Abstract: Disclosed herein is use of one or more aminopyridines in methods and compositions for improving walking capacity in patients with multiple sclerosis.
METHODS FOR IMPROVING WALKING CAPACITY IN PATIENTS WITH MULTIPLE SCLEROSIS USING AN AMINOPYRIDINE

[0001] This application claims the benefit of U.S. provisional application No. 61/682,742 filed August 13, 2012, which is incorporated by reference herein in its entirety.

1. FIELD OF INVENTION

[0002] The invention relates to improving walking capacity in patients with multiple sclerosis using one or more aminopyridines.

2. BACKGROUND

2.1 Multiple Sclerosis

[0003] Multiple Sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS) with both inflammatory and degenerative components. It is the most common neurologic, disabling disease in young adults (Frohman, 2003, The Medical Clinics of North America, 87(4): 867-897, viii-ix). Permanent neurological dysfunction can result from incomplete recovery from acute relapses or as a consequence of slow progression of disability.

[0004] Overall, about 75-85% of MS individuals have some degree of ambulatory impairment and over half need assistance both indoors and outdoors (Kraft et al., 1986, Arch Phys Med Rehabil 67:164-168; Weinshenker et al, 1989, Brain 112:133-146). More than one third do not retain the ability to walk 20 years after the diagnosis (Schapiro, 1991, A Rehabilitation Approach to Management, Demos, New York).

[0005] Between 350,000-400,000 Americans have MS. MS may affect different neurological systems such as visual, sensory, cerebellar and/or motor. Walking impairment and inactivity are primary concerns for individuals with MS. This was verified by Harris Interactive survey which reported 64% of individuals with MS experienced trouble walking. Approximately 94% found the walking and balance problems to be somewhat disruptive to their overall daily living. Overall, about 75-85% of MS individuals have some degree of ambulatory impairment and over half need assistance both indoors and outdoors (Kraft et al, 1986, Arch Phys Med Rehabil 67:164-168; Weinshenker et al, 1989, Brain 112:133-146).
More than one third do not retain the ability to walk 20 years after the diagnosis (Schapiro, 1991, A Rehabilitation Approach to Management, Demos, New York).

[0006] The effect of ambulatory dysfunction on regular activities is present in MS individuals with various degrees of disability. The functional implication varies from limiting the length of walking for someone with minimal deficits, to impairing the ability to transfer to the toilet for others with more significant disability. Prompt identification, characterization and treatment of impairment in walking capacity can be beneficial.

2.2 Aminopyridines

[0007] An exemplary property of certain aminopyridines is that they are potassium channel blockers.

[0008] 4-aminopyridine (4-AP) is an example of an aminopyridine with such potassium channel blocking properties. At 4-AP plasma concentrations obtained in clinical studies, which are typically < 1 μM (94 ng/mL), the potassium channel blocking activity of 4-AP appears to be selective for certain types of these channels. Interestingly, at high concentration (such as at millimolar concentrations) 4-AP is a broad-spectrum blocker of potassium channels. The clinical neurologic effects of 4-AP are consistent with the molecular mechanism of potassium channel blockade. At the cellular level, this action may increase neuronal excitability, relieve conduction block in demyelinated axons, and potentiate synaptic and neuromuscular transmission.

[0009] Studies of 4-aminopyridine have been conducted using intravenous (i.v.) administration and oral administration of 4-aminopyridine, and using immediate-release or sustained-release (also known as "extended-release") oral formulations.


[0011] Dalfampridine is the United States Adopted Name (USAN) for the chemical 4-aminopyridine (4-AP). It is FDA-approved as an extended-release (ER), 10 mg tablet (see AMPYRA® package insert) indicated to improve walking in subjects with multiple sclerosis (MS), as demonstrated by an increase in walking speed. The approved therapeutic dose of
Dalfampridine is a 10 mg extended release tablet to be taken twice daily, approximately 12 hours apart, with or without food.

[0012] The effectiveness of dalfampridine in improving walking in patients with multiple sclerosis was evaluated in two double-blind, placebo-controlled phase 3 trials involving a total of 540 patients (Goodman et al., 2009, Lancet 373: 732-738; Goodman et al., 2010, Ann Neurol 68:494-502. The primary measure of efficacy in both trials was walking speed (in feet per second) as measured by the Timed 25-Foot Walk (T25FW), using a responder analysis. A Responder was defined as a patient who showed faster walking speed for at least three visits out of a possible four during the double-blind period than the maximum value achieved in the five non-treatment visits. A statistically significantly greater proportion of patients taking dalfampridine-ER 10 mg twice daily were Responders, compared to patients taking placebo. During the double-blind treatment period, a statistically significantly greater proportion of patients taking dalfampridine had increases in walking speed of at least 10%, 20%, or 30%> from baseline, compared to placebo. In both trials, consistent improvements in walking speed were shown to be associated with improvements on a patient self-assessment of ambulatory disability, the 12-item Multiple Sclerosis Walking Scale (MSWS-12).

[0013] Leg strength, assessed using the Lower Extremity Manual Muscle Test (LEMMT) was also studied in patients with multiple sclerosis. Leg strength was found to be statistically significantly improved with dalfampridine relative to placebo (p<0.05) (Goodman et al, 2008, Neurology 71: 1134-1 141; Goodman et al, 2009, Lancet 373: 732-738; Goodman et al, 2010, Ann Neurol 373: 494-502).

[0014] Citation of a reference herein shall not be construed as an admission that such is prior art to the present invention.

3. SUMMARY OF THE INVENTION

[0015] The present invention provides methods for improving walking capacity in patients with multiple sclerosis, comprising orally administering greater than 5 mg, preferably 10 mg, of 4-aminopyridine twice daily in a sustained release composition. In specific embodiments, the multiple sclerosis patient has a particular multiple sclerosis subtype, particular race, body weight in a particular range, and/or has been treated for a
particular period of time.

[0016] In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has relapsing remitting multiple sclerosis. In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has secondary progressive multiple sclerosis. In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has primary progressive multiple sclerosis. In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises administering to the patient 10 mg of an 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has progressive relapsing multiple sclerosis.

[0017] In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is Caucasian. In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is African-American. In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is Hispanic. In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is Asian.
In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has a body weight in the range of 40 kg to 150 kg. In some embodiments, the patient has a body weight in the range of 40 kg to 110 kg. In some embodiments, the patient has a body weight in the range of 40 kg to 80 kg. In some embodiments, the patient has a body weight in the range of 50 kg to 90 kg. In some embodiments, the patient has a body weight in the range of 60 kg to 100 kg. In some embodiments, the patient has a body weight in the range of 70 kg to 120 kg.

In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof comprises orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the administering step is performed over a period of time that is greater than 4 weeks. In some embodiments, the administering step is performed over a period of time that is greater than 5 weeks. In some embodiments, the administering step is performed over a period of time that is greater than 6 weeks. In some embodiments, the administering step is performed over a period of time that is greater than 2 months. In some embodiments, the administering step is performed over a period of time that is greater than 6 months. In some embodiments, the administering step is performed over a period of time that is greater than 1 year.

In one embodiment, the 4-aminopyridine is formulated in a form of a tablet for administration to a patient. In one embodiment, the 4-aminopyridine is formulated in a form of a capsule for administration to a patient. In one embodiment, the patient has a creatinine clearance rate of greater than 50 mL/min.

In some embodiments, a method for improving walking capacity in a patient with multiple sclerosis in need thereof further comprises measuring walking capacity of the patient by the 6 Minute Walk Test. In some embodiments, the measuring of walking capacity by the 6 Minute Walk Test is prior to treatment with 4-aminopyridine. In some embodiments, the measuring of walking capacity by the 6 Minute Walk Test is during a treatment period (i.e. during a same day that 4-aminopyridine is being administered) with 4-aminopyridine. In some embodiments, the measuring of walking capacity by the 6 Minute Walk Test...
Walk Test is after a treatment period with 4-aminopyridine. In some embodiments, the measuring of walking capacity by the 6 Minute Walk Test is prior to treatment and during a treatment period (i.e. during a same day that 4-aminopyridine is being administered) with 4-aminopyridine. In some embodiments, the patient exhibits an at least 20% improvement in walking speed as measured by the Timed 25 Foot Walk test relative to walking speed of the patient prior to treatment with 4-aminopyridine.

3.1 Terminology

[0022] In order to provide a clear and consistent understanding of the specification and claims, the following definitions are provided:

[0023] As used herein, if no fluid is mentioned or the context does not indicate otherwise, Cminss, Cmaxss, Cavss values generally relate to blood plasma.

[0024] The term "gait," as used herein, refers to the pattern of movement of the limbs during locomotion over a solid substrate. In one embodiment, gait is the manner and style of walking.

[0025] The term "improvement" or "improving" with respect to walking capacity designates an alteration or altering in a therapeutic direction. As used herein, "improvement" or "improving" also comprises stabilization or stabilizing of walking capacity that would otherwise be deteriorating or moving in a non-therapeutic direction or moving to a greater amount or degree in a non-therapeutic direction.

[0026] By "pharmaceutically acceptable", with respect to a carrier, diluent or excipient, is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not prohibited for human or veterinary administration (as the case may be) by a regulatory agency such as the Food and Drug Administration or European Medicines Agency.

