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(54) **METHODS OF USING SUSTAINED RELEASE AMINOPYRIDINE COMPOSITIONS**

VERFAHREN ZUR VERWENDUNG VON AMINOPYRIN-ZUSAMMENSETZUNGEN MIT VERZÖGERTER FREISETZUNG

UTILISATION DE COMPOSITIONS D'AMINOPYRIDINE A LIBERATION SOUTENUE

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## Description

### BACKGROUND

**[0001]** This invention relates a sustained release oral dosage form of an aminopyridine pharmaceutical composition that can be used to treat individuals affected with neurological disorders wherein said pharmaceutical composition maximizes the therapeutic effect, while minimizing adverse side effects.

**[0002]** The sustained release oral dosage form of the present invention may be utilized to treat neurological disorders such as multiple sclerosis, spinal cord injuries, Alzheimer's disease and ALS.

**[0003]** Multiple sclerosis (MS) is a degenerative and inflammatory neurological disease that affects the central nervous system, more specifically the myelin sheath. The condition of MS involves demyelination of nerve fibers resulting in "short-circuiting" of nerve impulses and thus a slowing or blocking of transmission along the nerve fibers, with associated disabling symptoms. Treatment alternatives for promoting transmission along affected nerves have thus far been limited.

**[0004]** Potassium channel blockers are a class of compounds that has been found to improve the conduction of nerve impulses. As a result, they have become the focus of attention in the symptomatic treatment of spinal cord injury, MS and Alzheimer's disease. One sub-class of potassium channel blockers, aminopyridines have shown promise in the treatment of neurological diseases. 4-aminopyridine (4-AP), a mono-aminopyridine known as fampridine, has been found to reduce the potassium flow in nerve impulse transmission and, thereby, shows effectiveness in restoring conduction in blocked and demyelinated nerves.

**[0005]** Early studies of monoaminopyridines were conducted using an intravenous composition, comprising 4-AP. This was followed by the development of an immediate-release (IR) composition for oral administration of 4-AP, commonly known as fampridine. The IR composition consisted of 4-AP powder in a gelatin-based capsule and produced rapid peak plasma concentrations shortly after dosing with a time to maximum concentration of about 1 hour and a plasma half life of about 3.5 hours. The rapid release and short half life of fampridine makes it difficult to maintain effective plasma levels without producing high peaks following each dose that may cause undesirable side effects such as seizures and trembling.

**[0006]** Electrophysiological recordings from isolated spinal cord have shown chronic failure of action potential conduction in surviving myelinated axons, following a blunt contusion injury (Blight, A.R., "Axonal physiology of chronic spinal cord injury in the cat: intracellular recording in vitro", Neuroscience. 10:1471-1486 (1983b)). Some of this conduction block can be overcome, at the level of single nerve fibers, using the drug 4-aminopyridine (4-AP) (Blight, A.R., "Effect of 4-aminopyridine on axonal conduction-block in chronic spinal cord injury", Brain Res. Bull. 22:47-52 (1989)). Intravenous injection of this compound in animals with experimental or naturally occurring spinal cord injuries produces significant improvements in electrophysiological (Blight, A.R. and Gruner, J.A., "Augmentation by 4-aminopyridine of vestibulospinal free fall responses in chronic spinal-injured cats," J. Neurol. Sci. 82:145-159, (1987)) and behavior function (Blight, A.R., "The effects of 4-aminopyridine on neurological deficits in chronic cases of traumatic spinal cord injury in dogs: a phase I clinical trial," J. Neurotrauma, 8:103-119 (1991)).

**[0007]** An initial study in spinal cord injury patients was organized by Dr. Keith Hayes and indicated a potential for a therapeutic benefit, mostly at the electrophysiological level, combined with a lack of serious side effects (Hayes et al, "Effects of intravenous 4-aminopyridine on neurological function in chronic spinal cord injured patients: preliminary observations," Proc. IBRO World Conf. Neurosci., p. 345 1991).

**[0008]** A recent study of fampridine in patients with chronic incomplete SCI was reported in Clinical Neuropharmacology 2003: Keith C. Hayes; Patrick J. Potter; Robert R. Hansebout; Joanne M. Bugaresti; Jane T. C. Hsieh; Sera Nicosia; Mitchell A. Katz; Andrew R. Blight; Ron Cohen 26(4):185-192.

Schwid et al. (Neurology 48: 817-821, 1997) describes the use of 4AP in a sustained release composition to treat MS patients, but found that a serum level of at least 60ng/ml led to benefit.

### SUMMARY OF THE INVENTION

**[0009]** The present invention relates to a pharmaceutical composition which contains one or more potassium channel blockers and which can be used in the effective treatment of multiple sclerosis. Embodiments of the present invention are directed to compositions that include a matrix and a potassium channel blocker. The potassium channel blockers will include aminopyridines, for example, 4-aminopyridine, 3,4-diaminopyridine and the like, most preferably 4-aminopyridine. The composition provides for sustained-release of the aminopyridine from the matrix to maintain the efficacious and safe plasma level of an aminopyridine. The aminopyridine dispersed in the matrix is capable of providing, upon administration to a patient, a desired release profile. The composition may be used to establish in patients in need of such treatment, a therapeutically effective blood plasma level of the aminopyridine for a period of at least about 6 hours and preferably up to at least about 12 hours in the patient in a twice-daily administration while avoiding excessive peaks and troughs in the level of the aminopyridine. The composition may include a mono- or di-aminopyridine, preferably 4-AP or 3,4-DAP or a combination thereof, homogeneously dispersed in a rate-controlling polymer matrix, preferably

including a hydrophilic polymer like hydroxypropylmethylcellulose (HPMC). The composition of the present invention may also include one or more additional active ingredients and/or one or more pharmaceutically acceptable excipients. These compositions can be used to treat various neurological diseases, for example, spinal cord injury, multiple sclerosis, Alzheimer's disease, and ALS.

**[0010]** In one embodiment, the present invention is a stable pharmaceutical composition that comprises a therapeutically effective amount of an aminopyridine dispersed in a matrix that provides a release profile of the aminopyridine to a patient that has a desired $C_{max}$ to $C_{\tau}$ ratio. The composition is used to establish and/or maintain in a patient, a therapeutically effective level of the aminopyridine. Preferably the aminopyridine in the composition is released over time so that a therapeutically effective level of the aminopyridine in the patient can be achieved with twice daily dosing of the composition. In a more preferred embodiment, undesirable spikes or peaks in the release of the aminopyridine are avoided.

**[0011]** Another embodiment of the present invention is a stable, sustained-release oral dosage formulation of a composition which includes a therapeutically effective amount of a 4-aminopyridine dispersed in a matrix that provides a release profile of 4-aminopyridine in the blood plasma of the patient extending over a period of at least 6 hours, preferably at least 8 hours, and more preferably, at least about 12 hours. In another embodiment, a stable, sustained-release oral dosage formulation of a composition includes a therapeutically effective amount of a 4-aminopyridine dispersed in a matrix that provides a therapeutically effective blood plasma level of 4-aminopyridine in the patient extending over about 24 hours.

**[0012]** Preferably, the oral dosage formulation of the composition is a monolithic tablet formed by compression of the pharmaceutical composition of the present invention. In preferred embodiments, the oral dosage formulation includes a compressed tablet of a therapeutically effective amount of 4-aminopyridine dispersed in matrix that includes a hydrophilic polymer such as HPMC. The oral dosage form of the present invention may also include one or more pharmaceutically acceptable excipients.

**[0013]** The dispersion of 4-aminopyridine throughout the matrix imparts chemical and physical stability to the composition while providing a sustained-release profile. This enhanced dosage stability is most notably observed in compositions and dosage forms of the present invention having low concentrations of 4-aminopyridine, and stability is achieved while maintaining the desired controlled-release profile. Specifically, the compressed tablet formulation of the present invention exhibits superior resistance to moisture absorption by ambient humidity and maintains a uniform distribution of the 4-aminopyridine throughout the tablet while providing a release profile of 4-aminopyridine that permits establishment of a therapeutically effective concentration of the potassium channel blocker with once daily or twice daily dosing of the formulation. Preferably the therapeutically effective concentration released by the formulation extends over at least about 6 hours, preferably at least about 8 hours, and more preferably at least about 12 hours. In addition, the homogeneity of the dosage form renders it amenable to formation by simple and inexpensive manufacturing processes as compared with the multi-layered structure of prior sustained-release dosage formulations.

**[0014]** The compositions of the present invention are used in the treatment of multiple sclerosis in a patient in need thereof. The compositions may be used for building up a level and or maintaining a therapeutically effective concentration of an aminopyridine in the patient by twice daily dosing. The dosages of the present compositions can be made with a lower concentration of the aminopyridine to facilitate restful periods for the patient during the day or night, depending on desired results or dosage schedule. Where desirable, the compositions of the present invention may be formulated to avoid large peaks in initial release of the aminopyridine. The compositions of the present invention when administered to a patient in need thereof provide for the treatment of multiple sclerosis. Preferably, the compositions are a stable, sustained-release tablet of a therapeutically effective amount of a mono- or di-aminopyridine, dispersed in HPMC such that therapeutically effective blood plasma level of the mono- or di-aminopyridine is maintained in the patient for a period of at least 6 hours, Preferably at least 8 hours, and more preferably at least about 10-12 hours in a once or twice daily administration.

**[0015]** The present invention is as defined in the claims. In a preferred embodiment, the effective amount is about 10 to about 15 milligrams of aminopyridine.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0016]**

Figure 1 is a histogram to show the number of treatment visits at which subjects showed faster walking speed on the timed 25 foot walk than at all of the five non-treatment visits.

Figure 2 is a graph of the average walking speeds (ft/sec) by study day (observed cases, ITT population).

Figure 3 is a histogram of the percent change in average walking speed during the 12-week stable dose period (observed cases, ITT population).

Figure 4 is a histogram of the percentage of protocol specified responders (subjects with average changes in walking

speed during the 12-week stable dose period of at least 20%) by treatment group [(observed cases, ITT population]).
Figure 5 is a graph of LEMMT by study day (observed cases, ITT population).
Figure 6 is a histogram of change in LEMMT during the 12-week stable dose period (observed cases, ITT population).
Figure 7 is a histogram of the percentage of post hoc responders by treatment group (ITT population) according to a responder analysis of the present invention.
Figure 8 is a histogram of the percentage of responders for placebo subjects vs. fampridine subjects pooled (ITT population) according to a responder analysis of the present invention.
Figure 9 are histograms of the validation of the post hoc responder variable using subjective scales (observed cases, ITT population).
Figure 10 is a graph of percent change in walking speed at each double-blind visit by responder analysis grouping (observed cases, ITT population).
Figure 11 is a graph of the change in LEMMT at each double-blind visit by responder analysis grouping (observed cases, ITT population).
Figure 12 is a graph of change in overall Ashworth Score at each double-blind visit by responder analysis grouping (observed cases, ITT population).

## DETAILED DESCRIPTION OF THE INVENTION

**[0017]** Before the present compositions and methods are described, it is to be understood that this invention is not limited to the particular molecules, compositions, methodologies or protocols described, as these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

**[0018]** The terms used herein have meanings recognized and known to those of skill in the art, however, for convenience and completeness, particular terms and their meanings are set forth below.

**[0019]** It must also be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, reference to a "spheroid" is a reference to one or more spheroid and equivalents thereof known to those skilled in the art, and so forth. Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of embodiments of the present invention, the preferred methods, devices, and materials are now described.

**[0020]** "Local Administration" means direct administration by a non-systemic route at or in the vicinity of the site of affliction, disorder, or perceived pain.

**[0021]** The terms "patient" and "subject" mean all animals including humans. Examples of patients or subjects include humans, cows, dogs, cats, goats, sheep, and pigs.

**[0022]** The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention.

**[0023]** The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compounds of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

**[0024]** The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, tetramethylammonium, tetramethylammonium, methlyamine, dimethlyamine, trimethlyamine, triethlyamine, ethylamine, and the like. (See, for example, S.M. Barge et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977, 66:1-19).

**[0025]** A "therapeutically effective amount" is an amount sufficient to decrease or prevent the symptoms associated with a medical condition or infirmity, to normalize body functions in disease or disorders that result in impairment of specific bodily functions, or to provide improvement in one or more of the clinically measured parameters of the disease.

Preferably, improvement in symptoms associated with the disease including walking speed, lower extremity muscle tone, lower extremity muscle strength, or spasticity. As related to the present application, a therapeutically effective amount is an amount sufficient to reduce the pain or spasticity associated with the neurological disorder being treated, or an amount sufficient to result in improvement of sexual, bladder or bowel function in subjects having a neurological disorder which impairs nerve conduction, which hinders normal sexual, bladder or bowel functions.

**[0026]** "Treatment" refers to the administration of medicine or the performance of medical procedures with respect to a patient, for either prophylaxis (prevention), to cure the infirmity or malady in the instance where the patient is afflicted refers, or amelioration the clinical condition of the patient, including a decreased duration of illness or severity of illness, or subjective improvement in the quality of life of the patient or a prolonged survival of the patient.

**[0027]** In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

**[0028]** In one embodiment the invention is a sustained-release pharmaceutical composition comprising an aminopyridine dispersed in a sustained release matrix such as a rate-controlling polymer. The composition of the present invention is capable of providing, upon administration to a patient, a release profile of the aminopyridine extending over at least 6 hours, preferably least about 12 hours, and more preferably at least 24 hours or more. The aminopyridine concentration in the composition is a therapeutically effective amount, and preferably the aminopyridine is dispersed uniformly throughout the release matrix. A therapeutically effective amount is an amount of an aminopyridine compound, that when administered to a patient or subject, ameliorates a symptom of multiple sclerosis.

**[0029]** When the compositions of the present invention are administered to a patient, the concentration of the aminopyridine in the patient's plasma over time (release profile) may extend over a period of at least 6 hours, preferably over at least 8 hours, and more preferably over 12 hours. The compositions may provide in single dose a mean maximum plasma concentration of aminopyridine in the patient of from 15 to 180 ng/ml; a mean $T_{max}$ from about 1 to about 6 hours, more preferably 2 to 5.2 hours after administration of the composition to the patient.

**[0030]** In one embodiment, aminopyridine is administered to a subject at a dose and for a period sufficient to allow said subject to tolerate said dose without showing any adverse effects and thereafter increasing the dose at selected intervals of time until a therapeutic dose is achieved. In one embodiment, the medicament is administered to a subject at a dose and for a period sufficient to allow said subject to tolerate said dose without showing any adverse effects and thereafter increasing the dose of aminopyridine at selected intervals of time until a therapeutic dose is achieved. For example, at the commencement of treatment aminopyridine is preferably administered at a dose less than 15 mg/day until a tolerable state is reached. Suitably when said tolerable state is reached, the dose administered may be increased by amounts of at least 5-15 mg/day until said therapeutic dose is reached.

**[0031]** Preferably, aminopyridine is administered at a dose of 10-15 mg twice daily (20-30 mg/day) depending upon the condition or symptoms being treated. The composition can be for administration of doses of the pharmaceutical so that the concentration of the aminopyridine in the patient is at about the minimum therapeutically effective level to ameliorate multiple sclerosis, yet relatively lower compared to the maximum concentration in order to enhance restful periods for the patient during the day or night, depending on desired results or dosage schedule. Preferably the composition is for the treatment of multiple sclerosis comprising the step of administering to a patient a composition of the present invention.

