multiple Sclerosis Walking Scale (MSWS-12). To determine whether response or non-response to fampridine by the T25FW can be easily determined using self reported changes in the MSWS-12 alone within 4 weeks in the course of active therapy. To determine whether response or non-response to fampridine by the 9HPT or JTT can be easily determined using self reported changes in the DASH and AMSQ alone within 4 weeks on the course of active therapy. To determine whether any relation exists between improvement / lack of improvement on the T25FW and improvement/ lack of improvement on the 9-HPT or JTT. To examine the safety of fampridine in this patient population. To assess the impact of fampridine on health related quality of life in patients with multiple sclerosis (HRQOL) as measured by the SF-36 questionnaire.
Trial design	Crossover, randomized, double blind, placebo-controlled trial.
Key inclusion criteria	Patients with SPMS or PPMS, male and female, aged 18-70, who have Kurtzke EDSS scores in the range 4.0 to 7.0 inclusive and evidence of significant upper limb dysfunction as defined by a 9HPT of 15 – 90 seconds (dominant or non-dominant hand), will be recruited. Women in reproductive years will be required to use barrier or hormonal methods of contraception.

Key exclusion criteria	Patients with a history of seizures, significant liver dysfunction, renal dysfunction, significant upper or lower limb arthritis or any other disorder including cognitive dysfunction which would affect the ability to accurately complete questionnaires and give full informed consent. Patients with clinically significant upper limb ataxia or upper limb proprioceptive sensory loss, which in the opinion of the Clinician affect upper limb functional assessment. Patients concomitantly using medicinal products that are inhibitors of Organic Cation Transporter 2 (OCT2). Patients on concurrent treatment with other medicinal products containing fampridine (4-aminopyridine). Pregnant or breast-feeding patients.
Number of subjects	80
Test product, dose and mode of administration	Oral PR-Fampridine 10mg b.d Oral Placebo one tablet b.d.
Duration of treatment	Two 8 week treatment periods
Statistical methods	Participants will be classified as to whether they are “responders” or “non-responders” by the 9-HPT and the T25FW according to defined criteria. Change in the MSWS-12, the MSIS-29 (physical) and the DASH and AMSQ in responders and non-responders will be examined by the Wilcoxin Signed Rank test to assess the significance of the mean differences between groups.
Sample size	80

7.0 ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CA	Competent authority
CI	Chief investigator/Co-ordinating investigator
CRF	Case report form
CRO	Contract research organisation
CT	Clinical trial
CTA	Clinical trial authorization
DASH	Disabilities arm, shoulder, hand questionnaire
ECG	Electrocardiogram
EDSS	Expanded Disability Status Scale
EU	European Union
e-CRF	Electronic case report form
GCP	Good Clinical Practice
GP	General Practitioner
9-HPT	Hole Peg test
IB	Investigators brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMB	Irish Medicines Board
IMP	Investigational medicinal products
IMPD	Investigational medicinal product dossier
HSE	Health Service Executive
JTT	Jebson Taylor Hand Function Test
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale 29
MSWS-12	Multiple Sclerosis Walking Scale
OCT-2	Organic Cation Transporter 2
PI	Principal investigator
PIL	Patient/subject information leaflet
PPMS	Primary Progressive MS
REC	Research ethics committee
ROI	Republic of Ireland
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPMS	Secondary Progressive MS
SVUH	St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland
SUSAR	Suspected unexpected serious adverse reaction
T25FW	Twenty-five foot timed walk

8.0 INTRODUCTION

8.1 BACKGROUND INFORMATION

Patients with secondary progressive MS (SPMS) and primary progressive MS (PPMS) have significant walking disability and impaired upper limb function due to repeated demyelination and axonal injury affecting the corticospinal pathways. In some patients this motor deficit may be predominantly due to demyelination resulting in motor conduction slowing and/or block which is potentially reversible by blocking potassium channels of demyelinated axons. Fampyra® (fampridine-PR) is a prolonged-release formulation of the active drug substance 4-aminopyridine {4-AP; fampridine [International Nonproprietary Name (INN)]. Fampridine is able to block certain voltage-gated K+ channels in neurons, particularly in demyelinated nerves. Blockade of repolarising 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 (BID) was approved in Europe (20 July 2011) for this indication under the brand name of Fampyra®.

8.2 RATIONALE FOR THE STUDY

Treatment with fampridine (4-aminopyridine), a potassium channel blocker,[1,2] has been shown to cause significant improvement in walking speed in one third of MS patients with motor disability.[3-5] In those patients who respond, approximately a 25% improvement in walking speed was obtained with a self-reported 7 point improvement in the Multiple Sclerosis Walking Scale (MSWS-12), a patient-rated measure of walking quality and ability, [6,7] in comparison to non-responding patients and placebo control subjects.

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 repolarising 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, 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 BID 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[18]. 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 post marketing 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.

The FDA has recently approved Fampridine, a slow release preparation, for use in the MS patient population.[8] It has also recently been approved in Europe (20th July 2011).[17] Most studies of fampridine assessed timed walking over twenty-five feet and the Multiple Sclerosis Walking Scale-12 (MSWS-12).[3-5] Deficits in arm and hand function are commonly found in patients with SPMS and PPMS and can have an impact in performing many activities of daily living. We propose to examine the efficacy of fampridine in upper limb function and in overall disease impact in a single centre, double blind, randomized, placebo-controlled, crossover study of patients attending St Vincent's University Hospital with significant walking and upper limb disability due to SPMS and PPMS.