[0027] The term "pharmaceutically acceptable salt(s)," with reference to an aminopyridine, as used herein, refers to a salt prepared from a pharmaceutically acceptable non-toxic acid or base, including an inorganic acid or base, or an organic acid or base. In certain embodiments, the pharmaceutically acceptable salt is prepared from a pharmaceutically acceptable non-toxic acid which can be an inorganic or organic acid. In
some embodiments, non-toxic acids include, but are not limited to, inorganic and organic acids such as acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothentic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, and p-toluenesulfonic acid. In one embodiment, the non-toxic acid is hydrochloric acid. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in S.M. Barge et al., "Pharmaceutical Salts," 1977, J. Pharm. Sci. 66:1-19, which is incorporated herein by reference in its entirety.

[0028] Other terms and/or abbreviations are provided below in Table 1:

### Table 1: Abbreviations and Specialist Terms.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>b.i.d. (bid)</td>
<td>Twice daily</td>
</tr>
<tr>
<td>CCR</td>
<td>Creatinine clearance rate</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>C_{max}</td>
<td>Maximum measured plasma concentration</td>
</tr>
<tr>
<td>C_{max,s}</td>
<td>Maximum measured plasma concentration at steady state</td>
</tr>
<tr>
<td>C_{min}</td>
<td>Minimum measured plasma concentration</td>
</tr>
<tr>
<td>C_{min,s}</td>
<td>Minimum measured plasma concentration at steady state</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>Dalfampridine</td>
<td>Fampridine</td>
</tr>
<tr>
<td>DAP</td>
<td>di-aminopyridine</td>
</tr>
<tr>
<td>DER</td>
<td>Dalfampridine extended-release</td>
</tr>
<tr>
<td>ER</td>
<td>Extended release</td>
</tr>
<tr>
<td>Fampridine</td>
<td>Dalfampridine, 4-aminopyridine</td>
</tr>
<tr>
<td>g, kg, mg, μg, ng</td>
<td>Gram, kilogram, milligram, microgram, nanogram</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Explanation</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>h, hr</td>
<td>Hour</td>
</tr>
<tr>
<td>IR</td>
<td>Immediate-release</td>
</tr>
<tr>
<td>IV, i.v., or iv</td>
<td>Intravenous</td>
</tr>
<tr>
<td>K+</td>
<td>Ionic Potassium</td>
</tr>
<tr>
<td>L, mL</td>
<td>Liter, milliliter</td>
</tr>
<tr>
<td>Min</td>
<td>Minute</td>
</tr>
<tr>
<td>mM, µM</td>
<td>Millimolar, micromolar</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>12-item Multiple Sclerosis Walking Scale</td>
</tr>
<tr>
<td>NF</td>
<td>National Formulary</td>
</tr>
<tr>
<td>p.o.</td>
<td>Oral</td>
</tr>
<tr>
<td>q.d. (qd)</td>
<td>Once a day</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>SR</td>
<td>Sustained-release, also known as Extended-release (&quot;ER&quot;)</td>
</tr>
<tr>
<td>SS</td>
<td>Steady state</td>
</tr>
<tr>
<td>T25FW</td>
<td>Timed 25 Foot Walk</td>
</tr>
<tr>
<td>t.i.d. (tid)</td>
<td>Three times daily</td>
</tr>
<tr>
<td>T(_{\text{max}})</td>
<td>Time of the maximum measured plasma concentration post-dose</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
</tr>
<tr>
<td>WS</td>
<td>Walking speed</td>
</tr>
<tr>
<td>3AP, or 3-AP</td>
<td>3-aminopyridine</td>
</tr>
<tr>
<td>4AP, or 4-AP</td>
<td>4-aminopyridine</td>
</tr>
<tr>
<td>3,4 DAP, or 3,4-DAP</td>
<td>3,4, di-aminopyridine</td>
</tr>
<tr>
<td>6MW</td>
<td>6 Minute Walk</td>
</tr>
<tr>
<td>6MWT</td>
<td>6 Minute Walk Test</td>
</tr>
</tbody>
</table>
4. **BRIEF DESCRIPTION OF DRAWINGS**

[0029] **Figure 1** shows information regarding 4-aminopyridine.

[0030] **Figure 2** shows the agenda/outline for the Figures presented hereinafter, which describe the study set forth in Example 1.

[0031] **Figure 3** is a study overview of the study set forth in Example 1.

[0032] **Figure 4** is a title page entitled "Study Design and Baseline Demographics" for figures hereinafter that describe the study set forth in Example 1.

[0033] **Figure 5** shows a summary of the Study Design of the study set forth in Example 1.

[0034] **Figure 6** is a table showing an abbreviated schedule of events of the study set forth in Example 1.

[0035] **Figure 7** shows a summary of the primary efficacy variables and the secondary variables of the study set forth in Example 1.

[0036] **Figure 8** shows a summary of the baseline demographics of the study set forth in Example 1.

[0037] **Figure 9** is a title page entitled "Study Results" for figures hereinafter that describe the study set forth in Example 1.

[0038] **Figure 10** is a table showing the mean change from baseline in walking speed (ft/sec) at Tmax at Visit 3 for the three treatment groups: placebo, dalfampridine-ER at 5 mg twice a day, and dalfampridine-ER at 10 mg twice a day. The p-values are shown for dalfampridine-ER at 5 mg twice a day versus placebo and for dalfampridine-ER at 10 mg twice a day versus placebo.

[0039] **Figure 11** is a table showing the average change in walking speed between pre-treatment and on-treatment periods (ft/sec) for the three treatment groups: placebo, dalfampridine-ER at 5 mg twice a day, and dalfampridine-ER at 10 mg twice a day. The p-values are shown for dalfampridine-ER at 5 mg twice a day versus placebo and for dalfampridine-ER at 10 mg twice a day versus placebo.

[0040] **Figure 12** is a histogram showing the percent of study participants who had an average \( \geq 20\% \) improvement in walking speed for the three treatment groups: placebo, dalfampridine-ER at 5 mg twice a day, and dalfampridine-ER at 10 mg twice a day.

[0041] **Figure 13** is a table showing the average change from baseline in Six-Minute
Walk Distance at Visit 2 (ft) for the three treatment groups: placebo, dalfampridine-ER at 5 mg twice a day, and dalfampridine-ER at 10 mg twice a day. The p-values are shown for dalfampridine-ER at 5 mg twice a day versus placebo and for dalfampridine-ER at 10 mg twice a day versus placebo.

[0042] Figure 14 is a table showing the average change from baseline using the patient self-assessment tool, the 12-Item Multiple Sclerosis Walking Scale for the three treatment groups: placebo, dalfampridine-ER at 5 mg twice a day, and dalfampridine-ER at 10 mg twice a day. The p-values are shown for dalfampridine-ER at 5 mg twice a day versus placebo and for dalfampridine-ER at 10 mg twice a day versus placebo.

[0043] Figure 15 is a title page entitled "Safety" for the figure hereinbelow that describes the study set forth in Example 1.

[0044] Figure 16 is a summary of the adverse events observed for the study set forth in Example 1.

[0045] Figure 17 is a summary of the study conclusions of the study set forth in Example 1.

[0046] Figure 18 is a graphic display of the study design set forth in Example 1.

5. **DETAILED DESCRIPTION**

[0047] The present invention provides methods for improving walking capacity in patients with multiple sclerosis, comprising orally administering greater than 5 mg, preferably 10 mg, of 4-aminopyridine twice daily in a sustained release composition. In specific embodiments, the multiple sclerosis patient has a particular multiple sclerosis subtype, particular race, body weight in a particular range, and/or has been treated for a particular period of time, as described herein below.

5.1 **Aminopyridines for Use in the Methods of the Invention**

[0048] Dalfampridine is the current United States Adopted Name (USAN) for the chemical 4-aminopyridine (4-AP). Dalfampridine-ER (DER) is an extended release formulation of dalfampridine. The invention provides use of an aminopyridine (preferably 4-AP) or a pharmaceutically acceptable salt thereof, in a sustained release composition, for improving walking capacity at particular doses and dosing frequencies and in particular
patient populations.

[0049] The structure of an aminopyridine is well known in the art. As shown in U.S. Patent No. 5,952,357, a mono- or diaminopyridine has the following structure:

\[
\text{structure}
\]

wherein \(x\) is 1 or 2.

[0050] Aminopyridines having the above structural formula wherein \(x\) is 1 are, e.g., 2-aminopyrididine, 3-aminopyrididine and 4-aminopyrididine. Aminopyridine compounds having the above structural formula wherein \(x\) is 2 are, e.g., 2,3-diaminopyrididine; 2,5-diaminopyrididine; 2,6-diaminopyrididine; 3,4-diaminopyrididine; and 2,4-diaminopyrididine.

[0051] In one embodiment, the aminopyridine is a mono- or di-aminopyridine. In one embodiment, the mono- aminopyridine is 3-aminopyrididine or 4-aminopyrididine. In one embodiment the di-aminopyridine is 3,4-diaminopyrididine.