**[0032]** The formulations and compositions of the present invention exhibit a specific, desired release profile that maximizes the therapeutic effect while minimizing adverse side effects. The desired release profile may be described in terms of the maximum plasma concentration of the drug or active agent ($C_{max}$) and the plasma concentration of the drug or active agent at a specific dosing interval ($C\tau$). A ratio of $C_{max}$ to $C_\tau$ ($C_{max}$:$C_\tau$) may be calculated from the observed $C_{max}$ and $C_\tau$. A dosing interval ($\tau$) is the time since the last administration of the drug or active agent. In the present application, the dosing interval ($\tau$) is twelve (12) hours, therefore $C_\tau$ is the concentration of the drug or active agent at twelve (12) hours from the last administration.

**[0033]** Additionally, the formulations and compositions of the present invention exhibit a desired release profile that may be described in terms of the maximum plasma concentration of the drug or active agent at steady state ($C_{maxSS}$) and the minimum plasma concentration of the drug or active agent at steady state ($C_{minSS}$). Steady state is observed when the rate of administration (absorption) is equal to the rate of elimination of the drug or active agent. A ratio of $C_{maxSS}$ to $C_{minSS}$ ($C_{maxSS}$:$C_{minSS}$) may be calculated from the observed $C_{maxSS}$ and $C_{minSS}$. In addition, the formulations and compositions of the present invention exhibit a desired release profile that may be described in terms of the average maximum plasma concentration of the drug or active agent at steady state ($C_{avSS}$).

**[0034]** Another embodiment is a sustained release tablet of a sustained release matrix and an aminopyridine, said tablet exhibits a release profile to obtain a $C_{max}$:$C_\tau$ ratio in vivo of 1.0 to 3.5, and more preferably a $C_{max}$:$C_\tau$ ratio of about 1.5 to about 3.0. In another preferred embodiment, the $C_{max}$:$C_\tau$ ratio is 2.0 to 3.0. The aminopyridine may comprise 4-aminopyridine. The sustained release matrix may include for example, hydroxypropylmethylcellulose, or other rate controlling matrices that are suitable for controlling the release rate of an aminopyridine for use in the pharmaceutical

compositions of the present invention.

**[0035]** Another embodiment is a sustained release tablet of a sustained release matrix and an aminopyridine, said tablet exhibits a release profile to obtain a $C_{max}$:$C_{\tau}$ ratio in vivo of 1.0 to 3.5 and a $C_{avSS}$ of 15 ng/ml to 35 ng/ml, and more preferably a $C_{max}$:$C_{\tau}$ ratio of 1.5 to 3.0. In another preferred embodiment, the $C_{max}$:$C_{\tau}$ ratio is 2.0 to 3.0.

**[0036]** A further aspect is a sustained release composition comprising a sustained release matrix and an aminopyridine, wherein said composition provides a $C_{avSS}$ of 15 ng/ml to 35 ng/ml. In a further aspect, a sustained release tablet comprising a sustained release matrix and an aminopyridine, said tablet exhibiting a $C_{maxSS}$ of 20 ng/ml to 35 ng/ml is provided. The pharmacokinetic characteristics of sustained release aminopyridine compositions and methods of treating various neurological disorders are described in co-pending PCT/US2004/008101 entitled "Stable Formulations of Aminopyrdines and Uses Thereof" filed April 17, 2004 and U.S. Application No. 11/010,828 entitled "Sustained Release Aminopyridine Composition" filed December 13, 2004.

**[0037]** The amount of a pharmaceutically acceptable quality aminopyridine, salt, solvated, or prodrug thereof included in the pharmaceutical composition of the present invention will vary, depending upon a variety of factors, including, for example, the specific potassium channel blocker used, the desired dosage level, the type and amount of rate-controlling polymer matrix used, and the presence, types and amounts of additional materials included in the composition. Preferably, the aminopyridine comprises from 0.1 to 13%w/w, more preferably from 0.5 to 6.25 %w/w. In an even more preferable embodiment of the present invention the aminopyridine is present from 0.5 to 4.75 %w/w of the pharmaceutical composition. Accordingly, a weight percentage less than 4.75% is desired. The amount of aminopyridine, or a derivative thereof, in the formulation varies depending on the desired dose for efficient drug delivery, the molecular weight, and the activity of the compound. The actual amount of the used drug can depend on the patient's age, weight, sex, medical condition, disease or any other medical criteria. The actual drug amount is determined according to intended medical use by techniques known in the art. The pharmaceutical dosage formulated according to the invention may be administered once or more times per day, preferably two or fewer times per day as determined by the attending physician.

**[0038]** Suitable formulations and methods of manufacture are further described in co-pending PCT/US2004/008101 entitled "Stable Formulations of Aminopyrdines and Uses Thereof" filed April 17, 2004 and U.S. Application No. 11/010,828 entitled "Sustained Release Aminopyridine Composition" filed December 13, 2004.

**[0039]** The release matrix aminopyridine formulation is preferably fabricated into tablets, capsules or granules for oral use. The rate of aminopyridine release from the tablets may be controlled by the erosion mechanism of the release matrix from which aminopyridine is released. In general, for producing a tablet on an industrial scale, the drug and polymer are granulated alone or in combination. Preferably the release of the aminopyridine from the matrix of the pharmaceutical composition is relatively linear over time. Preferably the matrix provides a release profile that gives a therapeutically effective concentration of the aminopyridine in the plasma of the patient permitting a once per day or twice per day dosing. Preferably the sustained release aminopyridine formulation for oral administration to patients includes from 0.0001 mole to 0.0013 mole aminopyridine that provides a mean maximum plasma concentration of aminopyridine from 15 to 180 ng/ml, a mean $T_{max}$ of 2 to 5 hours after administration, and a mean minimum plasma concentration of from 10 to 60 ng/ml at 8-24 hours after administration.

**[0040]** The formulations of the invention are prepared by procedures known in the art, such as, for example, by the dry or wet method. The method selected for manufacturing affects the release characteristics of the finished tablet. In one method, for example, the tablet is prepared by wet granulation in the presence of either water or an aqueous solution of the hydrophilic polymer or using other binder as a granulating fluid. In alternative, organic solvent, such as isopropyl alcohol, ethanol and the like, may be employed with or without water. The drug and polymer may be granulated alone or in combination. Another method for preparation of the tablet which may be used requires using a drug-polymer dispersion in organic solvents in the presence or absence of water. Where the aminopyridine or its derivative has very low solubility in water it may be advantageous to reduce the particle size, for example, by milling it into fine powder and in this way to control the release kinetics of the drug and enhance its solubility.

**[0041]** The hardness of the tablets of the present invention may vary, depending on a variety of factors, including, for example, the relative amounts and specific types of ingredients used, the tableting equipment employed, and the selected processing parameters. The pressure used to prepare the tablets can influence the release profile of the aminopyridine into the patient. The pressure used to prepare the tablets of the present invention may vary depending upon their surface area and the amount and particle size of aminopyridine, additive, excipients, or binders included in the tablet. The degree of hydration and solvation of the components in the composition will also be important in determining the hard ness of the tablets. Preferably the formed tablets have a hardness in the range of from 80-400 N, and more preferably from 150 to 300 N.

**[0042]** The effects of various matrices, concentrations of aminopyridine, as well as various excipients and additives to the composition on the concentration of the channel blocker on the dissolution rate may be monitored for example using a type H dissolution apparatus according to U.S. Pharmacopoeia XXII, or USP Apparatus II (Paddle Method). Clinical evaluations may be used to study the effects on plasma levels of various release matrices, concentrations of aminopyridine, as well as various excipients and additives. Plasma aminopyridine concentrations may be used to calculate

pharmacokinetic data (release profiles) including apparent absorption and elimination rates, area-under-the curve (AUC), maximum plasma concentration ($C_{max}$), time to maximum plasma concentration ($T_{max}$), absorption half-life ($T_{1/2}$(abs)), and elimination half life ($T_{1/2}$(elim)). Pharmacodynamic effects may be assessed based upon response tests, such as muscle strength improvement or reduction in spasticity for patients with multiple sclerosis or spinal cord injury or other tests as would be known to those skilled in the art. Plasma aminopyridine concentration in blood plasma or cerebral spinal fluid may be monitored using liquid chromatography/MS/MS assay methods.

**[0043]** The drug delivery of the invention can utilize any suitable dosage unit form. Specific examples of the delivery system of the invention are tablets, tablets that disintegrate into granules, capsules, sustained release microcapsules, spheroids, or any other means that allow for oral administration. These forms may optionally be coated with pharmaceutically acceptable coating which allows the tablet or capsule to disintegrates in various portions of the digestive system. For example a tablet may have an enteric coating that prevents it from dissolving until it reaches the more basic environment of the small intestine.

**[0044]** The dispersion of the aminopyridine throughout the release matrix imparts enhanced stability characteristics in the dosage formulation. This enhanced stability is achieved without loss of the desired sustained-release profile. Preferably the release profile, which may be measured by dissolution rate is linear or approximately linear, preferably the release profile is measured by the concentration of the aminopyridine in the plasma in the patient and is such to permit twice daily (BID) dosing.

**[0045]** The pharmaceutical composition of the present invention can include also auxiliary agents or excipients, for example, glidants, dissolution agents, surfactants, diluents, binders including low temperature melting binders, disintegrants, solubilizing agents and/or lubricants as described in co-pending PCT/US2004/008101 entitled "Stable Formulations of Aminopyrdines and Uses Thereof" filed April 17, 2004 and U.S. Application No. 11/010,828 entitled "Sustained Release Aminopyridine Composition" filed December 13, 2004.

**[0046]** The active ingredient of the present invention may be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein. Various excipients may be homogeneously mixed with the aminopyridines of the present invention as would be known to those skilled in the art. For example, aminopyridines may be mixed or combined with excipients such as but not limited to microcrystalline cellulose, colloidal silicon dioxide, lactose, starch, sorbitol, cyclodextrin and combinations of these.

**[0047]** To further improve the stability of the aminopyridine in the sustained release composition, an antioxidant compound can be included. Suitable antioxidants include, for example: sodium metabisulfite; tocopherols such as $\alpha$, $\beta$, $\delta$-tocopherol esters and $\alpha$-tocopherol acetate; ascorbic acid or a pharmaceutically acceptable salt thereof; ascorbyl palmitate; alkyl gallates such as propyl gallate, Tenox PG, Tenox s-1; sulfites or a pharmaceutically acceptable salt thereof; BHA; BHT; and monothioglycerol.

**[0048]** In another embodiment, the pharmaceutical composition of the present invention comprises a rate-controlling polymeric matrix comprising of a hydrogel matrix. For instance, an aminopyridine may be compressed into a dosage formulation containing a rate-controlling polymer, such as HPMC, or mixture of polymers which, when wet, will swell to form a hydrogel. The rate of release of the aminopyridine from this dosage formulation is sustained both by diffusion from the swollen tablet mass and by erosion of the tablet surface over time. The rate of release of the aminopyridine may be sustained both by the amount of polymer per tablet and by the inherent viscosities of the polymers used.

**[0049]** According to one embodiment of the invention, there is provided a stable, sustained-release oral dosage formulation which includes an effective amount a aminopyridine dispersed in a release matrix, and which, upon administration to a patient or as part of a therapy regiment, provides a release profile (of therapeutically effective blood plasma level of the aminopyridine) extending for a period of at least 6 hours, preferably at least 12 hours. In another embodiment, the stable, controlled-release oral dosage form provides, upon administration to a patient, a therapeutically effective blood plasma level of the aminopyridine for a period of at least 6 hours, preferably at least 12 hours, and more preferably at least 24 hours.

**[0050]** The dosage formulation may assume any form capable of delivering orally to a patient a therapeutically effective amount of an aminopyridine dispersed in a rate-controlling polymer. Preferably, the dosage formulation comprises a monolithic tablet.

**[0051]** Tablet weight will also vary in accordance with, among other things, the aminopyridine dosage, the type and amount of rate-controlling polymer used, and the presence, types and amounts of additional materials. Assuming 4-aminopyridine dosages of from 2 mg to 120 mg; tablet weights can range from 50 mg to 1200 mg per tablet, and preferably from 250 to 500 mg, and more preferably 400 mg.

**[0052]** The dosage formulation of the present invention may comprise also one or more pharmaceutically acceptable excipients as mentioned above. In preferred embodiments, the dosage formulation will comprise diluents and a lubricant in addition to the aminopyridine unit dose and the rate-controlling polymer. Particularly preferred diluents is microcrystalline cellulose sold under the name Avicel PH101, and a particularly preferred lubricant is magnesium stearate. When these materials are used, the magnesium stearate component preferably comprises from 0.2 to 0.75 %w/w of the dosage

formulation, and the microcrystalline cellulose along with the rate controlling polymer and aminopyridine comprises the balance of the formulation. For example, a tablet formulation including a aminopyridine x % w/w, a rate-controlling polymer y % w/w, and microcrystalline cellulose z %, the magnesium stearate amount would be (100-(x+y+z)) where $0.2\% \leq (100-(x+y+z)) \leq 0.75\%$ w/w. As would be known to those skilled in the art, the amount of an additives such as magnesium stearate may vary depending upon the shear rate used to perform the mixing and the amount of such an additive may be changed without limitation to obtain a satisfactory dissolution rate or plasma level of the aminopyridine.

**[0053]** As used herein, the term "sustained-release" as it relates to the aminopyridine compositions includes the release of a aminopyridine from the dosage formulation at a sustained rate such that a therapeutically beneficial blood level below toxic levels of the aminopyridine is maintained over a period of at least about 12 hours, preferably about 24 hours or more. Preferably, the amount of the aminopyridine in the oral dosage formulations according to embodiments of the present invention establish a therapeutically useful plasma concentration through BID administration of the pharmaceutical composition.

**[0054]** If desired, the dosage formulations of this invention may be coated with a sustained-release polymer layer so as to provide additional sustained-release properties. Suitable polymers that can be used to form this sustained release layer include, for example, the release matrices listed above. As desired, the dosage formulation of the invention can be provided also with a light-protective and/or cosmetic film coating, for example, film-formers, pigments, anti-adhesive agents and politicizes. Such a film-former may consist of fast-dissolving constituents, such as low-viscosity hydroxypropylmethylcelluose, for example, Methocel E5 or D14, or Pharmacoat 606 (Shin-Etsu). The film coating may also contain excipients or enteric coatings customary in film-coating procedures, such as, for example, light-protective pigments, for example, iron oxide, or titanium dioxide, anti-adhesive agents, for example, talc, and also suitable plasticizers such as, for example, PEG 400, PEG 6000, diethyl phthalate or triethyl citrate.

**[0055]** The compositions of the present invention may be used for the treatment of multiple sclerosis by oral administration. Preferably, the administration is twice daily dosage of a therapeutically effective amount of an aminopyridine, even more preferably, 4-AP dispersed in HPMC. The administration can also include scheduling administration of doses of the pharmaceutical so that the concentration of the aminopyridine in the patient is at about the minimum therapeutically effective level to ameliorate the neurological condition, yet relatively low compared to the maximum concentration in order to minimize side effects. The compositions may be administered to a subject at a dose and for a period sufficient to allow said subject to tolerate said dose without showing any adverse effects and thereafter increasing the dose of said active agent in the tablets at selected intervals of time until a therapeutic dose is achieved in the subject. For example, at the commencement of treatment the active agent is preferably administered at a dose less than 15 mg/day until a tolerable state is reached. The dose administered may then be increased by amounts of at least 5-10 mg/day until a therapeutic dose is reached, preferably less than 30 mg/day.

**[0056]** Compositions of the present invention where the potassium channel blocker is a mono- or di-aminopyridine active agent are particularly suitable for use in the treatment of a neurological disease that is characterized by demyelination of the central nervous system, more especially multiple sclerosis.