9.0 STUDY OBJECTIVE

The objective of this study is to assess the affect of PR-fampridine medication compared to placebo for upper limb function in patients with progressive multiple sclerosis

9.1 PRIMARY OBJECTIVE

The primary objective is to assess the effect of treatment with oral PR-fampridine in patients with secondary progressive MS (SPMS) or primary progressive MS (PPMS) with upper limb dysfunction (as defined by a 9-HPT time of between 15-90 seconds) and Kurtzke EDSS[14] scores in the range 4.0-7.0 on Upper limb function assessed by the nine-hole peg test (9-HPT) and the Jebson Taylor Hand Function Test (JTT). Scores of the MSIS-29 (physical), MSWS-12 and the Disabilities of the Arm, Shoulder and Hand Score (DASH)[10] and the Arm Function in Multiple Sclerosis Questionnaire (AMSQ)[19].

9.2 SECONDARY OBJECTIVE

Secondary objectives are:

To assess the effect of treatment with fampridine on walking mobility assessed by the Timed 25 foot Walk (T25FW) and the Multiple Sclerosis Walking Scale (MSWS-12)[6,7]

To determine whether response or non-response to fampridine by the T25FW can be easily determined using self reported changes in the MSWS-12 alone within 4 weeks in the course of active therapy
To determine whether response or non-response to fampridine by the 9HPT or JTT can be easily determined using self reported changes in the DASH and AMSQ alone within 4 weeks on the course of active therapy
To determine whether any relation exists between improvement / lack of improvement on the T25FW and improvement/ lack of improvement on the 9-HPT or JTT.
To examine the safety of fampridine in this patient population
To assess the impact of fampridine on health related quality of life in patients with multiple sclerosis (HRQOL) as measured by the SF-36 questionnaire.

9.3 EXPLORATORY OBJECTIVES

None

9.4 PRIMARY AND SECONDARY/ EXPLORATORY ENDPOINTS/OUTCOME MEASURES

Primary endpoint:
The primary end point will be identifying an upper limb responder to fampridine defined as a patient with both of the two "on treatment" 9-HPT assessments (assessments 4 & 5 or 7 & 8) improving 20% from the average of the baseline assessments (1, 2 & 3).

Secondary endpoints:
A secondary measure of upper limb responsiveness will be defined as a 20% improvement in from baseline in the average time taken to complete all seven tasks on the JTT "on treatment" (assessments 4 & 5 or 7 & 8) compared with baseline assessments (assessments 1,2 & 3).
A mobility responder to Fampridine will be defined as a patient with both of the two "on treatment" T25FW assessments (assessments 4 & 5 or 7 & 8) being better than the maximum of any of the four "off treatment" assessments (assessments 1, 2, 3, & 9). Otherwise the patient will be deemed a non-responder.
The responders to the 9-HPT and/or JTT will be compared to the non-responders in relation to their changes in the DASH and AMSQ on treatment and off treatment at the baseline assessment. The change in the DASH and AMSQ in responders at Assessment 5 or 8 (week 10 or 20) will be compared to non-responders at that time-point.
Upper limb response will be examined at the end of treatment phase 1 and repeated at the end of the trial by comparing patients receiving active drug with those receiving placebo to assess any placebo effect and allow assessment of any residual beneficial effect on those who receive fampridine in treatment phase 1 and then switch to placebo in treatment phase 2. Response will again be considered as a 20% improvement in the 9HPT in the active treatment group compared with placebo and a 20% improvement from baseline in the time taken to complete all seven tasks in the JTT. See earlier comment
The responders to the T25FW will be compared to the non-responders in relation to their changes in the MSWS-12 on treatment and off treatment at the baseline assessment. The change in the MSWS-12 in responders at Assessment 5 or 8 (week 10 or 20) will be compared to non-responders at that time-point.
The patients' scores on the MSIS-29 (physical) and SF-36 will be examined in relation to the objective changes (responder/non-responder) in the 9-HPT, JTT and the T25FW.