[0052] As will be appreciated, a pharmaceutically acceptable salt of an aminopyridine may be used instead of or in addition to an aminopyridine in any or all of the methods of treating discussed herein. Thus, in specific embodiments, a pharmaceutically acceptable salt of an aminopyridine (i.e., any pharmaceutically acceptable salt of any of the aminopyridine compounds listed above) is used in the methods of improving walking capacity in a patient with multiple sclerosis. These salts can be prepared, for example, 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. In some embodiments, a salt of a mono- or di-aminopyridine is used in the methods of the invention. In another embodiment, a salt of 3-aminopyrididine or 4-aminopyridine is used. In yet another embodiment, a salt of 3,4-diaminopyridine is used. In some embodiments, the pharmaceutically acceptable salt of an aminopyridine is prepared using acetic, alginic, anthranilic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, furoic, galacturonic, gluconic, glucuronic, glutamic, glycolic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic,
mucic, nitric, pamoic, pantothenic, phenylacetic, phosphoric, propionic, salicylic, stearic, succinic, sulfanilic, sulfuric, tartaric acid, or p-toluenesulfonic acid. In one embodiment, one equivalent of an aminopyridine, as used herein, may form an acid salt with less than one or with one or more than one equivalent of an acid. In one embodiment an aminopyridine, as used herein, may form a dihydrochloride salt. In one embodiment an aminopyridine, as used herein, may form a phosphate salt. For further description of pharmaceutically acceptable salts that can be used in the methods described herein see, for example, S.M. Barge et al, "Pharmaceutical Salts," 1977, J. Pharm. Sci. 66:1-19, which is incorporated herein by reference in its entirety.

[0053] In preferred embodiments, an aminopyridine itself, and not a pharmaceutically acceptable salt thereof, is used in any of the methods described herein.

5.2 Impairments Treated in Accordance with the Invention

[0054] In particular, provided herein are methods for treating an impairment in walking capacity in a patient with multiple sclerosis comprising administering an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition. Accordingly, provided herein are methods for improving walking capacity in a patient with multiple sclerosis comprising administering an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition.

[0055] In a particular embodiment, provided herein are methods for treating an impairment in, or improving (or increasing), endurance for physical activity in a patient with multiple sclerosis comprising administering an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition. In a particular embodiment, provided herein are methods for treating an impairment in, or improving (or increasing), ambulatory capacity, ambulatory endurance or ambulatory range in a patient with multiple sclerosis comprising administering an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition. In a particular embodiment, provided herein are methods for treating an impairment in, or improving (or increasing), walking capacity, walking endurance or walking range in a patient with multiple sclerosis comprising administering an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition. As used herein, the term "capacity," with respect to physical activity,
ambulatory activity or walking, is synonymous to and is used interchangeably with the terms "endurance," and "range."

[0056] In some embodiments, capacity for physical activity is the total amount of time that a person (i.e., a subject or a patient) spends on his feet (i.e., the total amount of time with some activity, which is the converse of time in no activity) over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). Physical activity includes, without limitation, standing, walking, jogging, running, aerobic activity, exercising. In certain embodiments, physical activity does not include any activity engaged in while sitting or lying. In certain embodiments, methods described herein improve or increase the total amount of time that a person spends on their feet over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In specific embodiments, methods described herein improve or increase the total amount of time that a person spends in ambulation over a period of time (e.g., greater than 4 weeks, greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In particular embodiments, methods described herein improve or increase the total amount of time that a person spends walking over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In some embodiments, methods described herein improve or increase the total amount of time that a person spends jogging, running, exercising and/or engaging in an aerobic activity over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In some embodiments, the methods described herein are effective to improve or increase said total amount of time by at least or more than 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, or 99%.

[0057] In some embodiments, capacity for physical activity is the percentage of time a person spends on his feet over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In certain embodiments, methods described herein improve or increase the percentage of time that a person spends on his feet over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In specific embodiments, methods described herein improve or increase the percentage of time that a person spends in ambulation over a period of time (e.g., greater than 4 weeks, greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4,
5, or 6 months, or 1 year). In particular embodiments, methods described herein improve or increase the percentage of time that a person spends walking over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In some embodiments, methods described herein improve or increase the percentage of time that a person spends jogging, running, exercising and/or engaging in an aerobic activity over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year). In some embodiments, the methods described herein are effective to improve or increase said percentage of time by at least or more than 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, or 99%.

[0058] In specific embodiments, the described methods increase total amount of walking over a period of time in a patient with MS relative to the total amount of walking over the same period of time prior to the administration of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition to the patient.

[0059] The impairment (or decrease in capacity) treated or improved in accordance with the methods described herein is not solely an impairment in walking speed in a patient with multiple sclerosis. The impairment (or decrease in capacity) treated or improved in accordance with the methods described herein is not solely an impairment in gait in a patient with multiple sclerosis. The impairment (or decrease in capacity) treated or improved in accordance with the methods described herein is not solely an impairment in spasticity (muscle tone) or muscle strength in a patient with multiple sclerosis. Thus, the impairment (or decrease in capacity) treated or improved in accordance with the methods described herein is not solely an impairment in walking speed, an impairment in gait, or an impairment in spasticity or muscle strength in a patient with multiple sclerosis. In specific embodiments, the impairment in capacity for physical activity treated or improved in accordance with the methods described herein is measured by at least one parameter that is not ambulatory speed and, optionally, also not gait, spasticity or muscle strength. Such parameter can be, for example, the duration over a period of time that the patient spends walking, standing, jogging, running, or exercising).

[0060] In a specific embodiment, walking capacity is measured by how far a patient walks during a defined time period. In a specific embodiment, the 6MWT is used to assess walking capacity, e.g., in order to diagnose a decreased walking capacity and/or to monitor
treatment efficacy (the latter when the test is administered after treatment). For example, walking capacity in a patient with multiple sclerosis can be assessed before and/or during and/or after administering 4-aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition, e.g., at or after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 days; 1, 2, 3, 4, 5, 6, 7, 8, weeks; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 months; or 1, 2, 3, 4, 5 years since the commencement of treatment in accordance with the methods described herein. In specific embodiments, the impairment in walking capacity that is treated or improved according to the methods of the invention is the impairment that is assessed by the 6MWT.

[0061] In specific embodiments, a patient is administered 10 mg twice daily of 4-aminopyridine in a sustained release composition to improve walking capacity as assessed by the 6MWT. In specific embodiments, the patient treated with 10 mg twice daily of 4-aminopyridine in a sustained release composition is a 4-aminopyridine responder, as indicated by the patient exhibiting an at least 20% improvement in walking speed as measured by the Timed 25 Foot Walk test relative to walking speed of the patient prior to treatment with 4-aminopyridine.

[0062] In certain embodiments, the treatment in accordance with the invention is to improve walking capacity in a patient with multiple sclerosis, over a period of time (e.g., greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1 year).

[0063] In certain embodiments, treating a MS patient by administering an amount of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is effective to improve (e.g., increase, ameliorate, alleviate the symptoms of, or reduce the severity of) an impairment in capacity for physical activity in a patient with multiple sclerosis. In a specific embodiment, treating a MS patient by administering an amount of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is effective to eliminate an impairment in capacity for physical activity in a patient with multiple sclerosis. In some embodiments, the methods described herein are effective to improve or increase capacity for physical activity by at least or more than 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, or 99% (e.g., relative to the patient's capacity for physical activity prior to administration of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition).
In specific embodiments, treating a MS patient by administering an amount of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is effective to improve or increase ambulatory capacity (e.g., walking capacity) in a patient with multiple sclerosis. In a specific embodiment, treating a MS patient by administering an amount of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is effective to eliminate an impairment in ambulatory capacity (e.g., walking capacity) in a patient with multiple sclerosis. In some embodiments, the methods described herein are effective to improve or increase ambulatory (e.g., walking) capacity by at least or more than 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 90%, 95%, or 99%, (e.g., relative to the patient's capacity for physical activity prior to administration of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition).

In some embodiments, treating a MS patient by administering an amount of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is effective to improve average daily capacity for physical activity in the patient, for example, such that the patient can stay physically active (such as standing or in ambulation, e.g., walking, jogging, running) for at least or more than about 5%, 10%, 20%, 30%, 40%, 50%, 60%, or 70% of the day. In some embodiments, treating a MS patient by administering an amount of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is effective to improve average daily capacity for physical activity in the patient, for example, such that the patient can stay physically active (such as standing or in ambulation, e.g., walking, jogging, running) for at least or more than about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16 hours per day. In particular embodiments, such improvement in the patient is maintained for greater than 4 weeks; greater than or equal to 5, 6, or 7 weeks; 1, 2, 3, 4, 5, or 6 months, or 1, 2, 3, 4, or 5 years.

In particular embodiments, a method for maintaining improvement in capacity for physical activity such as ambulatory capacity (e.g., walking capacity) in a patient with multiple sclerosis is provided, said method comprising: administering an amount (e.g., a therapeutically effective amount) of an aminopyridine (such as 3,4-diaminopyridine, 4-aminopyridine and the like) or a pharmaceutically acceptable salt thereof in a sustained release composition to said patient after previously achieving an improvement in walking capacity.
capacity in said patient during administration of an aminopyridine or a pharmaceutically accepta

[0067] In one embodiment, a method for treating an impairment in or a method for improving (or increasing) capacity for physical activity or maintaining an improvement in capacity for physical activity in a patient with multiple sclerosis comprises administering an amount (e.g., a therapeutically effective amount) of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition to said patient over an extended period of time. In certain embodiments, a method for achieving sustained improvement of capacity for physical activity in a patient with multiple sclerosis comprises continuing administration of an amount (e.g., a therapeutically effective amount) of an aminopyridine (such as 3,4-diaminopyridine, 4-aminopyridine and the like) or a pharmaceutically acceptable salt thereof in a sustained release composition to said patient over an extended period of time. In a specific embodiment, the extended period of time is at least, or more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months.