**[0057]** In one embodiment of the present invention, a method of treating multiple sclerosis is provided. Compositions of the present invention containing a therapeutically effective amount of mono- or di-aminopyridine active agent may be administered to a patient in need thereof. In particular, sustained release compositions comprising at least 5 milligrams of an aminopyridine, preferably 4-aminopyridine may be administered at least once daily. In a preferred embodiment, a sustained release composition containing from 10 to 15 milligrams of 4-aminopyridine is administered twice daily. Treatment of multiple sclerosis includes increased walking speed, improved lower extremity muscle strength or improved lower extremity muscle tone. The sustained release aminopyridine composition is preferably administered twice daily. In certain embodiments, the composition may be administered about every 12 hours.

**[0058]** In one embodiment the composition increases walking speed in patients with multiple sclerosis, wherein at least 5 milligrams of a sustained release aminopyridine composition, preferably at least 10 to 15 milligrams of a sustained release aminopyridine composition is administered.

**[0059]** In a further embodiment the composition increases muscle tone or muscle strength in patients with multiple sclerosis, wherein at least 5 milligrams of a sustained release aminopyridine composition, preferably at least 10 to 15 milligrams of a sustained release aminopyridine composition, is administered.

**[0060]** Fampridine is a potential therapy for MS with a unique mechanism of action. At concentrations of 1-2 μM or less, fampridine appears to be a specific blocker of voltage dependent, neuronal potassium channels that affect conduction in demyelinated axons. Fampridine has been shown to restore action potential conduction in damaged, poorly myelinated nerve fibers, and it may also directly enhance synaptic transmission. In previous clinical trials, treatment with fampridine has been associated with a variety of neurological benefits in people with MS including faster walking and increased strength, as measured by standard neurological assessments. Clinicians who regularly prescribe compounded fampridine for MS have reported that only a proportion of their patients appear to respond with clear clinical benefits, and that, in their judgment, this proportion may be around one third. This extent of responsiveness may be related to the proposed mechanism of action, which is the restoration of conduction in demyelinated axons via the blockade of

voltage-dependent potassium channels. Only a proportion of MS patients would be expected to possess axons of appropriate functional relevance that are susceptible to these drug effects, given the highly variable pathology of the disease. Currently, there is insufficient understanding of the disease to allow for pre-trial selection of potentially responsive patients. However, the existence of a subset of patients who respond consistently to the drug can be supported by quantitative observations in our own clinical studies discussed below.

**[0061]** Before treatment, the subjects in these two trials exhibited average walking speeds on the TW25 measure of approximately 2 feet per second (ft/sec). This is a significant deficit, since the expected walking speed for an unaffected individual is 5-6 ft/sec. Subjects in MS-F202 were selected for TW-25 walking time at screening of 8-60, which is equivalent to a range in speed of 0.42-3.1 ft/sec. Variability of functional status is an inherent characteristic of MS, and this can be seen in repeated measurement of walking speed over the course of weeks or months. At any of the three visits during the stable treatment period, 15-20% of placebo-treated subjects showed >20% improvement from baseline walking speed, a threshold chosen as one that indicates a true change in walking speed over background fluctuations. A larger proportion of the Fampridine-SR treated subjects showed such improvements, but this difference was not statistically significant, given the sample size and placebo response rate.

**[0062]** Given the often large variations in function experienced by people with MS, it is difficult for the subject or a trained observer to separate a treatment-related improvement from a disease-related improvement without the element of consistency over time. Consistency of benefit might therefore be expected to be a more selective measure of true treatment effect than magnitude of change. Based on this rationale, the responses of the individual subjects in the MS-F202 trial were examined for the degree to which their walking speed showed improvement during the double-blind treatment period and returned towards pre-treatment values after they were taken off drug, at follow-up. This subject-by-subject examination yielded a subgroup of subjects whose pattern of walking speed over time appeared to be consistent with a drug response. This led to the analysis illustrated in Figure 1. This compares the placebo and Fampridine-SR treated groups with respect to the number of visits during the double-blind treatment period in which walking speed on the TW25 was faster than the maximum speed out of all five of the non-treatment visits (four visits prior to randomization and one follow-up visit after the drug treatment period).

**[0063]** The placebo-treated group showed a clear pattern of exponential decline in numbers of subjects with higher numbers of "positive" visits. This is what would be expected from a random process of variability. In contrast, the pattern of response in the Fampridine-SR treated group strongly diverged from this distribution; much larger numbers of Fampridine-SR treated subjects showed three or four visits with higher walking speeds than the maximum speed of all five non-treatment visits and less than half of the expected proportion had no visits with higher speeds. These results indicate that there was a subpopulation of subjects in the Fampridine-SR treated group that experienced a consistent increase in walking speed related to treatment.

**[0064]** This analysis suggests that a relatively highly selective criterion for a likely treatment responder would be: a subject with a faster walking speed for at least three (i.e., three or four) of the four visits during the double blind treatment period compared to the maximum value for all five of the non-treatment visits. The four visits before initiation of double-blind treatment provide an initial baseline against which to measure the consistency of response during the four treatment visits. The inclusion of the follow-up visit as an additional component of the comparison was found valuable primarily in excluding those subjects who did not show the expected loss of improvement after coming off the drug. These are likely to be subjects who happened by chance to have improved in their MS symptoms around the time of treatment initiation, but whose improvement did not reverse on drug discontinuation because it was actually unrelated to drug. Thus, incorporating the follow-up visit as part of the criterion may help to exclude false positives, if the TW25 speed remains high at follow-up.

**[0065]** As described in Example 5, below, this responder criterion was met by 8.5%, 35.3%, 36.0%, and 38.6% of the subjects in the placebo, 10 mg, 15 mg, and 20 mg b.i.d. treatment groups, respectively, showing a highly significant and consistent difference between placebo and drug treatment groups. Given that there was little difference in responsiveness between the three doses examined, more detailed analyses were performed comparing the pooled Fampridine-SR treated groups against the placebo-treated group. The full results of this analysis for study are described in the following sections. These show that the responder group so identified experienced a >25% average increase in walking speed over the treatment period and that this increase did not diminish across the treatment period. The responder group also showed an increase in Subject Global Impression score and an improvement in score on the MSWS-12.

**[0066]** Additional features and embodiments of the present invention are illustrated by the following non-limiting examples.

## EXAMPLE 1

**[0067]** This example illustrates preparation of compositions of the present invention and their release of an aminopyridine. Tablets in accordance with the present invention having dosages of 5 mg, 7.5 mg and 12.5 mg respectively were manufactured at 5Kg scale. Materials were used in the amounts shown in Table 1.

**TABLE 1**

| | % w/w | | % w/w | | % w/w | |
|---|---|---|---|---|---|---|
| Milled 4-AP (#50 mesh) | 1.25 | | 1.875 | | 3.125 | |
| Methocel K100LV | 60 | | 60 | | 60 | |
| Avicel PH101 | 38.15 | | 37.525 | | 36.275 | |
| Magnesium stearate | 0.2 | | 0.2 | | 0.2 | |
| Aerosil 200 | 0.4 | | 0.4 | | 0.4 | |
| Equipment Tablet Press | Horn Noak equipped with 13 x 8mm oval tooling press speed 42,000 tablets / hr | | | | | |
| Tablet Weight Range (mg) | 386-404 (96.5-101.0%) | | 388-410 (97.0-102.5%) | | 388-406 (97.0-101.5%) | |
| Tablet Hardness Range (N) | 200-262 | | 179-292 | | 150-268 | |
| Tablet Potency - mg/tab. (%LC) | 97.1 | | 99.1 | | 100.2 | |
| Mean CU (mg/tab.)/%CV | 5.0mg / 1.0% | | 7.4mg / 0.7% | | 12.4mg / 1.1% | |
| CU Discrete Samples (mg/tab.)/ %CV | 5.0mg / 1.2% | | 7.5mg / 1.8% | | 12.3 / 1.1% | |
| **Dissolution (%/hr)** | **Mean** | **(SD)** | **Mean** | **(SD)** | **Mean** | **(SD)** |
| 1 | 28.9 | 1.1 | 29.2 | 1.8 | 25.9 | 1.1 |
| 2 | 42.7 | 1.8 | 42.1 | 1.6 | 40.2 | 2.5 |
| 3 | 52.8 | 1.4 | 53.0 | 1.0 | 49.8 | 2.1 |
| 4 | 61.4 | 2.2 | 61.8 | 1.5 | 60.1 | 2.4 |
| 6 | 75.7 | 3.1 | 75.2 | 1.6 | 74.8 | 2.7 |
| 10 | 95.5 | 3.3 | 98.7 | 1.4 | 93.2 | 0.9 |

**[0068]** Prior to blending, 4-AP was milled through #50 mesh screen using a Fitzmill® comminutor. The materials were added into a Gral 25 bowl in the following order: half Methocel K100LV, Avicel PH101, Aerosil 200, milled 4-AP and the remaining Methocel K100LV. The mix was blended for 15 minutes at 175 rpm, then the magnesium stearate was added and was further blended for 5 minutes at 100 rpm. Samples were taken from top and bottom positions for blend potency analysis. Weight and hardness checks were performed every 15 minutes by the check-master E3049. Discrete tablet samples were taken during the compression process to evaluate intra batch content uniformity.

**EXAMPLE 2**

**[0069]** This example illustrates that the pharmacokinetic profile of fampridine in compositions of the present invention is altered by administration in a sustained release tablet matrix compared to immediate release and controlled release formulations.

**[0070]** There is a delay in absorption manifested by a lower peak concentration, without any effect on the extent of absorption. When given as a single 12.5 mg dose, the peak concentration is approximately two-thirds lower as compared to peak values following administration of the IR formulation; the time to reach peak plasma levels was delayed by about 2 hours. As with the IR formulation, food delayed the absorption of Fampridine-SR. The absorption of fampridine was approximately 50% slower following ingestion of a fatty meal, although due to the flatness of the absorption curve, this may be exaggerated value. Extent of absorption did not differ, as values for Cmax and AUC were comparable as summarized in Table 2.

**Table 2** Pharmacokinetic Parameter Values (Mean ± SD) in Studies Using Fampridine SR, CR, and IR Formulations: Single Dose Studies in Healthy Adult Male Volunteers

| Study Number | Dose (mg) | Fed/Fasted | $C_{MAX}$ (ng/mL) | $t_{MAX}$ (hours) | AUC (0-∞) (ng hr/mL) |
|---|---|---|---|---|---|
| 0494006 N=12 | 12.5 SR (PD12265) | Fed | 28.7 ± 4.3 | 5.3 ± 0.8 | 257.0 ± 62.7 |
| | | Fasted | 25.6 ± 3.8 | 2.8 ± 1.3 | 269.9 ± 44.4 |
| | 12.5 IR (PD12266) | Fasted | 79.3 ± 16.3 | 0.9 ± 0.4 | 294.2 ± 55.6 |
| 1194002 N= 12 | 12.5 SR (PD12907) | Fasted | 28.5 ± 4.3 | 2.9 ± 2.4 | 285.9 ± 37.8 |
| | 12.5 CR (4n806) | Fasted | 37.7 ± 9.9 | 3.6 ± 0.9 | 300.0 ± 53.6 |
| | 12.5 IR (PS644) | Fasted | 83.5 ± 23.5 | 0.79 ± 0.3 | 274.0 ± 59.2 |

**EXAMPLE 3**

**[0071]** This example details the pharmacokinetic properties of Fampridine-SR in tablets of the present invention administered to patients with multiple sclerosis. Plasma samples were analyzed for fampridine using a validated LC/MS/MS assay with a sensitivity of 2 ng/mL. Noncompartmental pharmacokinetic parameter values were calculated using standard methodology.

**[0072]** This was an open-label, multi-center, dose proportionality study of orally administered fampridine in patients with multiple sclerosis. Single doses of fampridine were to be given in escalating doses (5 mg, 10 mg, 15 mg, and 20 mg) with at least a four-day interval between administration of each dose of drug. Safety evaluations were to be performed during the 24 hour period following administration of fampridine and blood samples were to be taken at the following times to determine pharmacokinetic parameters: hour 0 (pre-dose), hours 1-8, and hours 10, 12, 14, 18, and 24.

**[0073]** Twenty-three subjects received all 4 treatments, and one subject received only 3 treatments; data from all treatments were analyzed. Dose-dependent parameters (e.g., peak plasma concentration and areas-under-the curve) were normalized to a 10 mg dose for among-dose comparisons. Overall observed time of the peak plasma concentration (mean and its 95% confidence interval) was 3.75 (3.52, 3.98) h, observed peak plasma fampridine concentration (normalized to a 10 mg dose) was 24.12 (23.8, 26.6) ng/ml, area-under-the-concentration-time curve (normalized to a 10 mg dose) was estimated to be 254 (238, 270) ng·h/ml, extrapolated area-under-the-concentration-time curve (normalized to a 10 mg dose) was 284 (266, 302) ng·h/ml, terminal rate constant equaled 0.14 (0.13, 0.15) $h^{-1}$, terminal half-life was 5.47 (5.05, 5.89) h and clearance divided by bioavailability (CL/F) was equal to 637 (600, 674) ml/ min.

**[0074]** Dizziness was the most common treatment-related adverse event. Other treatment related adverse events included amblyopia, asthenia, headache, and ataxia. There were no clinically significant changes in clinical laboratory values, ECG parameters, vital signs, physical examination findings, or neurological examination findings noted over the course of this study.

**[0075]** When the plasma concentrations of fampridine were normalized to the 10.0 mg dose levels, there were no significant differences between any pharmacokinetic parameter (AUC, $C_{max}$, $t_{1/2}$) in the 5-20 mg dose range. Fampridine was well tolerated at the doses used in this study. Dose-normalized (to a 10 mg dose) pharmacokinetic parameter values are summarized in Table3.

**Table 3**. Dose-Normalized (at 10 mg) Pharmacokinetic Parameter Values (Mean ± SEM) Following Single Oral Administration of Fampridine-SR to Patients with MS.

| Dose (mg) | $C_{MAX}$-norm (ng/mL) | $t_{MAX}$ (hours) | AUC-norm (ng hr/mL) | $t_{1/2}$ (hours) | Cl/F (mL/min) |
|---|---|---|---|---|---|
| 5 (n=24) | 26.2±0.6 | 3.9±0.2 | 244.2±9.4 | 5.8±0.5 | 619.8±36.2 |
| 10 (n=24) | 25.2±0.7 | 3.9±0.3 | 252.2±7.8 | 5.6±0.4 | 641.4±39.1 |

(continued)

| Dose (mg) | $C_{MAX}$-norm (ng/mL) | $t_{MAX}$ (hours) | AUC-norm (ng hr/mL) | $t_{1/2}$ (hours) | Cl/F (mL/min) |
|---|---|---|---|---|---|
| 15 (n=24) | 24.6±0.7 | 3.6±0.3 | 263.0±7.4 | 5.5±0.4 | 632.4±39.0 |
| 20 (n=23) | 24.6±0.8 | 3.6±0.3 | 255.6±6.9 | 5.1±0.3 | 653.9±37.1 |

**EXAMPLE 4**

**[0076]** This example describes the results of an open-label study to assess the steady state pharmacokinetics of orally administered fampridine (4-aminopyridine) compositions of the present invention in subjects with Multiple Sclerosis. This study was an open-label multiple dose study of Fampridine-SR intended to assess steady state pharmacokinetics in 20 patients with MS who previously completed the study summarized in Table 4. Fampridine-SR (40 mg/day) was administered as two 20 mg doses, given as one morning and one evening dose for 13 consecutive days, with a single administration of 20 mg on Day 14. Blood samples for pharmacokinetic analysis were collected on Days 1, 7/8, and 14/15 at the following intervals: immediately prior to drug administration (baseline), hourly for the first 8 hours, and 10, 12, and 24 hours post-dose. Additional blood samples were collected 14, 18, and 20 hours post-dose on Day 14, and 30 and 36 hours post-dose on Day 15.