10.0 TRIAL DESIGN

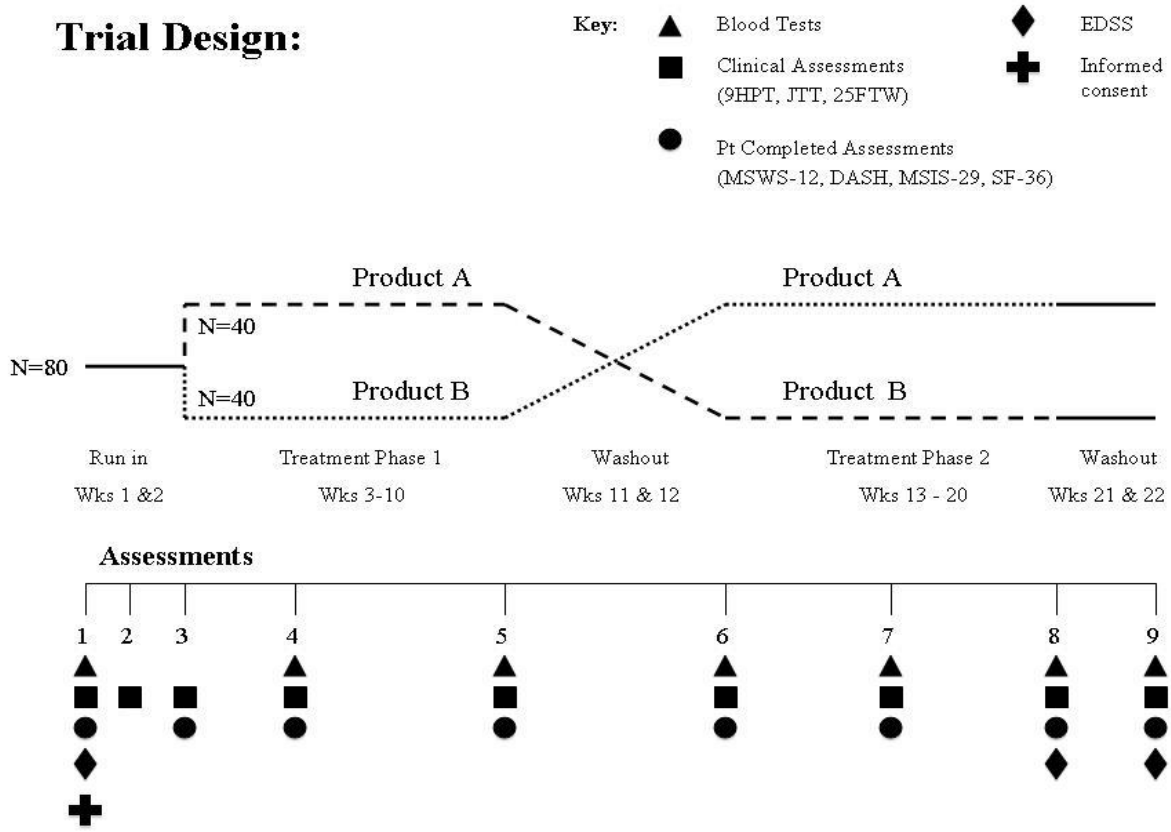
10.1 GENERAL CONSIDERATIONS

This will be a single centre, phase IV, double blind, randomized, placebo controlled, crossover study on the effectiveness of oral Fampridine-PR 10mg tablets BID on upper limb function for patients with progressive multiple sclerosis.

The trial will consist of a two week run in period followed by an eight week treatment period were enrolled subjects will be randomised to receive either study drug or placebo in a double blinded manner. This will be followed by a two-week wash out period followed by a further eight-week study period using active drug or placebo. There will be a two-week washout period at the end of the study. The total period of the study will be 22 weeks.

Each subject will attend for a screening visit and 8 assessment visits (total number of visits, 9).

Figure 1: Study Schema



10.2 SELECTION OF STUDY POPULATION

Overall description of trial subjects

The study will recruit male and female patients between the ages of 18 – 70 years with clinically definite primary or secondary progressive multiple sclerosis. Patients will be identified in and recruited from the multiple sclerosis clinics in St. Vincent's University Hospital, Dublin, Ireland.

Inclusion criteria

To be eligible for inclusion, each subject must meet each of the following criteria at Screening (Visit and must continue to fulfill these criteria at Baseline (Visit 2).

Subjects must be able and willing to give written informed consent and to comply with the requirements of this study protocol
Subjects must be diagnosed with clinically definite SPMS or PPMS and be judged to be in generally good health by the investigator based upon the results of the medical history, laboratory tests (liver and renal function), physical examination, 12-lead electrocardiogram performed during Screening
Subjects must be Male or female aged 18-70 at baseline
Kurtzke EDSS scores in the range 4.0 to 7.0 inclusive
Evidence of significant upper limb dysfunction as defined by a 9HPT of 15 – 90 seconds (dominant or non-dominant hand)
Female subjects with reproductive capabilities must have a negative serum pregnancy test at baseline and agree to using an acceptable form of contraception for the duration of the study (barrier, coil or oral contraceptives only).

Exclusion criteria

Subjects are excluded from the study if any of the following criteria are met at Screening (Visit 1) or at Baseline (Visit 2):

- Allergy/sensitivity to study medications or their ingredients
- Female subjects who are pregnant or breast-feeding or considering becoming pregnant during the study.
- Subjects unable to provide written informed consent
- Subjects with a history of epilepsy or previous seizures (including provoked seizures).
- Subjects who have a history of drug or alcohol use that, in the opinion of the investigator, would interfere with adherence to study requirements.
- Subjects with an AST or ALT $\geq$ 3 x ULN on liver function tests
- Subjects have clinically significant ECG findings as judged by the investigator, in particular evidence of a cardiac conduction defect.
- Significant upper or lower limb arthritis as considered by the investigator to interfere with study assessments.
- Significant cognitive impairment as considered by the investigator to interfere with study assessments

- Subjects with clinically significant upper limb ataxia considered by the investigator to interfere with ability to complete study outcome measures.
- Patients with mild, moderate or severe renal impairment (creatinine clearance<80ml/min) measured by 24-hour urine collection or estimated by the Cockcroft and Gault formula
- Subjects concomitantly using medicinal products that are inhibitors of Organic Cation Transporter 2 (OCT2) for example cimetidine
- Concurrent treatment with other medicinal products containing fampridine (4- aminopyridine)

10.3 STUDY ASSESSMENTS AND PROCEDURES

Patients likely to fulfill the inclusion criteria and not meet any exclusion criteria will be provided with information on the study and invited to attend a subsequent screening visit. Only patients who have signed the informed consent form will participate in any study related procedures including blood testing and ECG.
At screening visit (Assessment 1) subjects will have a physical examination and an EDSS score rated. Blood samples will be taken for renal and liver function and a baseline ECG performed. Patients will complete a nine-hole peg test and a JTT. T25FW will be recorded and the patients invited to complete the MSIS-29, MSWS-12, DASH, AMSQ and SF-36 questionnaires. Patients with any abnormalities on ECG, blood tests will not be invited to a baseline visit and considered a screening failure.
Following screening visit subjects fulfilling the inclusion / exclusion criteria will have two baseline visits (Assessments 2 and 3) at the end of week one and end of week two. The 9-HPT, JTT and T25FW will be repeated to allow for training effects. Patients will be randomised to group A or group B and receive study medication or placebo at baseline visit based on their blinded randomisation (Assessment 3).
The first treatment period will be from the start of week 3 until the end of week 10. Patients will have an assessment at the end of week 6 (Assessment 4) and the end of week 10 (Assessment 5). At both assessments patients will have the 9-HPT, JTT, T25FW, MSIs-29, MSWS-12, DASH, AMSQ and SF-36 recorded. Weeks 11 and 12 will be a washout period (no drug/placebo). Assessment 6 will occur at the end of week 12 and will include recording of 9-HPT, JTT, T25FW, MSIs-29, MSWS-12, DASH, AMSQ and SF-36. Any adverse events will be recorded at each visit as will the use of concomitant medications.
The second treatment period will begin at the start of week thirteen with groups A and B switching study drug / placebo in a blinded manner. The second treatment period will continue for a further 8 weeks with two more assessments ant week 16 (Assessment 7) and week 20 (Assessment 8). At both of these assessments subjects will complete the 9-HPT, JTT, T25FW, MSIs-29, MSWS-12, DASH, AMSQ and SF-36. At the end of week 20 and EDSS score will be recorded. Any adverse events will be recorded at each visit as will the use of concomitant medications.
There will be a final washout period (weeks 21 and 22) after which a final visit (assessment 9) will occur and subjects once again completing 9-HPT, JTT, T25FW, MSIs-29, MSWS-12, DASH, AMSQ and SF-36 and having n EDSS score recorded. Once again adverse events will be recorded.