[0068] In one embodiment, a method for improving ambulatory (e.g., walking) capacity or maintaining an improvement in ambulatory (e.g., walking) capacity in a patient with multiple sclerosis comprises administering an amount (e.g., a therapeutically effective amount) of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition to said patient over an extended period of time. In certain embodiments, a method for achieving sustained improvement of ambulatory (e.g., walking) capacity in a patient with multiple sclerosis comprises continuing administration of an amount (e.g., a therapeutically effective amount) of aminopyridine (such as 3,4-diaminopyridine, 4-aminopyridine and the like) or a pharmaceutically acceptable salt thereof in a sustained release composition to said patient over an extended period of time. In a specific embodiment, the extended period of time is at least, or more than, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months.

[0069] In certain embodiments, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered to a patient to improve walking capacity for more than 4 weeks or at least or more than: 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22 weeks; 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 months; or 1, 2, 3, 4, 5, 10 or greater than 5 or 10 years. In specific embodiments, the
aminopyridine is 4-aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition. In certain embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 7.5 mg twice daily over a period of time that is greater than 4 weeks. In certain embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 7.5 mg twice daily over a period of time that is greater than 5 weeks. In particular embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 7.5 mg twice daily over a period of time that is greater than 6 weeks. In some embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 7.5 mg twice daily over a period of time that is greater than 2 months. In specific embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 7.5 mg twice daily over a period of time that is greater than 6 weeks. In particular embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 7.5 mg twice daily over a period of time that is greater than 1 year.

[0070] In certain embodiments, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered to a patient to improve walking capacity for more than 4 weeks or at least or more than: 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22 weeks; 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 months; or 1, 2, 3, 4, 5, 10 or greater than 5 or 10 years. In specific embodiments, the aminopyridine is 4-aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition. In certain embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 10 mg twice daily over a period of time that is greater than 4 weeks. In certain embodiments, the 4-aminopyridine or
pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 10 mg twice daily over a period of time that is greater than 5 weeks. In particular embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 10 mg twice daily over a period of time that is greater than 6 weeks. In some embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 10 mg twice daily over a period of time that is greater than 2 months. In specific embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 10 mg twice daily over a period of time that is greater than 6 weeks. In particular embodiments, the 4-aminopyridine or pharmaceutically acceptable salt thereof in a sustained release composition for improving walking capacity in multiple sclerosis patients is administered at a dose of 10 mg twice daily over a period of time that is greater than 1 year.

[0071] In specific embodiments, the improvement(s) in capacity for physical activity such as ambulatory capacity (e.g., walking capacity) among patients with multiple sclerosis occur over periods of more than 4 weeks or at least or more than: 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21 or 22 weeks; 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 months; or 1, 2, 3, 4, 5, 10 or greater than 5 or 10 years.

[0072] In a specific embodiment, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered at a therapeutically effective dosage sufficient to improve capacity for physical activity such as ambulatory (e.g., walking) capacity in a patient with multiple sclerosis. In certain embodiments, the treatment increases capacity for physical activity in the patient by at least about 10%, 20%, more preferably 30%, more preferably by at least about 40% or 50%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects or relative to capacity of the patient prior to treatment. In some embodiments, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered at a therapeutically effective dosage sufficient to walking capacity in a patient with multiple
sclerosis. In certain embodiments, the treatment increases walking capacity in the patient by at least about 10%, 20%, more preferably 30%, more preferably by at least about 40% or 50%, even more preferably by at least about 60%, and still more preferably by at least about 80% relative to untreated subjects or relative to walking capacity of the patient prior to treatment. Such percent change quantification is preferably applied to assays that provide measurements of results in continuous linear scales. Other tests will not be expressed as percent change but would be predicted to result in a significant change with the appropriate statistical comparison. Such tests include semiquantitative measures that assign values to the ability to perform certain skills. In some embodiments, treatment in accordance with the invention results in a statistically significant improvement in capacity for physical activity such as ambulatory (e.g., walking) capacity in comparison to a control. Such control can be the patient's ability to perform the assessed task or skill prior to the commencement of treatment.

[0073] In a specific embodiment, a therapeutic outcome of treatment in accordance with the methods described herein is assayed for and detected at any one, two, three, four, five or more, or each, of the following time points, and/or at a time point later than any one of the following time points: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 days; 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24 weeks; 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 42, 48, 54, 60, or 66 months; 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 or 6.5 years post-commencement of treatment with an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition.

5.3 Patients

[0074] The patients or subjects that are treated by the methods of the invention include, but are not limited to, humans and non-human vertebrates such as wild, domestic and farm animals. In certain embodiments, the patient treated in accordance with the invention is a mammal, e.g., a human, a cow, a dog, a cat, a goat, a horse, a sheep, or a pig. In a preferred embodiment, the patient to whom an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered is a human. In some embodiments, the patient is 18 to 55 years old. In a specific embodiment, the patient is
greater than 55 years old. In certain embodiments, the patient has a body mass index (BMI) of 16 to 35. In particular embodiments, the patient has a BMI of 18 to 30. In certain embodiments, the patient has a body weight ranging from 40 kg to 150 kg. In specific embodiments, the patient has a body weight ranging from 40 kg to 110 kg. In some embodiments, the patient has a body weight ranging from 40 kg to 80 kg. In further embodiments, the patient has a body weight ranging from 50 kg to 90 kg. In certain embodiments, the patient has a body weight ranging from 60 kg to 100 kg. In some embodiments, the patient has a body weight ranging from 70 kg to 120 kg.

[0075] In some embodiments, the patient has a body weight of approximately 40 kg. In some embodiments, the patient has a body weight of approximately 45 kg. In some embodiments, the patient has a body weight of approximately 50 kg. In certain embodiments, the patient has a body weight of approximately 55 kg. In particular embodiments, the patient has a body weight of approximately 60 kg. In specific embodiments, the patient has a body weight of approximately 65 kg. In specific embodiments, the patient has a body weight of approximately 70 kg. In some embodiments, the patient has a body weight of approximately 75 kg. In some embodiments, the patient has a body weight of approximately 80 kg. In further embodiments, the patient has a body weight of approximately 85 kg. In certain embodiments, the patient has a body weight of approximately 90 kg. In specific embodiments, the patient has a body weight of approximately 95 kg. In particular embodiments, the patient has a body weight of approximately 100 kg. In certain embodiments, the patient has a body weight of approximately 105 kg. In some embodiments, the patient has a body weight of approximately 110 kg. In some embodiments, the patient has a body weight of approximately 115 kg. In specific embodiments, the patient has a body weight of approximately 120 kg. In certain embodiments, the patient has a body weight of approximately 125 kg. In further embodiments, the patient has a body weight of approximately 130 kg. In some embodiments, the patient has a body weight of approximately 135 kg. In some embodiments, the patient has a body weight of approximately 140 kg. In particular embodiments, the patient has a body weight of approximately 145 kg. In certain embodiments, the patient has a body weight of approximately 150 kg.

[0076] In specific embodiments, the patient is Caucasian (white). In particular
embodiments, the patient is African-American (black). In some embodiments, the patient is of Hispanic, Latino or Spanish origin. In some embodiments, the patient is Hispanic. In certain embodiments, the patient is Asian (e.g., Asian Indian, Chinese, Filipino, Japanese, Korean, or Vietnamese). In specific embodiments, the patient is a Pacific Islander (e.g., Native Hawaiian, Guamanian, Chamorro, or Samoan). In some embodiments, the patient is an American Indian or Alaskan Native. In certain embodiments, the patient is from South Korea or Japan. In some embodiments, the patient is from Brazil, Chile, or Germany. In specific embodiments, the patient is from the United Kingdom. In some embodiments, the patient is from the United States.

[0077] In a preferred embodiment, the patient has a body weight in the range of 40 kg to 80 kg and is from South Korea or Japan. In some embodiments, the patient has a body weight in the range of 50 kg to 90 kg and is from Brazil, Chile, or Germany. In certain embodiments, the patient has a body weight in the range of 60 kg to 100 kg and is from the United Kingdom. In specific embodiments, the patient has a body weight in the range of 70 kg to 120 kg and is from the United States.

[0078] In a preferred embodiment of the invention, a patient is selected, identified or diagnosed with multiple sclerosis and with an impairment in capacity for physical activity (i.e., in need of an improvement in capacity for physical activity). In certain embodiments of the invention, a patient is selected, identified or diagnosed with multiple sclerosis and with a reduced ambulatory capacity. In certain embodiments of the invention, a patient is selected, identified or diagnosed with multiple sclerosis and with a reduced walking capacity. In some embodiments, the MS patient treated in accordance with the methods described herein is diagnosed with an impairment in capacity for physical activity such as ambulatory capacity (e.g., walking capacity) using an accelerometer (or another test described herein or known in the art). In some embodiments, the MS patient treated in accordance with the methods described herein is diagnosed with an impairment in walking capacity or a reduced walking capacity using an accelerometer. In some embodiments, the patient treated in accordance with the methods described herein has MS-related walking impairment based on pre-treatment T25FW and/or MSWS-12 data.

[0079] In certain embodiments, the patient treated in accordance with the methods described herein has (e.g., is diagnosed with) any type of multiple sclerosis, e.g., relapsing
remitting, secondary progressive, primary progressive, or progressive relapsing. In some embodiments, the patient is diagnosed with relapsing remitting MS. In some embodiments, the patient is diagnosed with secondary progressive MS. In certain embodiments, the patient is diagnosed with primary progressive MS. In particular embodiments, the patient is diagnosed with progressive relapsing MS. Patients with an atypical type of MS, such as Devic's disease, Balo concentric sclerosis, Schilder's diffuse sclerosis or Marburg multiple sclerosis, can also be treated in accordance with the methods described herein.