**[0077]** Pharmacokinetic parameter estimates following the first dose in these patients in this study on Day 1 were comparable to those determined when they participated in the study summarized in Table 4. No significant difference in $T_{max}$ was detected among the four means (Single dose = 3.76 h; Day 1 = 3.78 h; Day 8 = 3.33 h; Day 15 = 3.25 h). $C_{max}$ and $C_{max}/C_{\tau}$ on Days 8 ($C_{max}$ = 66.7 ng/ml) and 15 ($C_{max}$ = 62.6 ng/ml) were significantly greater than those of the single dose treatment and of Day 1 ($C_{max}$ = 48.6 ng/ml), reflecting accumulation of the drug with multiple dosing.

**[0078]** There was no significant difference among the four occasions with regard to either T or C and no difference in $C_{max}$, $C_{max}/C_{\tau}$, CL/F or $AUC_{0-\tau}$ between Days 8 and 15. Further AUC on Days 8 and 15 did not differ significantly from total AUC with single dose treatment. Likewise, the estimates of CL/F on Days 8 and 15 and of $\lambda$ and $T_{1/2}$ on Day 15 did not differ significantly from those with single dose.

**[0079]** Steady-state was attained by Day 7/8 as evidence by the lack of differences in $C_{max}$ or AUC between Days 7/8 and 14/15; there was no apparent unexpected accumulation. Likewise, the estimates of Cl/F on Days 7/8 and 14/15 of and of $T_{1/2}$ on Day 14/15 did not differ significantly from those given a single dose. On the final day of dosing, mean $C_{max}$ was 62.6 ng/mL, occurring 3.3 hours post-dose. The $T_{1/2}$ was 5.8 hours. These values are similar to those observed in patients with chronic SCI receiving similar doses of this formulation. These results are summarized in Table 4.

**Table 4**. Pharmacokinetic Parameter Values (Mean and 95% CI) Following Multiple Oral Doses of Fampridine-SR (40 mg/day) to 20 Patients with MS.

| Day | Parameter | | | | |
|---|---|---|---|---|---|
| | $C_{MAX}$ (ng/mL) | $t_{MAX}$ (hours) | $AUC_{(0-12)}$ (ng hr/mL) | $t_{1/2}$ (hours) | Cl/F (mL/min) |
| **Day 1** | 48.6 (42.0, 55.3) | 3.8 (3.2, 4.3) | NE | NE | NE |
| **Day 7/8** | 66.7 (57.5, 76.0) | 3.3 (2.8,3.9) | 531 (452,610) | NE | 700 (557,884) |
| **Day 14/15** | 62.6 (55.7,69.4) | 3.3 (2.6,3.9) | 499 (446,552) | 5.8 (5.0,6.6) | 703 (621, 786) |

**[0080]** Dizziness was the most common treatment-related adverse event. Other treatment-related adverse events that occurred included nausea, ataxia, insomnia, and tremor. There were no clinically significant changes in mean clinical laboratory values, vital signs, or physical examination findings from baseline to last visit. There were no apparent clinically significant changes in corrected QT intervals or QRS amplitudes after administration of fampridine.

**[0081]** Fampridine was well tolerated in subjects with multiple sclerosis who receive twice daily doses (20 mg/dose) of fampridine for two weeks. A significant increase was observed in $C_{max}$, and $C_{max}/C_{\tau}$ on Days 8 and 15 relative to those on Day 1 and with single dose treatment, reflecting accumulation of fampridine with multiple dosing. A lack of

significant differences in $C_{max}$, $C_{max}/C_{\tau}$, CL/F or $AUC_{0-\tau}$ between Days 8 and 15 suggest that near steady-state is reached by Day 8. There was no evidence of significant changes in pharmacokinetics during a two-week period of multiple dosing with fampridine.

## EXAMPLE 5

**[0082]** This example provides an embodiment of a method of treating subjects with a sustained release fampridine formulation and a responder analysis of the present invention. This was a Phase 2, double-blind, placebo-controlled, parallel group, 20-week treatment study in 206 subjects diagnosed with Multiple Sclerosis. This study was designed to investigate the safety and efficacy of three dose levels of Fampridine-SR, 10 mg b.i.d., 15 mg b.i.d., and 20 mg b.i.d. in subjects with clinically definite MS. The primary efficacy endpoint was an increase, relative to baseline, in walking speed, on the Timed 25 Foot Walk. Secondary efficacy measurements included lower extremity manual muscle testing in four groups of lower extremity muscles (hip flexors, knee flexors, knee extensors, and ankle dorsiflexors); the 9-Hole Peg Test and Paced Auditory Serial Addition Test (PASAT 3"); the Ashworth score for spasticity; Spasm Frequency/Severity scores; as well as a Clinician's (CGI) and Subject's (SGI) Global Impressions, a Subject's Global Impression (SGI), the Multiple Sclerosis Quality of Life Inventory (MSQLI) and the 12-Item MS Walking Scale (MSWS-12).

**[0083]** At the first visit (Visit 0) subjects were to enter into a two-week single-blind placebo run-in period for the purpose of establishing baseline levels of function. At Visit 2 subjects were to be randomized to one of four treatment groups (Placebo or Fampridine-SR 10 mg, 15 mg, 20 mg) and begin two weeks of double-blind dose-escalation in the active drug treatment groups (B, C and D). Group A were to receive placebo throughout the study. Subjects in the 10 mg (Group B) arm of the study took a dose of 10 mg approximately every 12 hours during both weeks of the escalation phase. The 15 mg (Group C) and 20 mg (Group D) dose subjects took a dose of 10 mg approximately every 12 hours during the first week of the escalation phase and titrated up to 15 mg b.i.d. in the second week. Subjects were to be instructed to adhere to an "every 12 hour" dosing schedule. Each subject was advised to take the medication at approximately the same time each day throughout the study; however, different subjects were on differing medication schedules (e.g., 7 AM and 7 PM; or 9 AM and 9 PM). After two weeks, the subjects were to return to the clinic at Visit 3 for the start of the stable dose treatment period. The first dose of the double-blind treatment phase at the final target dose (placebo b.i.d. for the Group A, 10 mg b.i.d. for Group B, 15 mg b.i.d. for Group C, and 20 mg b.i.d. for Group D) was taken in the evening following Study Visit 4. Subjects were to be assessed five times during the 12-week treatment period. Following the 12-week treatment phase there was to be a one-week down titration starting at Visit 9. During this down-titration period, group B was to remain stable at 10 mg b.i.d. and Group C was to be titrated to 10 mg b.i.d., while group D was to have a change in the level of dose during the week (15 mg b.i.d. for the first three days and 10 mg b.i.d. for the last four days). At the end of the down titration period at Visit 10, subjects were to enter a two-week washout period where they did not receive any study medication. The last visit (Visit 11) was to be scheduled two weeks after the last dosing day (end of the downward titration). Plasma samples were collected at each study site visit other than Study Visit 0.

**[0084]** The primary measure of efficacy was improvement in average walking speed, relative to the baseline period (placebo run-in), using the Timed 25 Foot Walk from the Multiple Sclerosis Functional Composite Score (MSFC). This is a quantitative measure of lower extremity function. Subjects were instructed to use whatever ambulation aids they normally use and to walk as quickly as they could from one end to the other end of a clearly marked 25-foot course. Other efficacy measures included the LEMMT, to estimate muscle strength bilaterally in four groups of muscles: hip flexors, knee flexors, knee extensors, and ankle dorsiflexors. The test was performed at the Screening Visit and at Study Visits 1, 2, 4, 7, 8, 9 and 11. The strength of each muscle group was rated on the modified BMRC scale: 5 = Normal muscle strength; 4.5= Voluntary movement against major resistance applied by the examiner, but not normal; 4= Voluntary movement against moderate resistance applied by the examiner; 3.5= Voluntary movement against mild resistance applied by the examiner; 3= Voluntary movement against gravity but not resistance; 2= Voluntary movement present but not able to overcome gravity; 1= Visible or palpable contraction of muscle but without limb movement; and 0= Absence of any voluntary contraction. Spasticity in each subject was assessed using the Ashworth Spasticity Score. The Ashworth Spasticity Exam was performed and recorded at the Screening Visit and at Study Visits 1, 2, 4, 7, 8, 9 and 11.

**[0085]** Protocol Specified Responder Analysis. To supplement the primary analysis, a categorical "responder" analysis was also conducted. Successful response was defined for each subject as improvement in walking speed (percent change from baseline) of at least 20%. Subjects who dropped out prior to the stable dose period were considered non-responders. The proportions of protocol specified responders were compared among treatment groups using the Cochran-Mantel-Haenszel test, controlling for center.

**[0086]** Post hoc analysis of this study suggested that a relatively highly selective criterion for a likely treatment responder would be a subject with a faster walking speed for at least three visits during the double blind treatment period as compared to the maximum value among a set of five non-treatment visits (four before treatment and one after discontinuation of treatment). The four visits before initiation of double-blind treatment provided an initial baseline against which to measure the consistency of response during the four double-blind treatment visits. The inclusion of the follow-up visit

as an additional component of the comparison was useful primarily in excluding those subjects who may be false positives, i.e., did not show the expected loss of improvement after coming off the drug. Treatment differences in the proportion of theses post hoc responders were analyzed using the Cochran-Mantel-Haenszel (CMH) test, controlling for center.

**[0087]** To validate the clinical meaningfulness of the post hoc responder variable, (post hoc) responders were compared against the (post hoc) non-responders, on the subjective variables: (i) Change from baseline in MSWS-12 over the double-blind; (ii) SGI over the double-blind; and (iii) Change from baseline in the CGI over the double-blind; to determine if subjects with consistently improved walking speeds during the double-blind could perceive improvement relative to those subjects who did not have consistently improved walking speeds. For the subjective variables, differences between responder status classification (responder or non-responder) were compared using an ANOVA model with effects for responder status and center.

**[0088]** Results. A total of 206 subjects were randomized into the study: 47 were assigned to placebo, 52 to 10 mg bid Fampridine-SR (10 mg bid), 50 to 15 mg bid Fampridine-SR (15 mg bid), and 57 to 20 mg bid Fampridine-SR (20 mg bid). The disposition of subjects is presented in Table 5 below.

**Table 5 Summary of subject disposition (all randomized population)**

| | Treatment Group: N (%) | | | | |
|---|---|---|---|---|---|
| | **Placebo** | **10 mg bid** | **15mg bid** | **20 mg bid** | **Total** |
| **Subjects Randomized** | 47 | 52 | 50 | 57 | 206 |
| **Took at Least One Dose (Included in Safety Analysis)** | 47 (100%) | 52 (100%) | 50 (100%) | 57 (100%) | 206 (100%) |
| **ITT Population** | 47 (100%) | 51 (98.1%) | 50 (100%) | 57 (100%) | 205 (99.5%) |
| **Discontinued Subjects** | 2 (4.3%) | 2 (3.8%) | 1 (2.0%) | 6 (10.5%) | 11 (5.3%) |
| Note: Percentages are based on the number of randomized subjects. | | | | | |

**[0089]** All 206 randomized subjects took at least one dose of study medication and were included in the safety population. One subject (subject# 010/07 10 mg bid group) was excluded from the ITT population (lost to follow-up after 8 days of placebo run-in). A total of 11 subjects discontinued from the study.

**[0090]** The population consisted of 63.6% females and 36.4% males. The majority of the subjects were Caucasian (92.2%), followed by Black (4.9%), Hispanic (1.5%), those classified as 'Other' (1.0%), and Asian/Pacific Islander (0.5%). The mean age, weight, and height of the subjects were 49.8 years (range: 28-69 years), 74.44 kilograms (range: 41.4-145.5 kilograms), and 168.84 centimeters (range: 137.2-200.7 centimeters), respectively. Most of the subjects (52.4%) had a diagnosis type of secondary progressive with about equal amounts of relapsing remitting (22.8%) and primary progressive (24.8%) subjects. The mean duration of disease was 12.00 years (range: 0.1-37.5 years) while the mean Expanded Disability Status Scale (EDSS) at screening was 5.77 units (range: 2.5-6.5 units). The treatment groups were comparable with respect to all baseline demographic and disease characteristic variables.

**[0091]** Results for the key efficacy variables at baseline for the ITT population are further summarized in Table 6 below.

**Table 6 Summary of key efficacy variables at baseline (ITT population)**

| | Treatment Group: Mean (SD) | | | | |
|---|---|---|---|---|---|
| **Parameter** | **placebo N=47** | **10 mg bid N=51** | **15mg bid N=50** | **20 mg bid N=57** | **Treatment. p-value** |
| **Walking Speed (ft/sec)** | 1.87 (0.902) | 1.94 (0.874) | 1.99 (0.877) | 2.04 (0.811) | 0.752 |
| **LEMMT** | 4.05 (0.690) | 3.98 (0.661) | 4.00 (0.737) | 3.98 (0.634) | 0.964 |
| **SGI** | 4.38 (0.795) | 4.32 (0.999)* | 4.56 (1.110) | 4.25 (0.969) | 0.413 |
| **MSWS-12** | 75.71 (16.566) | 76.31 (16.186) | 74.60 (17.671) | 76.83 (18.124) | 0.923 |
| *: One subject did not have a baseline value. | | | | | |

**[0092]** With respect to the 205 subjects in the ITT population, mean values for baseline walking speed, LEEMT, SGI, and MSWS-12 were approximately 2 feet per second, 4 units, 4.5 units, and 76 units, respectively. The treatment groups

were comparable with respect to these variables as well as all the other efficacy variables at baseline.

**[0093]** Descriptive statistics for the average walking speed (ft/sec) by study day based on the Timed 25-Foot Walk are presented in Table 7 and Figure 2. The timed 25 foot walk showed a trend toward increased speed during the stable dose period for all three dose groups, though the average improvement declined during the treatment period.

**Table 7 Average walking speeds (ft/sec) by study day (observed cases, ITT population)**

| Summary Statistics Over Time | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Study day | | | | | | |
| Treatment | | base | titration | 1st stbl | 2nd stbl | 3rd stbl | follow-up |
| placebo | Mean | 1.87 | 1.89 | 1.90 | 1.89 | 1.89 | 1.86 |
| | (SD) | (0.902) | (0.876) | (0.908) | (0.891) | (0.914) | (0.933) |
| | N# | 47 | 47 | 46 | 46 | 45 | 45 |
| 10mg bid | Mean | 1.94 | 2.20 | 2.09 | 2.12 | 2.00 | 1.88 |
| | (SD) | (0.874) | (0.979) | (0.955) | (1.043) | (1.016) | (0.970) |
| | N | 51 | 51 | 51 | 51 | 50 | 48 |
| 15mg bid | Mean | 1.99 | 2.25 | 2.16 | 2.14 | 2.18 | 1.83 |
| | (SD) | (0.877) | (0.995) | (0.986) | (0.957) | (0.932) | (0.952) |
| | N | 50 | 49 | 49 | 48 | 48 | 47 |
| 20mg bid | Mean | 2.04 | 2.26 | 2.22 | 2.19 | 2.04 | 1.83 |
| | (SD) | (0.811) | (0.936) | (0.893) | (0.936) | (0.996) | (0.822) |
| | N | 57 | 55 | 52 | 51 | 49 | 55 |
| #: The treatment sample sizes presented in the figure legend represent the number of ITT subjects. Sample sizes at individual time points may be smaller than those in the ITT population due to dropouts or missed assessments. | | | | | | | |

**[0094]** During double-blind treatment, all the Fampridine-SR groups exhibited mean walking speeds between 2.00 and 2.26 feet per second, while the mean value in the placebo group was consistently about 1.90 feet per second. It should be noted that, at the third stable-dose visit, both the 10 mg bid and 20 mg bid group means dropped-off from what would be expected under the assumption that treatment benefit is consistent over time. This may or may not have been due to chance; further studies should provide additional evidence for either case. After double-blind medication was discontinued, all the treatment groups converged to approximately the same mean value at follow-up.