(See Schedule of Events, page 15)

Figure 2: Schedule of events

Assessment	1 Screening Visit	2 Baseline Visit	3 Base-line Visit	4 Rx Phase 1	5 End of Rx Phase 1	6 End Wash-out phase	7 Rx Phase 2	8 End of Rx Phase 2	9 End of 2 week washout
Time (start/end week)	week 1 (start)	week 1 (end)	week 2 (end)	week 6 (end)	week 10 (end)	week 12 (end)	week 16 (end)	week 20 (end)	week 22 (end of trial)
Informed consent	X								
Serum pregnancy test (female subjects)	X								
EDSS	x							X	X
ECG	X								
Receiving Medication	No	No	Start drug	Continue drug	Stop drug	Start drug	Continue drug	Stop drug	Wash out
9- HPT	x	x	x	x	x	x	x	x	X
JTT	x	x	x	x	x	x	x	x	X
T25FW	x	x	x	x	x	x	x	x	X
MSIS-29	x		x	x	x	x	x	x	X
MSWS-12	x		x	x	x	x	x	x	X
DASH	x		x	x	x	x	x	x	X
AMSQ	x		x	x	x	x	x	x	x
SF-36	X		X	X	X	X	X	X	X
Adverse event recording				X	X	X	X	X	X
Concomitant medication recording	X		X	X	X	X	X	X	X
Study Drugs dispensed			X			X			

Description of Study Assessments

Medical and Surgical History will be recorded with particular attention on the diagnosis of MS, duration of MS and MS subtype.
Demographics
The date of birth, gender and race will be recorded.
Physical Examination
The complete physical examination will include the evaluation of the neurological system and a recording of the EDSS score and T25FW.

ECG Test

One ECG including a 12-lead examination will be performed at Screening (assessment 1).
Abnormal findings will be noted for clinical significance. The report will be signed by the investigator.

Clinical Laboratory Tests

1. Haematology: haemoglobin, WBC, RBC, platelet count
2. Biochemistry: creatinine or creatinine-clearance, sodium, potassium, liver function tests
3. All laboratory results will be reviewed and the reports signed by the investigator who will record in the CRF whether they are normal, abnormal but not clinically significant, or abnormal and clinically significant.

Pregnancy Tests

Serum pregnancy test and urine pregnancy test in women of childbearing potential will be performed.

Concomitant Medication
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. Concomitant use of medicinal products that are inhibitors of OCT2 for example, cimetidine will be noted and will be deemed exclusion criteria. Concomitant use medicinal products that are substrates of OCT2 for example, carvedilol, propanolol and metformin will also be noted and the investigator will decide if the subject should successfully complete screening.

10.3.1 Endpoints assessments

Endpoint assessment will include the 9-HPT; JTT and T25FW test

10.3.2 Efficacy Assessment

A responder to study medication will be a subject who has a 20% improvement in the 9-HPT at both on treatment visits (assessment 4 & 5 or 7 & 8) compared with baseline visits.
A secondary measure of upper limb responsiveness will be defined as a 20% improvement in from baseline in the average time taken to complete all seven tasks on the JTT "on treatment" (assessments 4 & 5 or 7 & 8) compared with baseline assessments (assessments 1,2 & 3).
A mobility responder to fampridine will be defined as a patient with both of the two "on treatment" T25FW assessments (assessments 4 & 5 or 7 & 8) being better than the maximum of any of the four "off treatment" assessments (assessments 1, 2, 3, & 9). Otherwise the patient will be deemed a non-responder.
The responders to the 9-HPT and/or JTT will be compared to the non-responders in relation to their changes in the DASH and AMSQ on treatment and off treatment at the baseline assessment. The change in the DASH and AMSQ in responders at Assessment 5 or 8 (week 10 or 20) will be compared to non-responders at that time-point.
Upper limb response will be examined at the end of treatment phase 1 and repeated at the end of the trial by comparing patients receiving active drug with those receiving placebo to assess any placebo effect and allow assessment of any residual beneficial effect on those who receive fampridine in treatment phase 1 and then switch to placebo in treatment phase 2. Response will again be considered as a 20% improvement in the 9HPT in the active treatment group compared with placebo and a 20% improvement from baseline in the time taken to complete all seven tasks in the JTT. See earlier comment
The responders to the T25FW will be compared to the non-responders in relation to their changes in the MSWS-12 on treatment and off treatment at the baseline assessment. The change in the MSWS-12 in responders at Assessment 5 or 8 (week 10 or 20) will be compared to non-responders at that time-point.

The patients' scores on the MSIS-29 (physical) and SF-36 will be examined in relation to the objective changes (responder/non-responder) in the 9-HPT, JTT and the T25FW

Safety Assessment

Adverse events will be monitored, through out the study. Subjects will be required to inform the study team of all new or worsening symptoms within 24 hours of onset. All adverse events will be recorded in the CRF.