[0080] In some embodiments, the patients treated in accordance with the methods provided herein do not have a clinical history of seizures and/or epilepsy. In specific embodiments, the patients treated in accordance with the methods provided herein do not have a clinical history of seizures and/or epilepsy, with the exception of febrile seizures. For example, the patients have not experienced seizures and/or epilepsy in their lifetime, or have not experienced seizures and/or epilepsy 1, 2, 3, 4 or 5 years, or more than 5 years, prior to administration of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition. In some embodiments, the patients treated in accordance with the methods provided herein have a clinical history of seizures and/or epilepsy.

[0081] In a preferred embodiment, the patient treated in accordance with the methods herein has a creatinine clearance rate (CCR) of greater than 50 mL/min (i.e., the patient does not have moderate or severe renal impairment. In certain embodiments, the patient treated in accordance with the methods described herein does not have renal insufficiency, i.e., the patient has a CCR greater than 80 mL/min, or has either mild renal insufficiency (i.e., the patient has a CCR of 51-80 mL/min) or normal kidney function. In particular embodiments, the patient treated in accordance with the methods described herein does not have severe renal insufficiency (i.e., does not have a CCR of less than 30 mL/min) or moderate to severe renal insufficiency (i.e., does not have a CCR of less than 51 mL/min).

5.4 Dosing Regimens

[0082] Any of the therapeutic methods described above can be carried out using any of the following dosing regimens. The aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof used in such methods is in a sustained release composition. In specific embodiments, the aminopyridine used in such methods is 4-
aminopyridine in a sustained release composition.

[0083] In certain embodiments, the method in accordance with the invention comprises administering an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt in a sustained release composition, and is administered two times per day. In a specific embodiment, an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof is administered to the patient orally, in a sustained release composition b.i.d. (i.e., twice daily). In certain embodiments, twice daily administration comprises administration of a compound every 12 hours.

[0084] In some embodiments, an aminopyridine (e.g., 4-aminopyridine) in a sustained release composition provides a $T_{max}$ of about 2 hours to about 6 hours in a human.

[0085] In certain embodiments, for improvement of walking capacity, an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof in a sustained release composition is administered in an amount greater than 5 mg. In particular embodiments, the aminopyridine or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 7.5 mg to about 20 mg (e.g., about 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, 15, 16, 17, 17.5, 18, 19, or 20 mg), twice daily in a sustained release composition. In some embodiments, the aminopyridine or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 7.5 mg to about 15 mg (e.g., about 7.5, 8, 9, 10, 11, 12, 12.5, 13, 14, or 15 mg), twice daily in a sustained release composition. In certain embodiments, the aminopyridine or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 7.5 mg to about 10 mg (e.g., about 7.5, 8, 9, or 10 mg), twice daily in a sustained release composition. In some embodiments, an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 7.5 mg to 20 mg, 7.5 mg to 15 mg, 7.5 mg to 10 mg, 7.5 mg to 12.5 mg, or 7.5 to 10 mg twice daily, in a sustained release composition for improvement of walking capacity. In certain embodiments, an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof is administered at a dose of 7.5 mg twice daily in a sustained release composition for improvement of walking capacity. In certain embodiments, an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof is administered at a dose of 10 mg twice daily in a sustained release composition for improvement of walking capacity. In some of these embodiments, the
aminopyridine is 4-aminopyridine. In specific embodiments, 4-aminopyridine or a pharmaceutically acceptable salt thereof is administered in an amount ranging from about 5.5 mg to 20 mg, 7.5 mg to 15 mg, 7.5 mg to 10 mg, or 7.5 mg to 12.5 mg, twice daily, in a sustained release composition for improvement of walking capacity.

[0086] In specific embodiments, to improve walking capacity in a patient with relapsing remitting multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with secondary progressive multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with primary progressive multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition.

[0087] In specific embodiments, to improve walking capacity in a patient with relapsing remitting multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with secondary progressive multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with primary progressive multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition.

[0088] In some embodiments, to improve walking capacity in a Caucasian patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In
some embodiments, to improve walking capacity in an African-American patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a Hispanic patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In specific embodiments, to improve walking capacity in an Asian patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition.

[0089] In some embodiments, to improve walking capacity in a Caucasian patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in an African-American patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a Hispanic patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In specific embodiments, to improve walking capacity in an Asian patient with multiple sclerosis, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition.

[0090] In certain embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 40 kg to 150 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 40 kg to 110 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 40 kg to 80 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition.
embodiments, to improve walking capacity in a patient with multiple sclerosis from South Korea or Japan with a body weight in the range of 40 kg to 80 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In specific embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 50 kg to 90 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In specific embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 50 kg to 90 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 60 kg to 100 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 60 kg to 100 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In particular embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 70 kg to 120 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition. In specific embodiments, to improve walking capacity in a patient with multiple sclerosis from the United States with a body weight in the range of 70 kg to 120 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 7.5 mg twice daily in a sustained release composition.

[0091] In certain embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 40 kg to 150 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 40 kg to 110 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an
amount of 10 mg twice daily in a sustained release composition. In some embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 40 kg to 80 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In more embodiments, to improve walking capacity in a patient with multiple sclerosis from South Korea or Japan with a body weight in the range of 40 kg to 80 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In specific embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 50 kg to 90 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In specific embodiments, to improve walking capacity in a patient from Brazil, Chile or Germany with multiple sclerosis with a body weight in the range of 50 kg to 90 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In certain embodiments, to improve walking capacity in a patient from the United Kingdom with multiple sclerosis with a body weight in the range of 60 kg to 100 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In certain embodiments, to improve walking capacity in a patient with multiple sclerosis with a body weight in the range of 70 kg to 120 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition. In certain embodiments, to improve walking capacity in a patient with multiple sclerosis from the United States with a body weight in the range of 70 kg to 120 kg, 4-aminopyridine or a pharmaceutically acceptable salt thereof is orally administered in an amount of 10 mg twice daily in a sustained release composition.

[0092] In one embodiment, for improvement of walking capacity, lower doses, e.g., in the range 1 mg to 5 mg twice daily, are used for pediatric treatment in a sustained release
composition. In one embodiment, doses are for adult treatment and are in the range of 5 mg to 20 mg twice daily in a sustained release composition.

[0093] In particular embodiments, a patient with MS is treated with 4-aminopyridine-SR twice daily for improvement of walking capacity. In some embodiments, the patient is instructed to take 4-aminopyridine-SR in a dose of 4-aminopyridine selected from 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5 or 25 mg bid.

[0094] In some embodiments, a patient is treated in accordance with the methods described herein for a period of time that is, e.g., for more than 4 weeks, at least 5 weeks, at least 6 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, at least 5 years, at least 10 years, or more than 5 or 10 years. In certain embodiments, the treatment regimen (a particular dose and frequency of administration, which can be selected from any described herein) is stable over a period of time, e.g., for more than 4 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 6 months, or at least 1 year.

[0095] In one dosing embodiment, a sufficient amount of an aminopyridine, such as 4-aminopyridine in a sustained release composition, is provided such that it elicits the steady state levels that are within the range obtained by use of 4-aminopyridine-SR as illustrated by AMPYRA®; in one embodiment these steady state values are a maximum concentration at steady state (C_max) and minimum concentration at steady state (C_min). The steady state values can be plasma levels, levels on the brain side of the blood:brain barrier, or levels in the CSF. Preferably, these are plasma levels.

[0096] In specific embodiments a sufficient amount of aminopyridine, such as 4-aminopyridine in a sustained release composition, is provided that it elicits the steady state levels that differ not more than about 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1% from the average steady state level (C_avg) obtained by use of 4-aminopyridine-SR as illustrated by AMPYRA®. The steady state values can be plasma levels, levels on the brain side of the blood:brain barrier, or levels in the CSF. Preferably, these are plasma levels.
5.5 **Pharmaceutical compositions**

[0097] The invention also provides pharmaceutical compositions that are sustained release compositions comprising an aminopyridine (*e.g.*, 4-aminopyridine) or a pharmaceutically acceptable salt thereof as described herein. Such pharmaceutical compositions can comprise an amount (*e.g.*, a therapeutically effective amount) of an aminopyridine (*e.g.*, 4-aminopyridine) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier in a sustained release composition. In one embodiment, the pharmaceutical composition is suitable for oral administration and can be, for example, a pill, tablet or capsule. Pharmaceutical compositions can be as described, for example, in U.S. Patent Application Publication No. 2005/0276851, published December 15, 2005 and U.S. Patent Application Publication No. 2005/0228030, published October 13, 2005, the contents of each of which are incorporated by reference herein in their entireties. In one embodiment, the pharmaceutical composition comprises a sustained release composition of 4-aminopyridine. The pharmaceutical compositions of the invention are administered to a patient for any of the uses described herein.