**[0095]** Results for the primary efficacy variable (percent change in average walking speed during the 12-week stable dose period relative to baseline based on the 25-foot walk) are summarized in Figure 3. The timed 25 foot walk showed a trend toward increased speed during the stable dose period for all three dose groups, though the average improvement declined during the treatment period, as shown in Figure 3. The mean percent changes in average walking speed during the 12-week stable dose period (based on adjusted geometric mean change of the log-transformed walking speeds) were 2.5%, 5.5%, 8.4%, and 5.8% for the placebo, 10 mg bid, 15 mg bid, and 20 mg bid groups, respectively. There were no statistical differences between any Fampridine-SR groups and the placebo group.

**[0096]** Results for the protocol specified responder analysis (subjects with average changes in walking speed during the 12 weeks of stable double-blind treatment of at least 20%) are summarized in Figure 4. The percentages of subjects with average changes in walking speed during the 12-week stable dose period of at least 20% (pre-defined responders) were 12.8%, 23.5%, 26.5%, and 16.1% for the placebo, 10 mg bid, 15 mg bid, and 20 mg bid groups, respectively. There were no statistically significant differences between any of the Fampridine-SR groups and the placebo group.

**[0097]** Descriptive statistics for the average overall Lower Extremity Manual Muscle Testing (LEMMT) by study day are presented in Table 8 and in Figure 5.

**Table 8. Average overall LEMMT by Study Day**

| Summary Statistics Over Time | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Study day | | | | | | |
| Treatment | | base | titration | 1st stbl | 2nd stbl | 3rd stbl | follow-up |
| placebo | Mean | 4.05 | 4.00 | 4.02 | 4.03 | 4.00 | 4.02 |
| | (SD) | (0.690) | (0.705) | (0.687) | (0.696) | (0.679) | (0.738) |
| | N# | 47 | 46 | 46 | 46 | 45 | 45 |
| 10mg bid | Mean | 3.98 | 4.09 | 4.06 | 4.09 | 4.07 | 3.89 |
| | (SD) | (0.661) | (0.641) | (0.650) | (0.685) | (0.642) | (0.631) |
| | N | 51 | 50 | 51 | 51 | 50 | 49 |
| 15mg bid | Mean | 4.00 | 4.16 | 4.11 | 4.09 | 4.17 | 4.08 |
| | (SD) | (0.737) | (0.653) | (0.645) | (0.659) | (0.618) | (0.674) |
| | N | 50 | 49 | 49 | 49 | 49 | 46 |
| 20mg bid | Mean | 3.98 | 4.08 | 4.03 | 3.98 | 4.07 | 3.92 |
| | (SD) | (0.634) | (0.639) | (0.659) | (0.714) | (0.649) | (0.650) |
| | N | 57 | 54 | 52 | 52 | 48 | 55 |
| #: The treatment sample sizes presented at individual time points may be smaller than those in the ITT population due to dropouts or missed assessments. | | | | | | | |

**[0098]** During double-blind treatment, all the Fampridine-SR groups exhibited a numerical pattern of larger mean LEMMT scores than placebo (except the 20 mg bid group at the 2nd stable dose visit). After double-blind medication was discontinued, with the exception of the 15 mg bid group, all the group means were lower than they were at baseline.

**[0099]** Results for the average change in LEMMT during the 12-week stable dose period relative to baseline are summarized in Figure 6. The mean changes in overall LEMMT during the 12-week stable dose period were -0.05 units, 0.10 units, 0.13 units, and 0.05 units for the placebo, 10 mg bid, 15 mg bid, and 20 mg bid groups, respectively. Improvements in LEMMT were significantly greater in the 10 mg bid and 15 mg bid groups compared to the placebo group; there was no significant difference between the 20 mg bid group and the placebo group.

**[0100]** No statistically significant differences were detected among treatment group based on any of the other secondary efficacy variables, as shown in Table 9.

Table 9 Changes in secondary efficacy variables from baseline during the 12-week stable dose period

| | **Treatment Group** | | | |
|---|---|---|---|---|
| **Parameter** | **placebo N=47** | **10 mg bid N=51** | **15mg bid N=50** | **20 mg bid N=57** |
| Ashworth Score<br>N<br>Mean (SD)<br>p-value (each dose vs. placebo) | <br>46<br>-0.11 (0.377) | <br>51<br>-0.04 (0.449)<br>0.802 | <br>49<br>-0.06 (0.375)<br>0.826 | <br>53<br>0.02 (0.466)<br>0.275 |
| CGI<br>N<br>Mean (SD)<br>p-value (each dose vs. placebo) | <br>45<br>0.0 (0.66) | <br>50<br>-0.2 (0.72)<br>0.772 | <br>49<br>-0.1 (0.85)<br>0.997 | <br>52<br>0.0 (0.78)<br>0.996 |
| SGI<br>N<br>Mean (SD)<br>p-value (each dose vs. placebo) | <br>46<br>-0.2 (0.96) | <br>50<br>0.0 (1.27)<br>0.704 | <br>49<br>-0.1 (1.11)<br>0.953 | <br>53<br>-0.1 (0.86)<br>0.968 |
| PASAT | | | | |

(continued)

| | Treatment Group | | | |
|---|---|---|---|---|
| **Parameter** | **placebo N=47** | **10 mg bid N=51** | **15mg bid N=50** | **20 mg bid N=57** |
| N | 46 | 51 | 49 | 53 |
| Mean (SD) | 2.17 (4.016) | 2.13 (3.394) | 0.90 (3.274) | 0.65 (4.590) |
| p-value (each dose vs. placebo) | | >0.999 | 0.306 | 0.218 |
| MSFC | | | | |
| N | 46 | 51 | 49 | 52 |
| Mean (SD) | 0.08 (0.205) | 0.10 (0.310) | 0.90 (0.224) | 0.06 (0.194) |
| p-value (each dose vs. placebo) | | 0.977 | >0.999 | 0.968 |
| MSWS-12 | | | | |
| N | 46 | 51 | 49 | 52 |
| Mean (SD) | -3.56 (14.548) | -5.53 (16.154) | -7.32 (16.295) | -5.76 (15.296) |
| p-value (each dose vs. placebo) | | 0.718 | 0.445 | 0.617 |
| Note: The treatment sample sizes presented in the treatment heading represent the number of ITT subjects. Sample sizes for individual variables may be smaller due to dropouts or missed assessments.<br>Note: For each variable, the p-values (versus placebo) are Dunnett-adjusted. | | | | |

**[0101]** While pre-planned analyses of the primary efficacy endpoint provided insufficient evidence of treatment benefits for any of the Fampridine-SR doses, subsequent analysis revealed the existence of a subset of subjects who responded to the drug with clinical meaningfulness. These subjects exhibited walking speeds while on drug that were consistently better than the fastest walking speeds measured when the subjects were not taking active drug.

**[0102]** The post hoc responder rates based on consistency of improved walking speeds were significantly higher in all three active dose groups (35, 36 and 39%) compared to placebo (9%; $p<0.006$ for each dose group, adjusting for multiple comparisons) as shown in Figure 7.

**[0103]** Given that there was little difference in responsiveness between the three doses examined, more detailed analyses were performed comparing the pooled Fampridine-SR treated groups against the placebo-treated group. Figure 8 summarizes, for the placebo and the pooled Fampridine-SR group, the percentage of post hoc responders. The number of subjects who met he post hoc responder criterion in the pooled Fampridine-SR treated group was 58 (36.7%) compared to 4 (8.5%) in the placebo-treated group, and this difference was statistically significant ($p<0.001$).

**[0104]** To validate the clinical meaningfulness of the post hoc responder variable, the 62 responders (58 fampridine and 4 placebo) were compared against the 143 non-responders (100 fampridine and 43 placebo) on the subjective variables to determine if subjects with consistently improved walking speeds during the double-blind could perceived benefit relative to those subjects who did not have consistently improved walking speeds. The results are summarized in Figure 9 and indicate that consistency in walking speed had clinical meaningfulness for the subjects in this study since the responders had (over the double-blind period) significantly better changes from baseline in MSWS-12 and significantly better subjective global scores. In addition, the responders were rated marginally better than the non-responders by the clinicians during the double-blind. Thus, responders experienced clinically meaningful improvements in their MS symptoms, and treatment with fampridine significantly increased the chances of such a response.

**[0105]** To establish baseline comparability among the responder analysis groups, analyses were performed on the baseline demographic variables, key neurological characteristics and the relevant efficacy variables at baseline. In general, the responder analysis groups were comparable for all demographic and baseline characteristics variables.

**[0106]** Having demonstrated the clinical meaningfulness of consistently improved walking speeds during the double-blind as a criterion for responsiveness, the question of the magnitude of benefit becomes of interest. The fampridine non-responders, although providing no relevant efficacy information, do provide safety information regarding those individuals who are treated with fampridine but show no apparent clinical benefit. As such, responder analyses of these groups were performed.

**[0107]** With respect to magnitude of benefit, Figure 10 and Table 12 below summarizes the percent changes in walking speed at each double-blind visit by responder analysis grouping. The mean improvement for the fampridine responders during the double-blind across 14 weeks of treatment ranged from 24.6% to 29.0% compared to 1.7% to 3.7% for the placebo group; this was highly significant ($p<0.001$) at every visit. Although providing no relevant efficacy information, results for the fampridine non-responders are also illustrated and show that there was, and could be, some worsening in walking speeds after 12-weeks when a non-responder is treated with fampridine. The improvement was stable ($\pm$ 3%) across 14 weeks of treatment, and was associated with improvement in two global measures (Subject Global

Impression and Multiple Sclerosis Walking Scale-12). The four placebo responders showed a 19% improvement in walking speed but there were too few subjects in this group for meaningful statistical comparison. Response status was not significantly related to baseline demographics, including type or severity of MS. Adverse events and safety measures were consistent with previous experience for this drug.

**Table 12. Summary of percent change in Walking Speed at each double-blind visit by responder analysis grouping.**

| | | | | | |
|---|---|---|---|---|---|
| | Summary Statistics Over Time | | | | |
| | | Study day | | | |
| Treatment | | titration | 1st stbl | 2nd stbl | 3rd stbl |
| Placebo | Mean | 1.7 | 2.6 | 1.8 | 3.7 |
| | (SEM) | (2.21) | (3.23) | (3.11) | (3.38) |
| | N# | 47 | 46 | 46 | 45 |
| Fampridine | Mean | 8.3 | 3.5 | -0.2 | -6.5 |
| Non-responders | (SEM) | (2.05) | (1.90) | (1.76) | (2.49) |
| | N | 97 | 94 | 93 | 89 |
| Fampridine | Mean | 27.4 | 24.6 | 29.0 | 27.3 |
| Responders | (SEM) | (2.43) | (2.44) | (4.31) | (3.52) |
| | N | 58 | 58 | 57 | 58 |
| FR vs. Placebo | p-value^ | <0.001 | <0.001 | <0.001 | <0.001 |
| FR vs.FNR | p-value^ | <0.001 | <0.001 | <0.001 | <0.001 |
| FNR vs. PBO | p-value^ | 0.080 | 0.884 | 0.497 | 0.022 |
| | | | | | |

ABBREVIATIONS: FR=Fampridine Responders; FNR=Fampridine Non-responders.
#: The treatment sample sizes presented at individual time points may be smaller than those in the ITT population due to dropouts or missed assessments.
#: The treatment sample sizes presented in the figure legend represent the number of ITT subjects. Sample sizes at individual time points may be smaller due to dropouts or missed assessments.
^: P-values from t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis grouping and center.

**[0108]** Figure 11 and Table 13 summarize the changes in LEMMT at each double-blind visit by responder analysis grouping. The mean improvement for the fampridine responders during the double-blind ranged from 0.09 to 0.18 units compared to -0.04 units at each visit for the placebo group; this was significant at every visit except the second stable dose visit (p=0.106). Although providing no relevant efficacy information, results for the fampridine non-responders are also illustrated and show that there was, and could be, some significant improvement in leg strength when non-responder is treated with fampridine. This suggests that although a clinically meaningful response can be linked to about 37% of subjects treated with Fampridine-SR, additional subjects may have functional improvements on variables other than walking speed.

**Table 13. Summary of percent change in LEMMT at each double-blind visit by responder analysis grouping.**

| | | | | | |
|---|---|---|---|---|---|

(continued)

| Summary Statistics Over Time | | | | | |
|---|---|---|---|---|---|
| | | Study day | | | |
| Treatment | | titration | 1st stb1 | 2nd stbl | 3rd stbl |
| Placebo | Mean | -0.04 | -0.04 | -0.04 | -0.04 |
| | (SEM) | (0.035) | (0.042) | (0.039) | (0.042) |
| | N# | 46 | 46 | 46 | 45 |
| Fampridine | Mean | 0.12 | 0.10 | 0.09 | 0.10 |
| Non-responders | (SEM) | (0.028) | (0.033) | (0.036) | (0.038) |
| | N | 95 | 94 | 94 | 89 |
| Fampridine | Mean | 0.18 | 0.09 | 0.09 | 0.17 |
| Responders | (SEM) | (0.029) | (0.032) | (0.043) | (0.045) |
| | N | 58 | 58 | 58 | 58 |
| FR vs. Placebo | p-value^ | <0.001 | 0.023 | 0.106 | 0.004 |
| FRvs.FNR | p-value^ | 0.178 | 0.627 | 0.739 | 0.311 |
| FNR vs. PBO | p-value^ | <0.001 | 0.003 | 0.038 | 0.032 |
| | | | | | |

ABBREVIATIONS: FR=Fampridine Responders; FNR=Fampridine Non-responders.
#: The treatment sample sizes presented at individual time points may be smaller than those in the ITT population due to dropouts or missed assessments. Treatment sample sizes presented in the
figure legend represent the number of ITT subjects. Sample sizes at individual time points may be smaller due to dropouts or missed assessments.
^: P-values from t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis grouping and center.

**[0109]** Figure 12 and Table 14, below, summarize the changes in Overall Ashworth Score at each double-blind visit by responder analysis grouping. The mean reduction from baseline (indicative of improvement) for the fampridine responders during the double-blind ranged from -0.18 to -0.11 units compared to -0.11 to -0.06 for the placebo group. The fampridine responders were numerically superior to placebo but there was insufficient evidence to detect significant differences. Although appearing to provide little relevant efficacy information, results for the fampridine non-responders are also illustrated.