10.3.3 Method of assigning Subjects to treatment groups

Randomisation

Generation of Randomisation Codes
Subjects were randomised to each of two groups, A or B using the program:
http://www.graphpad.com/quickcalcs/randomize1.cfm

The randomisation sequence was generated on 07/03/2012.

Table 1. Randomisation Groups

Randomisation Groups	A = Initial treatment with Fampridine followed by placebo. B = Initial treatment with placebo followed by Fampridine.

Security and Distribution of Randomisation Codes
The randomisation codes will be kept on the Pharmacy Network Drive in St. Vincent's University Hospital. A hardcopy will be kept in the Pharmacy Department in the clinical trial folder.

The investigators and subjects will not have access to the randomisation codes (double blind).

A copy of the randomisation code and individual product codes will also be kept in a sealed envelope, with signature and date across the seal, which may be opened by the Principal Investigator if an emergency code-break is required. This will be stored in a secure location in the Neurology department but can be accessed by the Principle investigator if needed.

Handling
Pharmacy staff will use the information when dispensing clinical trial medication to each subject to ensure the appropriate medication is dispensed (ie placebo or active).

Retention
The study pharmacist will retain the randomisation codes until the database is locked at the end of the trial. Thereafter, the randomisation code will be made known to the investigators.

Code-Break Mechanisms

In the case of emergency, when knowledge of the subject's study treatment assignment is essential for the clinical management of the subject. Any intentional or unintentional breaking of the blind will be recorded and reported to the sponsor as soon as possible.

After database is locked at the end of the trial.

Blinding

Procedure for blinding of Fampridine versus placebo.

1. Capsules look identical.
Fampridine and placebo capsules look identical.

2. Identical packaging
Fampridine and placebo are packaged in identical packaging.

3. Identical labeling
The label instructions will be identical for both. See copy of label below

Figure 3. Study drug label.

FAMPYRA® 10MG TABLETS OR PLACEBO
Fampridine 10mg tablets or placebo 14 tablets

Take ONE tablet TWICE daily
To be taken orally. For clinical trial use only.

Patient Name/ID No. _____
Date_____

Product Code No. _____ Expiry Date _____

Keep out of reach of children.
Store at room temperature in original container.

Principal Investigator: Dr. C. McGuigan. Trial Sponsor: SVUH
Site: St. Vincent's University Hospital. Trial Ref. No. SVUHneur002

4. Use of numbers in random order for product codes
Each product will be labeled with a product code. It was decided that 4-digit codes would be used.

Using Microsoft Excel, a sequence of 1400 numbers in numerical order was generated. The numbers range from 1,000 to 2,199. The numbers were then shuffled into random order for use as product codes.

The first 700 numbers in random order will be used as the Fampyra codes
The last 700 numbers in random order will be used as the placebo codes.

Use of numbers in random order for the product codes means that the investigators and subjects will not be able to determine from the product codes whether the patient is on active or placebo treatment. The codes will used by the study pharmacist to ensure that patients are correctly dispensed active or placebo as required and to allow identification of active or placebo if unblinding required.

Who will be blinded?

The study will be conducted in a double-blind fashion. Study treatment assignment will be blinded for both the investigators and the subject.

The study pharmacist will retain the list of fampridine and placebo product codes.

Circumstances in which the blind would be broken

In the case of an emergency, when knowledge of the subject's study treatment assignment is essential for the clinical management of the subject, an investigator may unblind a subject. For example, the

blind would be broken in the event of a serious adverse effect experienced by a subject. Any intentional or unintentional breaking of the blind will be recorded and reported to the sponsor as soon as possible.

Procedure for unblinding

The Principal Investigator should be contacted if emergency unblinding is required. He will be provided with a sealed envelope (with signature and date across the seal) containing the Randomisation Code, active product codes and placebo product codes. The envelope may be opened if emergency unblinding is required.
This will be stored in a locked safe in the Neurology Department offices in St. Vincent's University Hospital.

The list of active and placebo product codes will be shuffled back into numerical order and saved as a separate file before being printed to allow quick identification of a particular product code if emergency unblinding is required.

10.4 DEFINITION OF END-OF-TRIAL

The trial will end on the date of the last visit of the last subject. The Sponsors and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.
The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The investigators will inform subjects and ensure that the appropriate follow-up is arranged for all involved. A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

10.4.1 End of study visits: procedures and assessments:
The end-of-trial is the date of the last visit of the last subject.
The end of study visit form will include:

- assessment 9-HPT, JTT, T25FW, MSIS-29, MSWS-12, DASH, AMSQ, EDSS.
- assessments of safety including general neurological examination and recording of adverse events.
- assessment of compliance with study treatment.
- recording of concomitant medication

Premature termination of the study

Health authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with the necessary timelines. This study will be terminated early if recruitment is slow. Recruitment should take 6 months. It recruitment targets are not met and recruitment has slowed to more than 12 months the trial will be terminated.

10.5 DISCONTINUATION/WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

Subjects have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason without any consequences. The investigator has the right to discontinue a subject from study treatment or withdraw a subject from the study at any time if it is in the best interest of the subject.
Subjects must discontinue the investigational medicinal product(s) and be withdrawn from the study for any of the following reasons:

- Withdrawal of consent by the subject
- Any medical condition that the investigator or sponsor determines may jeopardize the subject's safety if she or he continues receiving the study treatment
- Pregnancy
- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- An adverse event which requires discontinuation of the study medication
- Treatment failure and disease progression
- Lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits).
- Lost to follow-up following at least 3 documented attempts to contact any subject before defining them as lost to follow-up.

All subjects who discontinue should comply with protocol specified follow-up procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures.

If a subject is withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

If a subject is withdrawn due to an adverse event, the investigator will arrange for follow-up visits until the adverse event has resolved or stabilised.