[0098] An aminopyridine (*e.g.*, 4-aminopyridine) or a pharmaceutically acceptable salt thereof in a sustained release composition is preferably administered to a patient orally or parenterally in the conventional form of preparations, such as capsules, microcapsules, tablets, granules, powder, troches, pills, suppositories, suspensions, or syrups. Suitable formulations can be prepared by methods commonly employed using conventional, organic or inorganic additives, such as one or more of: an excipient (*e.g.*, sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate or calcium carbonate), a binder (*e.g.*, cellulose, methylcellulose, hydroxymethylcellulose, polypropylpyrrolidone, polyvinylpyrrolidone, gelatin, gum arabic, polyethylene glycol, sucrose or starch), a disintegrator (*e.g.*, starch, carboxymethylcellulose, hydroxypropylstarch, low substituted hydroxypropylcellulose, sodium bicarbonate, calcium phosphate or calcium citrate), a lubricant (*e.g.*, magnesium stearate, light anhydrous silicic acid, talc or sodium lauryl sulfate), a flavoring agent (*e.g.*, citric acid, menthol, glycine or orange powder), a preservative (*e.g.*, sodium benzoate, sodium bisulfite, methylparaben or propylparaben), a stabilizer (*e.g.*, citric acid, sodium citrate or acetic acid), a suspending agent (*e.g.*, methylcellulose, polyvinyl pyrrolidone or aluminum stearate), a dispersing agent (*e.g.*, hydroxypropylmethylcellulose),
a diluent (e.g., water), and base wax (e.g., cocoa butter, white petrolatum or polyethylene glycol). In some embodiments, suitable sustained release formulations of an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof can be prepared using one, two, three or more, or all, of the following additives: colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

[0099] A pharmaceutically acceptable carrier or vehicle can comprise an excipient, diluent, or a mixture thereof. In some embodiments, suitable sustained release formulations (e.g., suitable formulations for oral administration) of an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof are prepared using one or more of the following excipients: hydroxypropyl methylcellulose, USP; microcrystalline cellulose, USP; colloidal silicon dioxide, NF; magnesium stearate, USP; and Opadry White.

[00100] The amount of an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof that is present in the sustained release pharmaceutical composition is preferably an amount that will exercise the desired effect.

[00101] An aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof in a sustained release composition can be administered orally. In some of the embodiments wherein an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof in a sustained release composition is administered orally, the composition is formulated in a form of a tablet, a pill or a capsule. An aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof in a sustained release composition can also be administered intradermally, intramuscularly, intraperitoneally, percutaneously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, rectally, by inhalation, or topically to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the health-care practitioner.

[00102] The compositions can be in the form of tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions and the like. Compositions can be formulated to contain a daily dose, or a convenient fraction of a daily dose, in a dosage unit, which may be, e.g., a single tablet or capsule or convenient volume of a liquid.
Capsules can be prepared by any known method, such as mixing an aminopyridine (e.g., 4-aminopyridine) or a pharmaceutically acceptable salt thereof in a sustained release composition with a suitable carrier or diluent and filling the proper amount of the mixture in capsules. Carriers and diluents include, but are not limited to, inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets can be prepared by known methods such as direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

In a specific embodiment, the pharmaceutical composition is a sustained release tablet or capsule of 4-AP.

5.6 Combination Treatments

In a specific embodiment, one can combine an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition with one or more other agents and/or physical or occupational therapies for improving walking ability in a patient with multiple sclerosis. In some embodiments, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered to a patient concomitantly or sequentially with one or more additional drug or therapy. For example, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition can be administered to a patient at the same time, before, or after administration of a drug that controls seizures, a drug that alleviates pain, a drug that reduces fatigue, a drug that relaxes muscle spasms (e.g. benzodiazepines, baclofen, tizanadine and intrathecal phenol/baclofen), a drug that reduces inflammation (e.g., a corticosteroid), or
another drug that is approved for treatment of multiple sclerosis. In particular embodiments, the combination of an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition and one, two or more additional drug(s) is a fixed dose combination. For example, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition and one or more additional drug(s) can be formulated in one composition, such as a pill, a tablet or a capsule. In some embodiments, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered to a patient concomitantly (e.g., at the same time, before or after) with physical therapy, occupational therapy, or speech therapy, or plasmapheresis. In some embodiments, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered to a patient with multiple sclerosis who uses an assistive device (e.g., cane crutches, or a wheeled walker). In a specific embodiment, the aminopyridine (or salt thereof) in a sustained release composition and other drug or therapy is administered at the same doctor's visit, or within 1, 2, 3, 4, 5, 6, or 12 hours, or within 1, 2, 3, 4, 5, 6, or 7 days, of each other.

[00107] In some embodiments, an aminopyridine or a pharmaceutically acceptable salt thereof in a sustained release composition is administered to a patient without an additional drug or therapy, or without one or more of additional treatments (such as those described above). In certain embodiments, treatment in accordance with the invention (either with or without use of an additional drug or therapy), is more effective than treatment with another drug or therapy known to be used for the treatment walking impairments in patients with multiple sclerosis.

6. **EXAMPLES**

6.1 **Example 1: Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Doses of Oral Dalfampridine Extended Release Tablets (5 mg and 10 mg twice daily) in Patients with Multiple Sclerosis**

6.1.1 **SYNOPSIS**

[00108] The synopsis of Example 1 is presented in Table 2.
Table 2: Synopsis

<table>
<thead>
<tr>
<th>Name of Sponsor/Company:</th>
<th>Acorda Therapeutics, Inc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Investigational Product:</td>
<td>Dalfampridine-ER tablets</td>
</tr>
<tr>
<td>Name of Active Ingredient:</td>
<td>Dalfampridine</td>
</tr>
<tr>
<td>Title of Study:</td>
<td>Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of Two Doses of Oral Dalfampridine Extended Release Tablets (5 mg and 10 mg twice daily) in Patients with Multiple Sclerosis</td>
</tr>
<tr>
<td>Study center(s):</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Principal Investigator:</td>
<td>N/A</td>
</tr>
<tr>
<td>Investigators:</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Studied period (years):</td>
<td></td>
</tr>
</tbody>
</table>
  Estimated date first patient enrolled: 1 April 2011 
  Estimated date last patient completed: |
| Phase of development: | 3b |
| Objectives: | 
  Primary: |
  • To evaluate the efficacy (at the approximate time of peak plasma concentration) of two doses of dalfampridine-ER (5 and 10 mg twice daily) in the improvement of walking speed as measured by the Timed 25-Foot Walk (T25FW) in patients diagnosed with multiple sclerosis (MS) |
  Secondary: |
  • To evaluate the efficacy of these doses in the improvement of walking speed around the time of trough plasma concentration of dalfampridine |
  • To evaluate changes in patient mobility as measured by a self-report questionnaire (12-Item Multiple Sclerosis Walking Scale or MSWS-12) |
  • To evaluate changes in endurance as measured by the Six-Minute Walk (6MW) Test in a subset of centers |
  • To evaluate changes in general health status as measured by the EQ-5D™ questionnaire |
  • To evaluate the incidence of urinary tract infections |
| Methodology: | This is a multi-center, randomized, double-blind, placebo-controlled, parallel group, four-week study to assess the safety and efficacy of two doses of dalfampridine-ER in patients diagnosed with multiple sclerosis (MS). |

Patients will be consented and screened to determine eligibility (Screening Visit). Qualified patients will return approximately one week later for Visit 1 and be randomized to one of three treatment groups: extended release dalfampridine 5 mg twice daily, 10 mg twice daily, or matching placebo, in a ratio of 1:1:1. Following their baseline assessments of the MSWS-12, T25FW, EQ-5D™, and 6MW,* patients will be dispensed a two-week supply of their assigned investigational drug at Visit 1, and will return after two weeks for Visit 2, and again two weeks later for Visit 3. At Visit 2, patients will receive another two-week supply of investigational drug (DER or placebo). They will be asked to complete the MSWS-12 and then perform the T25FW and the 6MW.* Visit 3 marks the end of the four-week treatment period and the
completion of the study. Visit 3 will be scheduled to begin approximately 11 hours after the patient's previous dose of investigational drug. The patient will complete the MSWS-12 assessment at entry. There will be two assessment time points for the T25FW at this visit. The first will be scheduled to occur at approximately 12 hours post the prior dose of dalfampridine-ER, to correspond to trough plasma concentration of dalfampridine. The patient will then take his/her last dose of investigational drug and a second assessment of the T25FW will be performed 3-4 hours following this dose, to correspond to approximate peak plasma concentration of dalfampridine. Blood samples will be collected for determination of plasma dalfampridine immediately after the first and second sets of the T25FW tests. The EQ-5D™ health questionnaire will be administered again at Visit 3. Urinalysis will be performed at each visit to detect laboratory evidence of urinary tract infection. A urine culture will be performed for confirmation of the diagnosis.

The 6MW test will be performed by a subset of centers that have the appropriate facilities.

<table>
<thead>
<tr>
<th>Number of patients (planned):</th>
<th>405 (135 per treatment group)</th>
</tr>
</thead>
</table>

**Diagnosis and main criteria for inclusion:** The target population will consist of patients diagnosed with MS, 18-70 years of age, who have MS-related walking impairment but are able to complete the T25FW at the Screening Visit, according to the standard instructions, and are expected by the Investigator to be able to complete the test at every study visit. Patients may be eligible if they are non-pregnant females, have no history of seizure, no (moderate or severe) renal impairment, and have not experienced a urinary tract infection (UTI) within 4 weeks of Screening. Patients who have previously taken AMPYRA® or dalfampridine (fampridine or 4-aminopyridine: 4-AP) in any formulation (including compounded), may be included after a one-month washout period.

**Investigational product, dosage and mode of administration:**
The test products are dalfampridine 5 and 10 mg extended release tablets to be taken orally twice daily (every 12 hours).