**Table 14. Summary of change in overall Ashworth score at each double-blind visit by responder analysis grouping.**

| | | | | | |
|---|---|---|---|---|---|
| Summary Statistics Over Time | | | | | |
| | | Study day | | | |
| Treatment | | titration | 1st stbl | 2nd stbl | 3rd stbl |
| Placebo | Mean | -0.06 | -0.11 | -0.06 | -0.13 |
| | (SEM) | (0.069) | (0.073) | (0:070) | (0.073) |
| | N# | 46 | 46 | 46 | 45 |
| Fampridine | Mean | -0.16 | -0.08 | -0.07 | 0.00 |
| Non-responders | (SEM) | (0.044) | (0.053) | (0.054) | (0.056) |

(continued)

| Summary Statistics Over Time | | | | | |
|---|---|---|---|---|---|
| | | Study day | | | |
| Treatment | | titration | 1st stbl | 2nd stbl | 3rd stbl |
| | N | 95 | 94 | 94 | 89 |
| Fampridine | Mean | -0.14 | -0.18 | -0.11 | -0.18 |
| Responders | (SEM) | (0.058) | (0.066) | (0.060) | (0.055) |
| | N | 58 | 58 | 58 | 58 |
| FR vs. Placebo | p-value^ | 0.343 | 0.374 | 0.717 | 0.680 |
| FR vs. FNR | p-value^ | 0.675 | 0.210 | 0.911 | 0.064 |
| FNR vs. PBO | p-value^ | 0.151 | 0.823 | 0.772 | 0.189 |
| | | | | | |
| ABBREVIATIONS: FR=Fampridine Responders; FNR=Fampridine Non-responders.<br>#: The treatment sample sizes presented at individual time points may be smaller than those in the ITT population due to dropouts or missed assessments.<br>^: P-values from t-tests of the least-squares means using the mean square error via an ANOVA model with effects for responder analysis grouping and center. | | | | | |

**[0110]** Adverse events most commonly reported prior to treatment were accidental injury, reported by 12 (5.8%) subjects, nausea, reported by 9 (4.4%) subjects, and asthenia, diarrhea, and paresthesia, each reported by 8 (3.9%) subjects. Six (2.9%) subjects also reported headache, anxiety, dizziness, diarrhea, and peripheral edema. These adverse events are indicative of the medical conditions affecting people with MS.

**[0111]** Conclusions. The data does not appear to support either a number of anecdotal reports or expectations from preclinical pharmacology that doses higher than about 10 to 15 mg b.i.d., and even about 10 mg b.i.d., should be associated with greater efficacy. The data presented below in Table 15 support this, based on the new responder analysis methodology.

**Table 15. Comparison of 10 mg vs.15 mg among Responders**

| | 10 mg (N=51) | 15 mg (N=50) |
|---|---|---|
| Responders N (%) | 18 (35.3) | 18 (36.0) |
| Average % CFB in Walk Speed: Mean (SD) | 27.6% (18.39) | 29.6% (22.43) |
| %Change in Walk Speed by Visit: minimum - maximum | 26%-32% | 27%-31% |
| Average SGI | 4.8 (1.09) | 4.7 (1.09) |
| Average Change in MSWS-12 * | -11.1 (21.9) | -7.8 (19.6) |
| * For the average change in the MSWS-12, a negative score is indicative of subjective improvement. | | |

**[0112]** A responder analysis based on consistency of improvement provides a sensitive, meaningful approach to measuring effects on the timed 25 foot walk and may be used as a primary endpoint for future trials. This data suggest that for responsive subjects (approximately 37%), treatment with fampridine at doses of 10-20 mg bid produces substantial and persistent improvement in walking.

**[0113]** *Efficacy.* There are no notable differences between 10 mg bid and 15 mg bid among subjects who respond to drug. In fact, the largest difference, favors the 10 mg bid group (see MSWS-12 result).

**[0114]** *Safety.* With respect to safety, there are three considerations: There was an apparent decline below baseline walking speed at the last visit on drug in the fampridine non-responders in the 10 mg bid and 20 mg bid groups, but not the 15 mg bid group. This may or may not be significant, but is not clearly dose related. There was an apparent rebound effect, with walking speed dropping below baseline, among fampridine treated subjects at the two week follow-up visit; this occurred in the 15 and 20 mg but not the 10 mg bid group. Serious AE's were more frequent in the 15 mg and 20

mg bid groups 10% and 12% rates vs. 0% rate in 10 mg bid and 4% in placebo groups. This may or may not be significant, but the risk of potentially related SAEs, particularly seizures appears to be dose-related from all available data and based on mechanism of action. Based on this data, it would appear that a 10 mg bid dose is preferred because of its favorable risk to benefit ratio compared with the 15 and 20 mg doses.

## Claims

1. A sustained release aminopyridine composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 15 milligrams or less of aminopyridine.

2. A sustained-release aminopyridine composition for improving lower extremity muscle strength in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 15 milligrams or less of aminopyridine.

3. A sustained release aminopyridine composition for improving lower extremity muscle tone in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 15 milligrams or less of aminopyridine.

4. The composition of any one of claims 1 to 3 which provides a $C_{avss}$ of 15 ng/ml to 35 ng/ml.

5. The composition of any one of claims 1 to 3 wherein said therapeutic dose is at least 5 milligrams of aminopyridine.

6. The composition of any one of claims 1 to 3, wherein said therapeutic dose is 10 to 15 milligrams of aminopyridine.

7. The composition of any one of claims 1 to 3, wherein said therapeutic dose is 10 milligrams of aminopyridine.

8. The composition of any one of claims 1 to 3, wherein said stable dose treatment is greater than two weeks in duration.

9. The composition of any one of claims 1 to 7, wherein said aminopyridine is a mono- aminopyridine or a di-aminopyridine.

10. The composition of any one of claims 1 to 8, wherein said aminopyridine is 4-aminopyridine.

11. The composition of any one of claims 1 to 9, wherein said composition is for administration every 12 hours.

12. Use of aminopyridine in the manufacture of a sustained release composition for increasing the walking speed of a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 15 milligrams or less of aminopyridine.

13. Use of aminopyridine in the manufacture of a sustained release composition for improving lower extremity muscle tone in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 15 milligrams or less of aminopyridine.

14. Use of aminopyridine in the manufacture of a sustained release composition for improving lower extremity muscle strength in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment twice daily in a therapeutic dose of 15 milligrams or less of aminopyridine.

15. The use as claimed in any one of claims 12 to 14 which provides a $C_{avss}$ of 15 ng/ml to 35 ng/ml.

16. The use as claimed in any one of claims 12 to 14 wherein said therapeutic dose is at least 5 milligrams of aminopyridine.

17. The use as claimed in any one of claims 12 to 14 wherein said therapeutic dose is 10 to 15 milligrams of aminopyridine.

18. The use as claimed in any one of claims 12 to 14 wherein said therapeutic dose is 10 milligrams of aminopyridine.

**19.** The use of any one of claims 12 to 14, wherein said stable dose treatment is greater than two weeks in duration.

**20.** The use of any one of claims 12 to 19, wherein said aminopyridine is a mono- aminopyridine or a di-aminopyridine.

**21.** The use as claimed in any one of claims 12 to 20 wherein said aminopyridine is 4-aminopyridine.

**22.** The use as claimed in any one of claims 12 to 21 wherein said composition is for administration every 12 hours.

**23.** A sustained release aminopyridine composition for maintaining a therapeutically effective concentration of an aminopyridine in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment with a daily therapeutic dose of less than 30 milligrams of aminopyridine; and, wherein the sustained release aminopyridine composition has a therapeutically effective concentration for increasing the walking speed of a patient with multiple sclerosis.

**24.** A sustained release aminopyridine composition for maintaining a therapeutically effective concentration of an aminopyridine in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment with a daily therapeutic dose of less than 30 milligrams of aminopyridine; and, wherein the sustained release aminopyridine composition has a therapeutically effective concentration for improving lower extremity muscle strength in a patient with multiple sclerosis.

**25.** A sustained release aminopyridine composition for maintaining a therapeutically effective concentration of an aminopyridine in a patient with multiple sclerosis, said composition to be administered as a stable dose treatment with a daily therapeutic dose of less than 30 milligrams of aminopyridine; and, wherein the sustained release aminopyridine composition has a therapeutically effective concentration for improving lower extremity muscle tone in a patient with multiple sclerosis.

**26.** The composition of any one of claims 23 to 25 for administration twice daily.

**27.** The composition of any one of claims 23 to 25, wherein said stable dose treatment is greater than two weeks in duration.

**28.** The composition of any one of claims 23 to 25, wherein said aminopyridine is a mono- aminopyridine or a di-aminopyridine.

**29.** The composition of claim 28 wherein said aminopyridine is 4-aminopyridine.

**Patentansprüche**

**1.** Eine Aminopyridinzusammensetzung mit Langzeitfreisetzung zum Steigern der Gehgeschwindigkeit eines Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis zweimal täglich in einer therapeutischen Dosis von 15 Milligramm Aminopyridin oder weniger zu verabreichen ist.

**2.** Eine Aminopyridinzusammensetzung mit Langzeitfreisetzung zum Verbessern der Muskelkraft in den unteren Extremitäten eines Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis zweimal täglich in einer therapeutischen Dosis von 15 Milligramm Aminopyridin oder weniger zu verabreichen ist.

**3.** Eine Aminopyridinzusammensetzung mit Langzeitfreisetzung zum Verbessern des Muskeltonus in den unteren Extremitäten eines Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis zweimal täglich in einer therapeutischen Dosis von 15 Milligramm Aminopyridin oder weniger zu verabreichen ist.

**4.** Zusammensetzung gemäß einem der Ansprüche 1 bis 3, die eine $C_{avss}$ (mittlere Steady-state-Konzentration) von 15 ng/ml bis 35 ng/ml bereitstellt.

**5.** Zusammensetzung gemäß einem der Ansprüche 1 bis 3, wobei die therapeutische Dosis mindestens 5 Milligramm Aminopyridin beträgt.

6. Zusammensetzung gemäß einem der Ansprüche 1 bis 3, wobei die therapeutische Dosis 10 bis 15 Milligramm Aminopyridin beträgt.

7. Zusammensetzung gemäß einem der Ansprüche 1 bis 3, wobei die therapeutische Dosis 10 Milligramm Aminopyridin beträgt.

8. Zusammensetzung gemäß einem der Ansprüche 1 bis 3, wobei die Behandlung mit stabiler Dosis länger als zwei Wochen dauert.

9. Zusammensetzung gemäß einem der Ansprüche 1 bis 7, wobei das Aminopyridin ein Monoaminopyridin oder ein Diaminopyridin ist.

10. Zusammensetzung gemäß einem der Ansprüche 1 bis 8, wobei das Aminopyridin 4-Aminopyridin ist.

11. Zusammensetzung gemäß einem der Ansprüche 1 bis 9, wobei die Zusammensetzung alle 12 Stunden zu verabreichen ist.

12. Eine Verwendung von Aminopyridin bei der Herstellung einer Zusammensetzung mit Langzeitfreisetzung zum Steigern der Gehgeschwindigkeit eines Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis zweimal täglich in einer therapeutischen Dosis von 15 Milligramm Aminopyridin oder weniger zu verabreichen ist.

13. Eine Verwendung von Aminopyridin bei der Herstellung einer Zusammensetzung mit Langzeitfreisetzung zum Verbessern des Muskeltonus in den unteren Extremitäten eines Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis zweimal täglich in einer therapeutischen Dosis von 15 Milligramm Aminopyridin oder weniger zu verabreichen ist.

14. Eine Verwendung von Aminopyridin bei der Herstellung einer Zusammensetzung mit Langzeitfreisetzung zum Verbessern der Muskelkraft in den unteren Extremitäten eines Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis zweimal täglich in einer therapeutischen Dosis von 15 Milligramm Aminopyridin oder weniger zu verabreichen ist.

15. Verwendung gemäß einem der Ansprüche 12 bis 14, die eine $C_{avss}$ von 15 ng/ml bis 35 ng/ml bereitstellt.

16. Verwendung gemäß einem der Ansprüche 12 bis 14, wobei die therapeutische Dosis mindestens 5 Milligramm Aminopyridin beträgt.

17. Verwendung gemäß einem der Ansprüche 12 bis 14, wobei die therapeutische Dosis 10 bis 15 Milligramm Aminopyridin beträgt.

18. Verwendung gemäß einem der Ansprüche 12 bis 14, wobei die therapeutische Dosis 10 Milligramm Aminopyridin beträgt.

19. Verwendung gemäß einem der Ansprüche 12 bis 14, wobei die Behandlung mit stabiler Dosis länger als zwei Wochen dauert.

20. Verwendung gemäß einem der Ansprüche 12 bis 19, wobei das Aminopyridin ein Monoaminopyridin oder ein Diaminopyridin ist.

21. Verwendung gemäß einem der Ansprüche 12 bis 20, wobei das Aminopyridin 4-Aminopyridin ist.

22. Verwendung gemäß einem der Ansprüche 12 bis 21, wobei die Zusammensetzung alle 12 Stunden zu verabreichen ist.

23. Eine Aminopyridinzusammensetzung mit Langzeitfreisetzung zum Aufrechterhalten einer therapeutisch wirksamen Konzentration eines Aminopyridins bei einem Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis mit einer täglichen therapeutischen Dosis von weniger als 30 Milligramm Aminopyridin zu verabreichen ist, und wobei die Aminopyridinzusammensetzung mit Langzeitfreisetzung eine thera-

peutisch wirksame Konzentration zum Steigern der Gehgeschwindigkeit eines Patienten mit Multipler Sklerose aufweist.

**24.** Eine Aminopyridinzusammensetzung mit Langzeitfreisetzung zum Aufrechterhalten einer therapeutisch wirksamen Konzentration eines Aminopyridins bei einem Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis mit einer täglichen therapeutischen Dosis von weniger als 30 Milligramm Aminopyridin zu verabreichen ist, und wobei die Aminopyridinzusammensetzung mit Langzeitfreisetzung eine therapeutisch wirksame Konzentration zum Verbessern der Muskelkraft in den unteren Extremitäten eines Patienten mit Multipler Sklerose aufweist.

**25.** Eine Aminopyridinzusammensetzung mit Langzeitfreisetzung zum Aufrechterhalten einer therapeutisch wirksamen Konzentration eines Aminopyridins bei einem Patienten mit Multipler Sklerose, wobei die Zusammensetzung als eine Behandlung mit stabiler Dosis mit einer täglichen therapeutischen Dosis von weniger als 30 Milligramm Aminopyridin zu verabreichen ist, und wobei die Aminopyridinzusammensetzung mit Langzeitfreisetzung eine therapeutisch wirksame Konzentration zum Verbessern des Muskeltonus in den unteren Extremitäten eines Patienten mit Multipler Sklerose aufweist.

**26.** Zusammensetzung gemäß einem der Ansprüche 23 bis 25 zur zweimal täglichen Verabreichung.

**27.** Zusammensetzung gemäß einem der Ansprüche 23 bis 25, wobei die Behandlung mit stabiler Dosis länger als zwei Wochen dauert.

**28.** Zusammensetzung gemäß einem der Ansprüche 23 bis 25, wobei das Aminopyridin ein Monoaminopyridin oder ein Diaminopyridin ist.

**29.** Zusammensetzung gemäß Anspruch 28, wobei das Aminopyridin 4-Aminopyridin ist.

**Revendications**

**1.** Une composition d'aminopyridine à libération prolongée pour l'augmentation de la vitesse de marche d'un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables deux fois par jour en dose thérapeutique de 15 milligrammes ou moins d'aminopyridine.

**2.** Une composition d'aminopyridine à libération prolongée pour l'amélioration de la force musculaire des membres inférieurs chez un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables deux fois par jour en dose thérapeutique de 15 milligrammes ou moins d'aminopyridine.

**3.** Une composition d'aminopyridine à libération prolongée pour l'amélioration de la tonicité musculaire des membres inférieurs chez un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables deux fois par jour en dose thérapeutique de 15 milligrammes ou moins d'aminopyridine.

**4.** La composition de n'importe laquelle des revendications 1 à 3, laquelle fournit une $C_{avss}$ (Concentration moyenne à l'état d'équilibre) allant de 15 ng/ml à 35 ng/ml.