11.0 TREATMENT OF TRIAL SUBJECTS

11.1 DESCRIPTION OF STUDY TREATMENT(S)

Active therapy – Fampyra (fampridine) oral capsules 10 mg BID. (Supplied by Biogen Idec Ltd.)
Placebo – an identical placebo capsule administered BID will also be used (supplied by Biogen Idec)

11.2 FORMULATION, PACKAGING, AND HANDLING

Fampyra and Fampyra identical placebo are produced in tablet form for twice daily oral use. They will be supplied in a box of 14 tablets (one weeks supply). There is no secondary packaging.

The product label will look as follows:

FAMPYRA® 10MG TABLETS OR PLACEBO
Fampridine 10mg tablets or placebo 14 tablets

Take ONE tablet TWICE daily
To be taken orally. For clinical trial use only.

Patient Name/ID No. _____
Date_____

Product Code No. _____ Expiry Date _____

Keep out of reach of children.
Store at room temperature in original container.

Principal Investigator: Dr. C. McGuigan. Trial Sponsor: SVUH
Site: St. Vincent's University Hospital. Trial Ref. No. SVUHneur002

Name and address of supplier of Fampyra and Placebo medication:
Biogen Idec Ltd. United Drug House,
Magna Drive,
Magna Business Park,
Citywest Road,
Dublin 24,
Ireland

Name and Address of Pharmacy who will label the study treatment:
Pharmacy Department
St. Vincent's University Hospital,
Elm Park,
Dublin 4,
Ireland

11.3 STORAGE AND DISPOSITION OF STUDY TREATMENTS(S)

The Fampyra and Placebo tablets will be stored on separate shelves of a locked press at room temperature in the Pharmacy Department of St. Vincent's University Hospital until dispensed to subjects. Returns will be stored by the study nurse in a secure location in the Neurology department until authorised for destruction.

The temperature of study medications will be monitored during shipment to SVUH. On arrival to SVUH, temperature will be monitored and recorded daily on a temperature log. Subjects will be advised to store the study drug at room temperature.

The study treatments are for investigational use only and are only to be used within the context of this trial.

11.4 ACCOUNTABILITY OF THE STUDY TREATMENT(S)

The investigator is responsible for the control of the treatment under investigation. Adequate records for receipt and disposition of the IMP will be maintained.
The study medication will be supplied to pharmacy by Biogen Idec Ltd. and retrieved at the end of the study.
The investigator will use a standard prescription form and the investigator/research nurse will collect the medication from the pharmacy on the day of dosing.
Maintaining dispensing and return records will assess accountability and subject compliance with study treatments. A master accountability investigational product log will be maintained for each product. This will record the total quantity received and dispensed to each subject. Two single subject investigational product accountability logs will also be maintained for each subject, one for medication dispensed and one for medication returned.
The study nurse will monitor compliance at each return visit.

Prior consent will be obtained from the study sponsor to allow destruction of returns and unused excess stock provided by Biogen Idec Ltd. It will destroyed according to the SVUH Whole Hospital Waste Disposal and Management Policy, SVUH HS POL 01, May 2011 and a receipt of destruction will be provided to the sponsor.

10.5 ASSESSMENT OF COMPLIANCE

The investigator is responsible for ensuring that the study treatment is administered in compliance with the protocol. Maintaining dispensing records will assess subject compliance.

10.6 OVERDOSE OF STUDY TREATMENT

Patients who overdose will be admitted to SVUH and provided with supportive care. Repeated seizure activity will be treated with benzodiazepine, phenytoin, or other appropriate acute anti-seizure therapy.

10.7 PRIOR AND CONCOMITANT THERAPY

Any medication, other than the study medication taken during the study will be recorded in the CRF from the second baseline visit to the last visit.

Permitted medications/non- investigational medicinal products will include treatments of acute MS exacerbations including corticosteroids (high dose IV or short course of oral steroids) and symptom therapies such as baclofen. Antibiotics will be permitted for intercurrent infections.

Prohibited medications:
Concomitant use of medicinal products that are inhibitors of Organic Cation Transporter 2(OCT2) for example cimetidine are prohibited for the duration of the study. Concurrent treatment with other medicinal products containing fampridine (4- aminopyridine) is also prohibited.

12.0 SAFETY REPORTING

The safety and tolerability of the IMP will be evaluated throughout the study e.g. by AEs and neurological examination.

12.1 DEFINITIONS

12.1.1Adverse event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

12.1.2 Adverse reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.
The phrase 'responses to a medicinal product' means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

12.1.3 Serious adverse event

Any untoward medical occurrence or affect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Important medical events**

*Regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

**Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious' in accordance with the definition

12.1.4 Severe adverse events

The term ‘severity’ is used here to describe the intensity of a specific event. This has to be distinguished from the term ‘serious.

12.1.5 Suspected unexpected serious adverse reactions

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator’s brochure for an unauthorised investigational medicinal product or summary of product characteristics for an authorised medicinal product.

12.2 EVALUATIONS OF AES AND SAES

Seriousness, causality, severity and expectedness will be evaluated.

12.2.1 Assessment of seriousness

The investigator will make an assessment of seriousness as defined in section 12.1.4.

12.2.2 Assessment of casualty

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualifies as adverse reactions.
The sponsor should not downgrade the causality assessment given by the investigator.
The investigator/sponsor must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:
Unrelated
Where an event is not considered to be related to the study medication.
Possibly
Although a relationship to the study medication cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship makes other explanations possible.
Probably
The temporal relationship and absence of a more likely explanation suggest the event could be related to the study medication.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably) to the study medication will be considered as ARs/SARs.

All AEs/SAEs judged as being related (e.g. possibly, probably) to an interaction between the study medication and another medication will also be considered to be ARs/SAR.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the treatment should be considered.

12.2.3 Assessment of severity

The investigator will make an assessment of severity for each AE/SAE and record this on the CRF according to one of the following categories:

Mild
An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with every day activities.