**Duration of treatment:** Four weeks

**Reference therapy, dosage and mode of administration:**
Placebo tablets to be taken orally twice daily (every 12 hours).

**Criteria for evaluation:**

**Efficacy**
Efficacy will be primarily evaluated by improvements in walking speed as measured by the T25FW and secondarily by reductions in perceived walking disability as measured by the MSWS-12, and endurance as measured by the 6MW.

**Safety**
Safety will be assessed primarily by reviewing adverse events and urinalysis test results.

**Statistical methods:**
Assessment of treatment group comparability will include demographic, background, and baseline variables.

**Primary Efficacy Variable**
1. The primary efficacy variable will be change from baseline in walking speed (T25FW) at approximately 3-4 hours post dose at Visit 3 (i.e. near C^ss for dalfampridine-ER at the end of double-blind week 4).
## Secondary Efficacy Variables

The key secondary efficacy variables are:

2. Change from baseline in walking speed (T25FW) at approximately 12 hours post dose at Visit 3 (i.e. near C_{minSS} for dalfampridine-ER at the end of double-blind week 4)

3. Change from baseline in MSWS-12 at Visit 3

Other secondary efficacy variables will include:

- Change from baseline in MSWS-12 at Visit 2
- Change from baseline in walking speed (T25FW) at Visit 2
- Change from baseline in 6MW distance (feet) at Visit 2
- Changes from baseline in 5 specific dimensional scores, average scores across 5 dimensions and visual analogue self-rating (VAS) scores of EQ-5D™ at Visit 3.

## Statistical Analysis

Treatment differences (dalfampridine 10 mg ER twice daily vs. placebo and dalfampridine 5 mg ER twice daily vs. placebo) for all continuous efficacy variables will be analyzed via analysis of variance (ANOVA) with effects for treatment and corresponding baseline. Treatment differences for categorical variables will be analyzed via Cochran-Mantel-Haenszel (CMH) test, controlling for baseline. For each analysis, a corresponding sensitivity analysis will be performed with center as the additional control variable. Small sites will be combined together to form a center whenever applicable.

To analyze the plasma concentration response relationship, four variables of interest are as follows:

- Change in walking speed from baseline at C^{ss} at Visit 3
- Change in walking speed from baseline at C_{minSS} at Visit 3
- Observed plasma concentration level at C^{ss} at Visit 3
- Observed plasma concentration level at C_{minSS} at Visit 3

A linear regression analysis will be performed using the observed plasma concentration level as an explanatory variable and the change in walking speed from baseline as a response variable. A test of the slope will indicate if the plasma concentration response exists.

## Multiple Comparisons

This study was powered to detect differences between dalfampridine 10 mg ER and placebo on change from baseline in walking speed at approximately C^{ss} (Visit 3). No other comparisons were powered for this study. As such, to demonstrate study sensitivity with respect to efficacy and maintain an overall alpha level less than or equal to 0.05, the following stepwise procedures will be performed. If statistical significance is not achieved at a particular step, no subsequent comparisons will be eligible to be declared statistically significant.

### Study-Sensitivity Steps (dalfampridine 10 mg twice daily vs. placebo twice daily):

1. Change from baseline in walking speed at approximately C^{ss} at Visit 3.
2. Change from baseline in walking speed at approximately C_{minSS} at Visit 3.
3. Change from baseline in MSWS-12 for dalfampridine-ER at Visit 3.

### Efficacy Evaluation of 5 mg (dalfampridine 5 mg ER twice daily vs. placebo twice daily):

4. Change from baseline in walking speed at approximately C^{ss} at Visit 3.
5. Change from baseline in walking speed at approximately C_{minSS} at Visit 3.
6. Change from baseline in MSWS-12 at Visit 3.
The above protections for multiplicity pertain to the primary and key secondary efficacy endpoints. Regardless of the outcome of these comparisons, the comparisons for other secondary efficacy endpoints will be performed and nominal p-values will be reported to complete the full clinical picture.

**Efficacy Populations**

The primary efficacy analysis will be based on the intention-to-treat principle (i.e., on the initial treatment intent, not on the treatment eventually administered). According to ICH E9 (Statistical Principles for Clinical Trials), there are a limited number of circumstances that might lead to excluding randomized patients from analyses such as: 1) the failure to take at least one dose of trial medication or 2) the lack of any data post randomization. The Full Analysis Population (FAP) will be the basis of the primary efficacy analysis and will include all randomized patients who took at least one dose of double-blind investigational drug and who have a baseline T25FW assessment and at least one post-baseline T25FW assessment. The justification for excluding patients with no baseline value and at least one post-baseline T25FW assessment from the FAP is that there would be no reasonable imputation for the primary efficacy variable (change from baseline in walking speed at approximately 3-4 hours post dose at Visit 3).

If warranted, secondary efficacy analyses will be performed on a Per-Protocol Population (PPP). A PPP is a subpopulation of the FAP and will consist of all FAP patients with no major protocol violations.

**Assessment of Safety**

Adverse events and other safety parameters will be summarized. Urinalysis and adverse event data will be evaluated for evidence of a difference between treatment groups in frequency of urinary tract infection. The secondary safety variables (vital signs, physical exam and SMA-12 measures) may be summarized.

### 6.1.2 LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

**Table 3: Abbreviations and Specialist Terms.**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-AP</td>
<td>4-aminopyridine</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate transaminase</td>
</tr>
<tr>
<td>bpm</td>
<td>beats per minute</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>cc</td>
<td>cubic centimeter</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Explanation</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>CmaxSS</td>
<td>Maximum plasma concentration at steady state</td>
</tr>
<tr>
<td>CMH</td>
<td>Cochran-Mantel-Haenszel</td>
</tr>
<tr>
<td>CminSS</td>
<td>Minimum plasma concentration at steady state</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DER</td>
<td>Dalfampridine Extended Release</td>
</tr>
<tr>
<td>D-ER</td>
<td>Dalfampridine Extended Release</td>
</tr>
<tr>
<td>ER</td>
<td>Extended Release</td>
</tr>
<tr>
<td>FAP</td>
<td>Full Analysis Population</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (US)</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
</tr>
<tr>
<td>HDPE</td>
<td>high-density polyethylene</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>ICF</td>
<td>informed consent form</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-treat</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>MS</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>12-item MS Walking Scale</td>
</tr>
<tr>
<td>PPP</td>
<td>Per-Protocol Population</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell count</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>standard error of the mean</td>
</tr>
<tr>
<td>T25FW</td>
<td>Timed 25 Foot Walk</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopeia</td>
</tr>
<tr>
<td>UPT</td>
<td>urine pregnancy test</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analog scale</td>
</tr>
</tbody>
</table>
Abbreviation | Explanation
--- | ---
WBC | white blood cell count

### 6.1.3 CURRENT STUDY

[00110] The current study is designed as a prospective placebo-controlled trial to investigate the safety and efficacy of a lower dose of dalfampridine extended release tablets (5 mg twice daily) compared to the approved commercial dose of 10 mg twice daily in improving walking speed in MS patients during a four-week period of treatment.

### 6.1.4 STUDY OBJECTIVES

#### 6.1.4.1 Primary

[00111] The primary objective is to evaluate the efficacy (at the approximate time of peak plasma concentration) of two doses of dalfampridine (5 and 10 mg ER twice daily) in the improvement of walking speed as measured by the Timed 25 Foot Walk (T25FW) in patients diagnosed with MS.

#### 6.1.4.2 Secondary

[00112] The secondary objectives are as follows:

- To evaluate the efficacy of these doses in the improvement of walking speed around the time of trough plasma concentration of dalfampridine
- To evaluate changes in patient mobility as measured by a self-report questionnaire (12-Item Multiple Sclerosis Walking Scale or MSWS-12)
- To evaluate changes in endurance as measured by the Six-Minute Walk (6MW) Test in a subset of centers
- To evaluate changes in general health status as measured by the EQ-5D™ questionnaire
- To evaluate the incidence of urinary tract infections
6.1.5 INVESTIGATIONAL PLAN

6.1.5.1. Overall Study Design and Plan

[00113] This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group, four-week study designed to assess the safety and efficacy of two doses of dalfampridine-ER (DER, a sustained release formulation of 4-aminopyridine) in patients with MS.

[00114] After providing written informed consent, patients will be evaluated at the Screening Visit to determine eligibility. If they qualify, patients will return in one week to undergo baseline assessments (see Table 4) at Visit 1. At this visit, patients will be randomly assigned in a 1:1:1 ratio to receive (twice daily) dalfampridine 5 mg ER, dalfampridine 10 mg ER, or placebo during a four-week double-blind treatment period. Patients will be dispensed a two-week supply of investigational drug (DER or placebo) following completion of their baseline assessments of the MSWS-12, T25FW, EQ-5D™, and 6MW (The 6MW test will be performed by a subset of centers that have the appropriate facilities) and will return after two weeks for Visit 2. At Visit 2, they will receive another two-week supply of investigational drug. They will be asked to complete the MSWS-12 and then perform the T25FW and the 6MW. They will return to the clinic two weeks later for Visit 3.

[00115] Visit 3, the final visit, marks the end of the four-week treatment period. The visit will be scheduled to begin approximately 11 hours after the patient’s previous dose of investigational drug. The patient will complete the MSWS-12 assessment at entry. There will be two assessment time points for the T25FW at this visit. The first will be scheduled to occur at approximately 12 hours post the previous dose of dalfampridine-ER, to correspond to trough plasma concentration of dalfampridine. The patient will then take his/her last dose of DER and a second assessment of the T25FW will be performed 3-4 hours following this dose, to correspond to approximate peak plasma concentration of dalfampridine. Blood samples will be collected for determination of plasma dalfampridine immediately after the first and second sets of the T25FW. The EQ-5D™ health questionnaire will be administered again at Visit 3.