**5.** La composition de n'importe laquelle des revendications 1 à 3 dans laquelle ladite dose thérapeutique est d'au moins 5 milligrammes d'aminopyridine.

**6.** La composition de n'importe laquelle des revendications 1 à 3, dans laquelle ladite dose thérapeutique va de 10 à 15 milligrammes d'aminopyridine.

**7.** La composition de n'importe laquelle des revendications 1 à 3, dans laquelle ladite dose thérapeutique est de 10 milligrammes d'aminopyridine.

**8.** La composition de n'importe laquelle des revendications 1 à 3, dans laquelle ledit traitement à doses stables a une durée supérieure à deux semaines.

**9.** La composition de n'importe laquelle des revendications 1 à 7, dans laquelle ladite aminopyridine est une mono-

aminopyridine ou une di-aminopyridine.

**10.** La composition de n'importe laquelle des revendications 1 à 8, dans laquelle ladite aminopyridine est la 4-aminopyridine.

**11.** La composition de n'importe laquelle des revendications 1 à 9, dans laquelle ladite composition est destinée à être administrée toutes les 12 heures.

**12.** Utilisation d'aminopyridine dans la fabrication d'une composition à libération prolongée pour l'augmentation de la vitesse de marche d'un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables deux fois par jour en dose thérapeutique de 15 milligrammes ou moins d'aminopyridine.

**13.** Utilisation d'aminopyridine dans la fabrication d'une composition à libération prolongée pour l'amélioration de la tonicité musculaire des membres inférieurs chez un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables deux fois par jour en dose thérapeutique de 15 milligrammes ou moins d'aminopyridine.

**14.** Utilisation d'aminopyridine dans la fabrication d'une composition à libération prolongée pour l'amélioration de la force musculaire des membres inférieurs chez un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables deux fois par jour en dose thérapeutique de 15 milligrammes ou moins d'aminopyridine.

**15.** L'utilisation telle que revendiquée dans n'importe laquelle des revendications 12 à 14, laquelle fournit une $C_{avss}$ allant de 15 ng/ml à 35 ng/ml.

**16.** L'utilisation telle que revendiquée dans n'importe laquelle des revendications 12 à 14 dans laquelle ladite dose thérapeutique est d'au moins 5 milligrammes d'aminopyridine.

**17.** L'utilisation telle que revendiquée dans n'importe laquelle des revendications 12 à 14 dans laquelle ladite dose thérapeutique va de 10 à 15 milligrammes d'aminopyridine.

**18.** L'utilisation telle que revendiquée dans n'importe laquelle des revendications 12 à 14 dans laquelle ladite dose thérapeutique est de 10 milligrammes d'aminopyridine.

**19.** L'utilisation de n'importe laquelle des revendications 12 à 14, dans laquelle ledit traitement à doses stables a une durée supérieure à deux semaines.

**20.** L'utilisation de n'importe laquelle des revendications 12 à 19, dans laquelle ladite aminopyridine est une mono-aminopyridine ou une di-aminopyridine.

**21.** L'utilisation telle que revendiquée dans n'importe laquelle des revendications 12 à 20, dans laquelle ladite aminopyridine est la 4-aminopyridine.

**22.** L'utilisation telle que revendiquée dans n'importe laquelle des revendications 12 à 21, dans laquelle ladite composition est destinée à être administrée toutes les 12 heures.

**23.** Une composition d'aminopyridine à libération prolongée pour le maintien d'une concentration efficace d'un point de vue thérapeutique d'une aminopyridine chez un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables avec une dose thérapeutique quotidienne inférieure à 30 milligrammes d'aminopyridine ; et où la composition d'aminopyridine à libération prolongée a une concentration efficace d'un point de vue thérapeutique pour augmenter la vitesse de marche d'un patient atteint de sclérose en plaques.

**24.** Une composition d'aminopyridine à libération prolongée pour le maintien d'une concentration efficace d'un point de vue thérapeutique d'une aminopyridine chez un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables avec une dose thérapeutique quotidienne inférieure à 30 milligrammes d'aminopyridine ; et où la composition d'aminopyridine à libération prolongée a une concentration

efficace d'un point de vue thérapeutique pour améliorer la force musculaire des membres inférieurs chez un patient atteint de sclérose en plaques.

**25.** Une composition d'aminopyridine à libération prolongée pour le maintien d'une concentration efficace d'un point de vue thérapeutique d'une aminopyridine chez un patient atteint de sclérose en plaques, ladite composition devant être administrée sous forme de traitement à doses stables avec une dose thérapeutique quotidienne inférieure à 30 milligrammes d'aminopyridine ; et où la composition d'aminopyridine à libération prolongée a une concentration efficace d'un point de vue thérapeutique pour améliorer la tonicité musculaire des membres inférieurs chez un patient atteint de sclérose en plaques.

**26.** La composition de n'importe laquelle des revendications 23 à 25 destinée à être administrée deux fois par jour.

**27.** La composition de n'importe laquelle des revendications 23 à 25, dans laquelle ledit traitement à doses stables a une durée supérieure à deux semaines.

**28.** La composition de n'importe laquelle des revendications 23 à 25, dans laquelle ladite aminopyridine est une mono-aminopyridine ou une di-aminopyridine.

**29.** La composition de la revendication 28 dans laquelle ladite aminopyridine est la 4-aminopyridine.

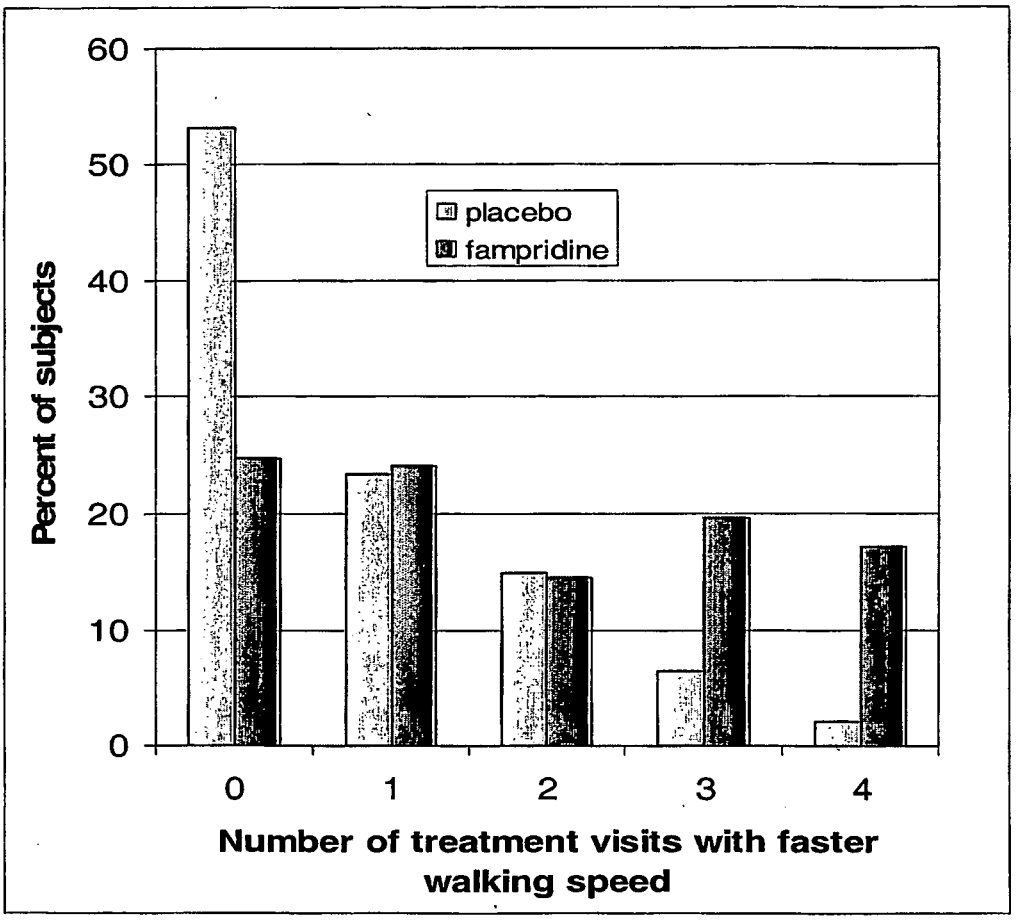

60
50
40
30
20
10
0
Percent of subjects
placebo
fampridine
0
1
2
3
4
Number of treatment visits with faster walking speed

Fig. 1

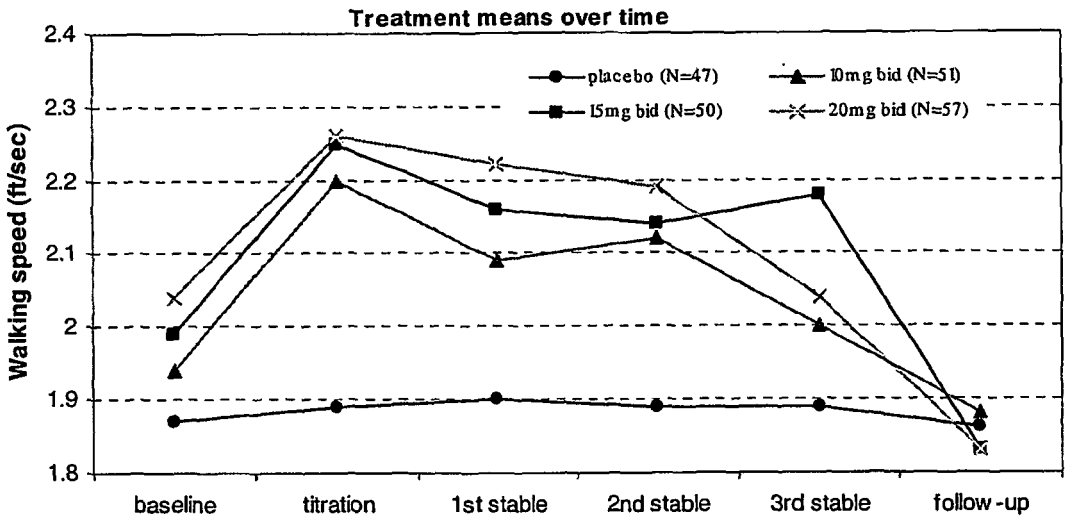
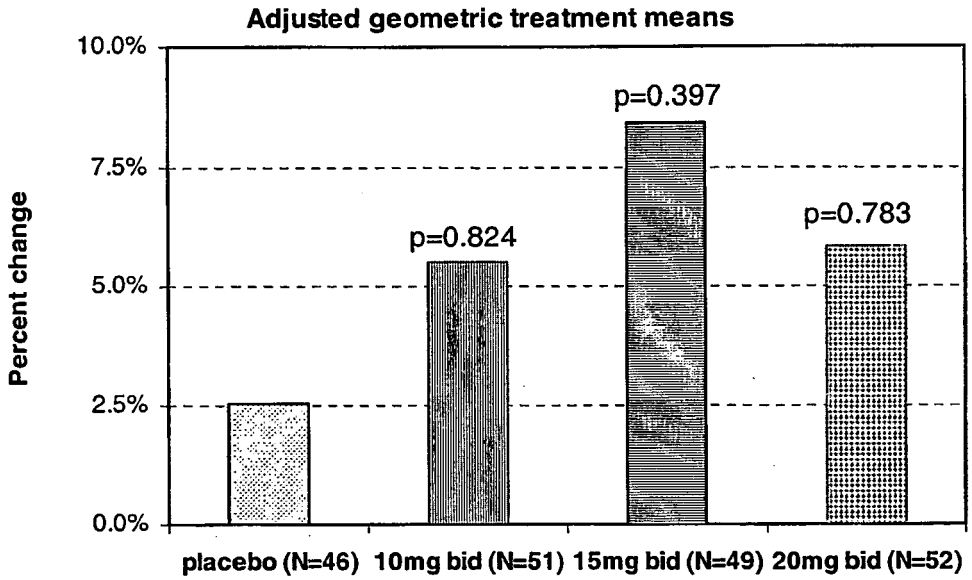

Treatment means over time
Walking speed (ft/sec)
2.4
2.3
2.2
2.1
2
1.9
1.8
placebo (N=47)
10mg bid (N=51)
15mg bid (N=50)
20mg bid (N=57)
baseline
titration
1st stable
2nd stable
3rd stable
follow-up

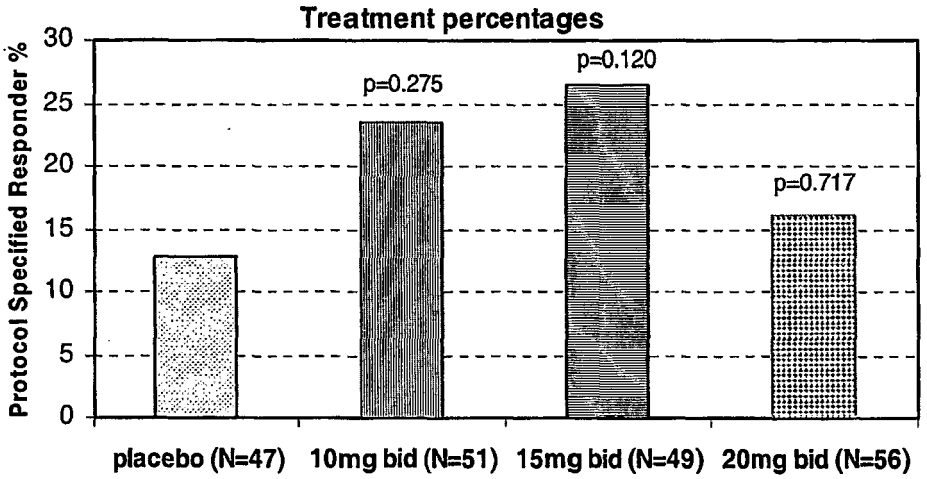
Fig. 2




Note: The treatment sample sizes are based on the number of ITT subjects with available data.

Note: The p-values (versus placebo) presented above the treatment mean bars are Dunnett-adjusted

Fig. 3




Note: The treatment sample sizes are based on the number of ITT subjects with available data.