Moderate
An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe
An event that prevents normal everyday activities.

12.2.4 Assessment of expectedness

The expectedness of an adverse reaction will be determined by the sponsor according to the reference document e.g. the investigator's brochure for a non-authorised investigational medicinal product, or the summary of product characteristics for an authorised medicinal product, which is used according to the terms and conditions of the marketing authorisation.

12.2.5 Emergency unblinding procedures

The principle investigator should be contacted if emergency unblinding is required. They will be provided with a sealed envelope (with a signature and date across the seal) containing the randomization code, active product codes and placebo product codes. The envelope may be opened if emergency unblinding is required.

12.3 REPORTING PROCEDURES FOR ALL ADVERSE EVENTS

All AEs occurring during the study observed by the investigator or reported by the subject, whether or not attributed to the study medication, will be recorded on the CRF.

The following information will be recorded: description, date of onset and end date, severity, and assessment of relatedness to the study medication, other suspect medication or device and action taken. Follow-up information should be provided as necessary.

AEs considered related to the study medication as judged by an investigator or the sponsor will be followed until resolution or until the event is considered stable. All related AEs that result in a subject’s withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator’s clinical judgment whether or not an AE is of sufficient severity to require the subject’s removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

The severity of events will be assessed on the following scale: mild, moderate, and severe.

The investigator will assess the relationship of AEs to the study medication.

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed-up for congenital abnormality or birth defect.

12.4 REPORTING PROCEDURES FOR SERIOUS ADVERSE EVENTS

The investigator will report all serious adverse events immediately to the sponsor except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report will be followed by detailed, written reports. The immediate and follow-up reports will identify subjects by unique code numbers assigned to the latter.

The investigator will make the immediate report within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event.

All SAE information must be recorded on an SAE forms and sent expeditiously to the sponsor. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form and sent expeditiously to the sponsor.

The sponsor will keep detailed records of all adverse events, which are reported to him by the investigator or investigators.

In cases where reporting is not required immediately the investigator will report within the appropriate time frame, taking account of the specificities of the trial and of the serious adverse event, as well as possible guidance in the protocol or the IB.

The sponsor will report all SUSARs to the competent authorities (the IMB in Ireland) and the ethics committees concerned. Fatal or life-threatening SUSARs must be reported within **7 days**. SUSARs which are not fatal and not life threatening are to be reported within **15 days**. The sponsor will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects.

If the initial report is incomplete, e.g. if the sponsor has not provided all the information/assessment within seven days, the sponsor will submit a completed report based on the initial information within an additional eight days.

If the sponsor receives significant new information on an already reported case, the clock starts again at day zero, i.e. the date of receipt of new information. This information will be reported as a follow-up report within 15 days.

In addition to the expedited reporting above, the sponsor shall submit once a year throughout the clinical trial or on request, a safety report to the competent authority (the IMB in Ireland) and ethics committees. The annual safety report will be presented in the DSUR format as per ICH guideline E2F - Note for guidance on development safety update reports. This is a legal requirement

12.5 DATA SAFETY MONITORING BOARD (DSMB)

Due to the short duration of this study the Trial Steering Committee has determined that a DSMB is not needed.

12.6 PREGNANCY

Pregnancy is not considered an AE or SAE however the investigator will collect pregnancy information for female trial subjects or female partners of male trial subjects who become pregnant while participating in a study.

The investigator will record the information on a Pregnancy Notification Form and submit this to the sponsor.

Any pregnancy that occurs in a trial subject or a trial subject's partner during a trial will be followed to outcome.

13.0 STATISTICS

13.1 DESCRIPTION OF STATISTICAL METHODS

Outcome will be assessed using the Wilcoxon Signed Rank test to establish whether there is a difference between the paired 'on treatment' outcome measures for each individual.

13.2 DETERMINATION OF SAMPLE SIZE SUBJECTS

Given the previous reports, one would anticipate in this observational study that approximately 30+ % of patients would experience a significant (25%) improvement in indices of upper limb and walking mobility. Using a crossover design and treating the observations as paired within individuals, and allowing for loss to follow up during the trial, a sample size of 80 (40 in each arm) will be used.

13.3 ANALYSIS SETS

The primary analysis will be an intention to treat analysis. A secondary per protocol analysis will be carried out should this differ.

13.4 DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

Demographic and baseline disease characteristic data will be summarized for each treatment group by presenting frequency distributions and descriptive statistics.

13.5 EFFICACY ANALYSIS

Primary efficacy endpoint:
An upper limb responder to fampridine will be defined as a patient with both of the two "on treatment" 9-HPT assessments (assessments 4 & 5 or 7 & 8) improving 20% from the average of the baseline assessments (1, 2 & 3).

Secondary efficacy endpoints:

a) A secondary measure of upper limb responsiveness will be defined as a 20% improvement in from baseline in the average time taken to complete all seven tasks on the JTT "on treatment" (assessments 4 & 5 or 7 & 8) compared with baseline assessments (assessments 1,2 & 3).
b) A mobility responder to dalfampridine will be defined as a patient with both of the two "on treatment" T25FW assessments (assessments 4 & 5 or 7 & 8) being better than the maximum of any of the four "off treatment" assessments (assessments 1, 2, 3, & 9). Otherwise the patient will be deemed a non-responder.
c) The responders to the 9-HPT and/or JTT will be compared to the non-responders in relation to their changes in the DASH and AMSQ on treatment and off treatment at the baseline assessment. The change in the DASH and AMSQ in responders at Assessment 5 or 8 (week 10 or 20) will be compared to non-responders at that time-point.

Upper limb response will be examined at the end of treatment phase 1 and repeated at the end of the trial by comparing patients receiving active drug with those receiving placebo to assess any placebo effect and allow assessment of any residual beneficial effect on those who receive fampridine in treatment phase 1 and then switch to placebo in treatment phase 2. Response will again be considered as a 20% improvement in the 9HPT in the active treatment group compared with placebo and a 20% improvement from baseline in the time taken to complete all seven tasks in the JTT. See earlier comment

d) The responders to the T25FW will be compared to the non-responders in relation to their changes in the MSWS-12 on treatment and off treatment at the baseline assessment. The change in the MSWS-12 in responders at Assessment 5 or 8 (week 10 or 20) will be compared to non-responders at that time-point.

The patients' scores on the MSIS-29 (physical) and SF-36 will be examined in relation to the objective changes (responder/non-responder) in the 9-HPT, JTT and the T25FW.

13.6 SAFETY ANALYSIS

All AEs occurring in the trial will be recorded and compared across the two groups. Comparison of prevalence of SEs between study groups will be expressed as a percentage.

13.7 THE LEVEL OF STATISTICAL SIGNIFICANCE

A significance level of 0.05 will be used for all analyses.

13.8 CRITERIA FOR THE TERMINATION OF THE TRIAL

The trial will be terminated after the last visit of the last participant.

13.9 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED AND SPURIOUS DATA

Data will be analysed as is, with the primary analysis being based on complete case data. The amount and nature of missing data, together with demographic and baseline summaries of these cases will be documented.

13.10 PROCEDURE FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any deviations from the statistical plan, and additional analyses will be documented and noted in the final report.

14.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

15.0 DATA HANDLING AND RECORD KEEPING

Source documents will be kept in the hospital charts of all participants. Data on CRFs and all other hard copies will be locked in filing cabinets in the Department of Neurology, SVUH. Electronic data will be held coded on a password-protected database on the H-Drive of the Department of Neurology, SVUH accessible only to members of the study group. Pharmacy records will be kept in the Pharmacy Department SVUH. Electronic files will be kept on the Pharmacy network drive.

15.1 DATA COLLECTION, SOURCE DOCUMENTS AND CASE REPORT FORMS (CRF):

Source documents for this study will include hospital records and procedure reports and data collection forms. These documents will be used to enter data on the CRFs. All data entered on CRFs must be entered legibly. If an error is made, the error will be crossed through with a single line in such a way that the original entry can still be read. The correct entry will then be clearly inserted, and the alterations will be initialed and dated by the investigator.
Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.
All documents will be stored safely in confidential conditions. On all study-specific documents other than the signed consent, the subject will be referred to by the study subject identification number/code.

15.2 DATA REPORTING

Data will be entered in hospital notes and these will act as source data. In addition a number of CRFs will be generated for each study participant. Summary data coded for each participant will be entered in a database stored in a coded password protected excel datasheet accessible only to the study personnel listed above. A study specific number and / or code in the database will identify subjects. The name of any subject or other identifiable information will not be included in any study data electronic file.

16.0 RETENTION OF ESSENTIAL DOCUMENTS

Essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in

an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.
The investigator/institution should agree to retain the trial-related essential documents as required by the applicable regulatory requirements and until the sponsor informs the investigator/institution these documents are no longer necessary.
All records and documents will be maintained by the investigator for a period of at least 5 years after FDA/European Medicines Agency (EMA) approval of the medicinal product or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product, whichever is longer.

17.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

This study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. All study participants hold up-to-date GCP training certification. The internal monitor shall ensure excellent quality of data collection and recording is maintained.

18.0 AUDITS AND INSPECTIONS

This trial may be subject to internal or external auditing or inspections procedure to ensure adherence to GCP. Access to all trial-related documents will be given at that time.

19.0 ETHICS

The investigator will have obtained ethics committee approval for the study protocol, PIL and other required study documents prior to starting the study.
Any changes to the protocol will be submitted to the ethics committee. The principle investigator will ensure that all aspects of institutional review are conducted in accordance with current governmental regulations. Protocol amendments will be subject to the same requirements as the original protocol. A progress report will be submitted to the ethics committee at the study end. At the completion or termination of the study, the investigational site will submit a closeout letter to the ethics committee.

19.1 DECLARATION OF HELSINKI

The sponsor will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

19.2 GOOD CLINICAL PRACTICE

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC.

19.3 APPROVALS

Required documents including the protocol, informed consent form, subject information leaflet, investigational medicinal product dossier, investigators brochure and any other required documents will be submitted to a recognized research ethics committee and the competent authority for written approval.
The sponsor will submit and obtain approval from the above parties for substantial amendments to the original approved documents.

19. 4 INFORMED CONSENT

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent form.

19.5 BENEFITS AND RISKS ASSESSMENT

Fampyra medication has been shown to be safe and effective for improving mobility in patients with progressive multiple sclerosis. This study aims to assess whether subjects with upper limb dysfunction due to MS also derive a benefit from the medication. The medication already has been shown to have a favorable side effect profile and the benefits may significantly improve patients quality of life and ability to perform their activities of daily living.

19.6 SUBJECT CONFIDENTIALITY

The trial staff will ensure that the subjects' anonymity is maintained. Only initials and a subject's identification number on the CRF and any database will identify the subjects. All documents will be stored securely. The study will comply with the Data Protection Act.

20.0 FINANCING AND INSURANCE/INDEMNITY

St. Vincent's University Hospital holds Public Liability ('negligent harm') and Clinical Trial ('non-negligent harm') insurance policies, which apply to this trial.
The Department of Neurology, St. Vincent's University Hospital, Dublin 4, Ireland will fund the study.
Study medication and placebo will be supplied free of charge by Biogen Idec Ltd.

21.0 CLINICAL STUDY REPORT AND PUBLICATION POLICY

Dr C McGuigan, Prof N Tubridy and Prof M Hutchinson will sign the study report. Papers resulting from the study will be published under the authorship of all the personnel listed.

22.0 REFERENCES

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