Fig. 4

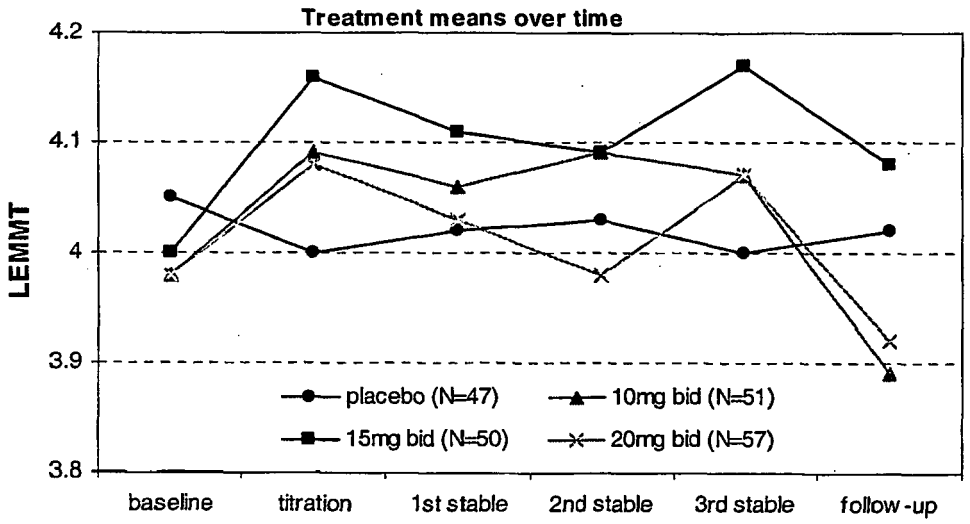
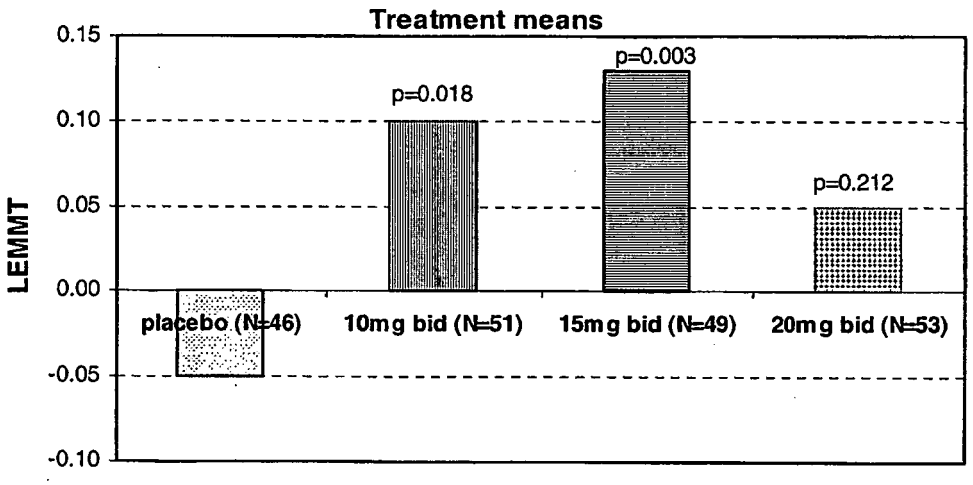

Treatment means over time
LEMMT
4.2
4.1
4
3.9
3.8
placebo (N=47)
10mg bid (N=51)
15mg bid (N=50)
20mg bid (N=57)
baseline
titration
1st stable
2nd stable
3rd stable
follow-up

Fig. 5




Note: The treatment sample sizes are based on the number of ITT subjects with available data.
Note: The p-values (versus placebo) presented above the treatment mean bars are Dunnett-adjusted

Fig. 6

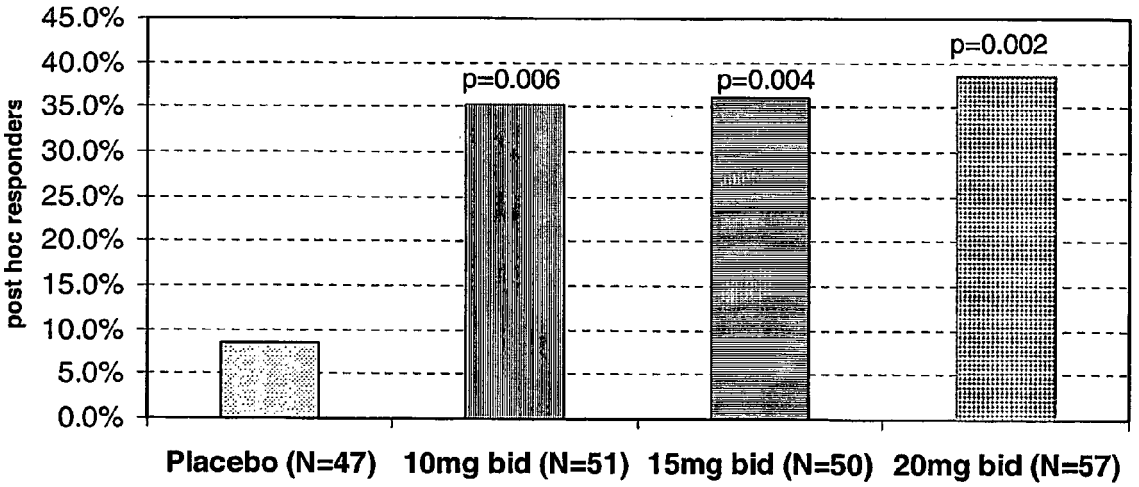
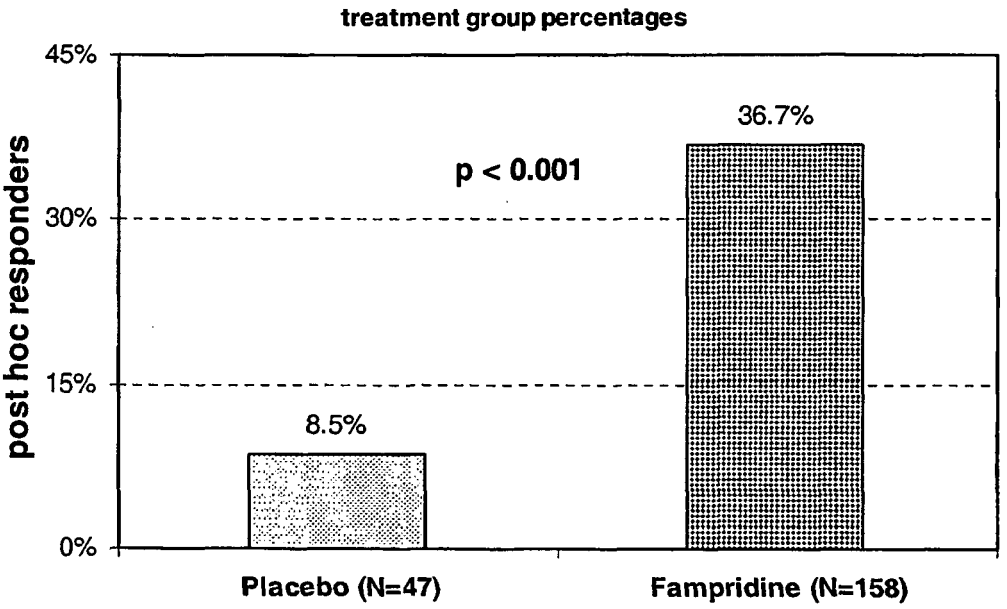

45.0%
40.0%
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
post hoc responders
p=0.006
p=0.004
p=0.002
Placebo (N=47)
10mg bid (N=51)
15mg bid (N=50)
20mg bid (N=57)

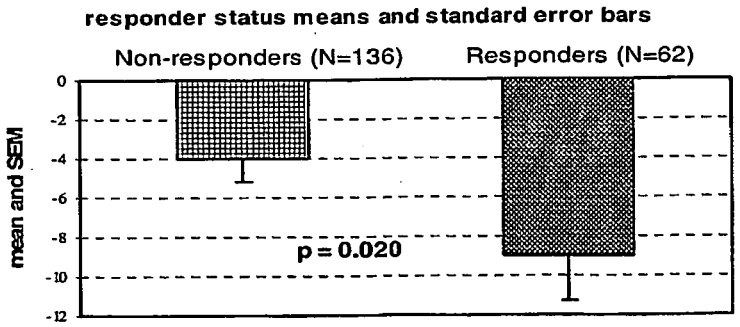
Fig. 7



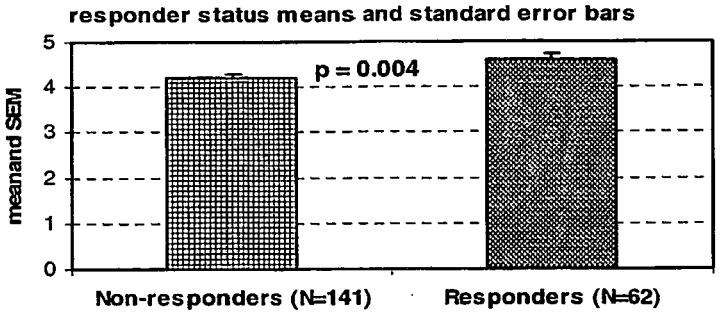

Note: Treatment p-value from the Cochran-Mantel Haenszel test controlling for center.

Fig. 8

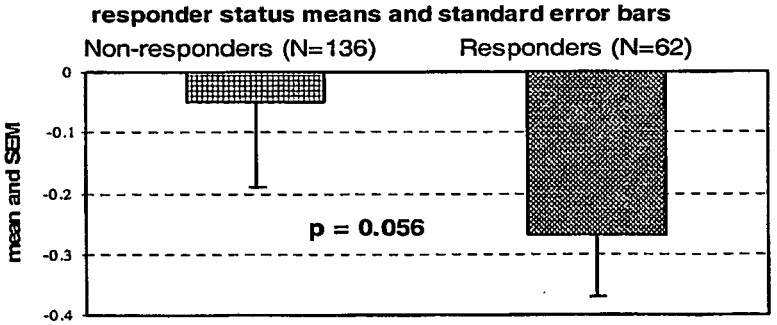
*Change from baseline in the MSWS-12 over the double-blind**




*SGI over the double-blind*

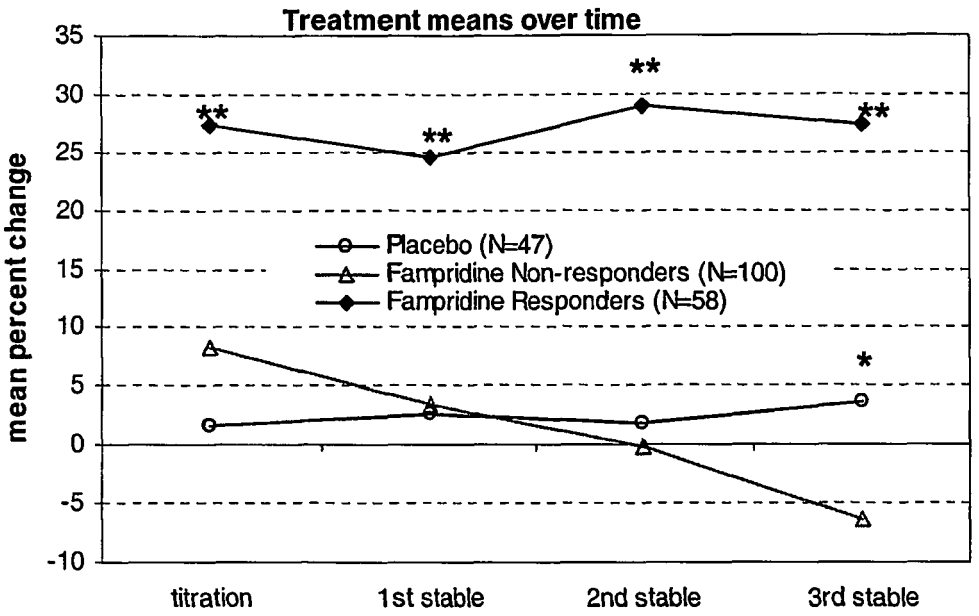



*Change from baseline in the CGI over the double-blind*




•Double blind measurements at first and last stable dose visits only.
•Note: For the changes from baseline, a negative score is indicative of clinical benefit.
•Note: Some non-responders had no post-baseline data for a particular variable; so the sample sizes for the non-responders (with respect to that variable) may be less than the actual number of non-responders.
•Note: the p-values comparing responders to non-responders are from ANOVA models with effects for responder status and center.

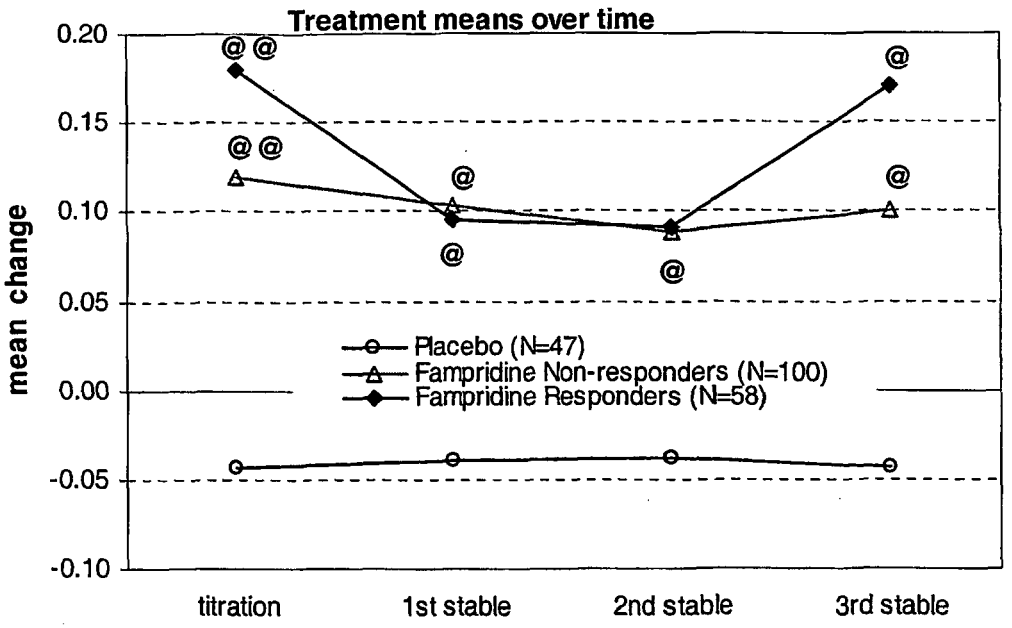
Fig. 9




**: Significantly better than placebo and fampridine non-responders ($p < 0.001$ for each).

*: Significantly better than fampridine non-responders.

Fig. 10




@@: Significantly better than placebo ($p < 0.001$).
@: Significantly better than placebo ($p < 0.05$).

Fig. 11

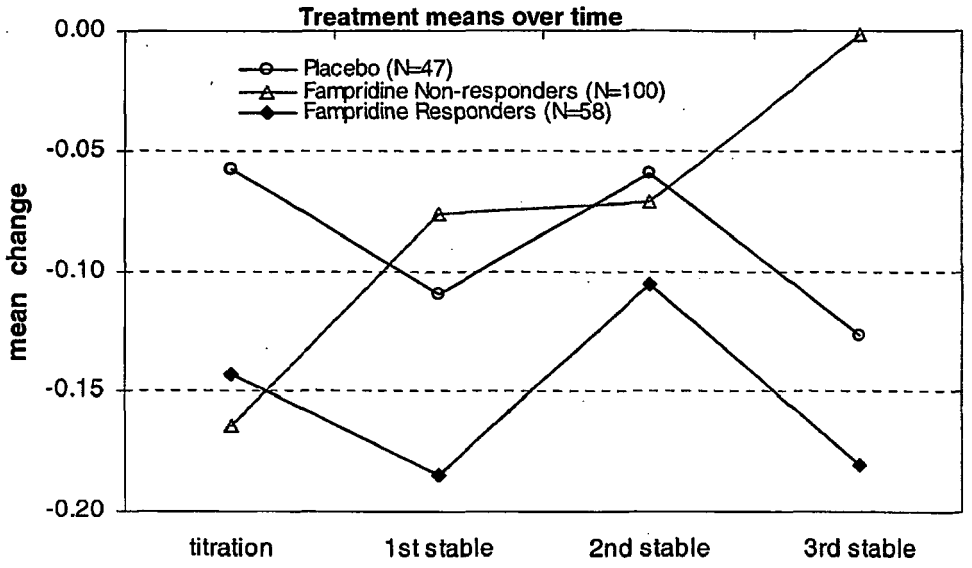

Treatment means over time
Placebo (N=47)
Fampridine Non-responders (N=100)
Fampridine Responders (N=58)
mean change
0.00
-0.05
-0.10
-0.15
-0.20
titration
1st stable
2nd stable
3rd stable

Fig. 12

## REFERENCES CITED IN THE DESCRIPTION

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