[00116] At each visit, urinalysis will be performed to detect laboratory evidence of urinary tract infection. If positive, or symptoms of a urinary tract infection are present, a urine culture will be performed for confirmation of the diagnosis.
The study design is displayed graphically in Figure 18.

The schedule of assessments at each visit can be found below in Table 4 and details of the study procedures can be found in Section 6.1.7.2.

### Table 4: Schedule of Assessments

<table>
<thead>
<tr>
<th>Visits</th>
<th>Screening</th>
<th>Visit 1 Baseline</th>
<th>Visit 2 2 weeks</th>
<th>Telephone Contact</th>
<th>Visit 3 4 weeks</th>
<th>Unscheduled/Early Term ¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Double-Blind Study Day</strong></td>
<td>-7</td>
<td>1</td>
<td>15</td>
<td>22</td>
<td>29</td>
<td>X</td>
</tr>
<tr>
<td><strong>Period</strong></td>
<td>Baseline</td>
<td>Double-blind treatment</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Written Informed Consent</td>
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<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical History</td>
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<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Physical Exam²/Vital Signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>12-lead ECG</td>
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<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SMA-12³</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urine pregnancy test</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>EDSS</td>
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<td>Randomization</td>
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<td>On-Drug Visit</td>
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<tr>
<td>Urinalysis⁴</td>
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<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>T25FW⁵</td>
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<td>X</td>
<td>X</td>
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<td>MSWS-12</td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Six-Minute Walk Test</td>
<td>X</td>
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<tr>
<td>EQ-5DTM</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PK plasma samples</td>
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<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Meds/Therapy</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dispense Investigational drug</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Investigational Drug Accountability</td>
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<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<td>Final Status Assessment</td>
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<td>X</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Schedule Next Visit</td>
<td>1 week ± 1 day</td>
<td>2 weeks ± 2 days</td>
<td>2 weeks⁶ ± 2 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone contact</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

¹When indicated, Unscheduled and Early Termination Visit may include any of the safety assessments checked.
²Full physical examination at Screening; brief physical examinations at all other visits.
³Plus creatinine clearance calculation.
Confirmatory urine culture, if needed.

Two back-to-back trials of T25FW; Peak time at Visit 2 and Trough at Visit 3

Two sets of (2) back-to-back trials of T25FW, 3-4 hours apart.

Draw blood immediately after each set of T25FW trials.

Schedule Visit 3 to occur approximately 11 hours after previous dose of DER.

Telephone call to patient one week before Visit 3 (as reminder to shift dosing schedule to meet Visit 3 scheduling requirements).

### 6.1.6 SELECTION AND WITHDRAWAL OF PATIENTS

[00119] Patients will be enrolled at a minimum of 60 investigational centers until a minimum of 405 patients have been randomized.

[00120] Each patient must meet the following eligibility criteria (i.e., have all of the Inclusion criteria and none of the Exclusion criteria) before enrollment in the study:

#### 6.1.6.1. Inclusion Criteria

1. Patient has clinically definite multiple sclerosis as defined by the McDonald Criteria (Version 2005)\(^3\) (See Section 6.1.13.1).
2. Patient must be 18 to 70 years of age, inclusive (i.e., on or after their 18\(^{th}\) birthday, up to the day before their 71\(^{st}\) birthday at the Screening Visit).
3. Patient who has previously taken AMPYRA® or dalfampridine (fampridine or 4-aminopyridine; 4-AP) in any formulation (including compounded), must have withdrawn from the drug for at least one month prior to the Screening Visit.
4. Patient must be mentally competent to understand and sign the IRB-approved informed consent prior to the performance of any study-specific procedures.
5. Patient is able to perform all the required study procedures.
6. In the judgment of the Investigator, the patient has MS-related walking impairment but has sufficient ambulatory ability to be able to complete two trials of the T25FW at the Screening Visit and every study visit thereafter, with the two trials completed within 5 minutes of one another and in accordance with the specific instructions provided by the National Multiple Sclerosis Society MS Functional Composite Manual.\(^4\)
7. Patient who is female and of childbearing potential (see Exclusion Criterion 1 for definition) must have a negative urine pregnancy test at the Screening Visit.

6.1.6.2. Exclusion Criteria

1. Patient is a female of childbearing potential (i.e., has not had a hysterectomy or bilateral oophorectomy, or is not at least two years postmenopausal), who is engaged in active heterosexual relations and is not using one of the following birth control methods: tubal ligation, implantable contraception device, oral, patch or injectable contraceptive, double barrier method, or sexual activity restricted to vasectomized partner.

2. Patient is pregnant or breastfeeding.

3. Patient has any history of seizures.

4. Patient has moderate or severe renal impairment as defined by a calculated creatinine clearance of ≤ 50 mL/minute.

5. Patient has active urinary tract infection (UTI) at Screening or within the 4 weeks before Screening.

6. Patient has had an onset (as assessed by the treating physician) of an MS exacerbation within 60 days prior to the Screening Visit.

7. Patient has started on a concomitant prescription medication regimen within the last three weeks, and/or their concomitant medication regimen is expected to change during the course of the study.

8. Patient has received cyclophosphamide (Cytoxan®) or mitoxantrone (Novantrone®) for MS treatment within six months prior to the Screening Visit.

9. Patient has started a treatment regimen of Betaseron®, Extavia®, Avonex®, Copaxone®, Rebif®, Tysabri®, or Gilenya® within 90 days prior to the Screening Visit or has had any change in the dosing regimen of these drugs within 30 days prior to the Screening Visit.

10. Patient has received corticosteroids (other than topical or inhaled preparations) within 30 days prior to the Screening Visit and/or is expected to receive regularly scheduled corticosteroid treatment during the course of the study.
11. Patient has been administered botulinum toxin in the lower extremities within six months prior to the Screening Visit and/or is expected to receive botulinum toxin in the lower extremities during the course of the study.

12. Patient has a known allergy to pyridine-containing substances or any of the inactive ingredients of the dalfampridine-ER tablet (colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide).

13. Patient has a history of drug or alcohol abuse within the past year.

14. Patient has clinically significant abnormal laboratory values.

15. Patient has angina, uncontrolled hypertension, clinically significant cardiac arrhythmias, or any other clinically significant cardiovascular abnormality.

16. Patient has any medical condition (including psychiatric disease) that would interfere with the interpretation of the study results or the conduct of the study.

17. Patient has participated, within 30 days prior to Screening Visit, in an investigational drug or medical device trial, or plans to enroll in such trial at any time during this study. Non-drug (i.e. observational, registry) and non-medical device trials are allowed.

6.1.6.3. **Withdrawal Criteria**

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Patient experiences an adverse event. (Please note: if the patient has a seizure, the patient must discontinue the investigational drug immediately and be withdrawn from the study).
- Patient is non-compliant with the investigational drug
- Patient is non-compliant with the protocol
- Lack of efficacy
- Patient is lost to follow-up
- Pregnancy
- Death
- Patient requests to withdraw
- Investigator decision, which may include: patient abuses alcohol or drugs or no longer meets another eligibility criterion, to the extent that, in the judgment of the Investigator and/or Sponsor, it would affect assessments of clinical status to a significant degree, require discontinuation of the investigational drug, or both.
- Other

[00122] The reason(s) for a patient's withdrawal from the study must be recorded on the Case Report Form (CRF).

6.1.6.3.1 Seizures

[00123] Any patient who experiences a seizure must be discontinued from the investigational drug immediately. Patients should be instructed to contact the Investigator immediately in the event of any sign of seizure activity. The patient should be evaluated as soon as possible after the event, and a detailed description of the event should be documented.

6.1.7 TREATMENT OF PATIENTS

6.1.7.1. Treatments to be Administered

[00124] Patients will receive one of three treatments:
  a. Dalfampridine 10 mg ER twice daily
  b. Dalfampridine 5 mg ER twice daily
  c. Placebo

[00125] Double-blind investigational treatment will be administered only to eligible patients under the supervision of the investigator or a medically appropriate sub-investigator. Patients will take one tablet approximately every 12 hours throughout the treatment period of the study. Each patient should take the investigational drug at approximately the same times each day throughout the study; however, different patients may be on differing medication schedules (e.g., 7 am and 7 pm; or 9 am and 9 pm).

[00126] Investigational drug (DER or placebo) will be dispensed to the patient at Visit 1 and Visit 2 after assessments have been completed. The investigational drug will be dispensed in kits containing two bottles (numbered Bottle "1 of 2" and "2 of 2"). Each bottle
contains a one-week supply of investigational drug (14 tablets) plus 2 extra tablets in case of loss, damage, etc. for a total of 16 tablets per bottle. Patients will be instructed to use all investigational drug from the first bottle before beginning the second bottle.

[00127] Patients will be instructed to take the first dose in the evening of Visit 1, and the next dose the following morning, approximately 12 hours later. The patient should be instructed to choose times that will make subsequent dosing every 12 hours compatible with his/her normal schedule of sleeping and waking. Patients will be instructed to return all bottles and unused drug at the subsequent study visit.

[00128] Study site staff must emphasize the importance of the dosing regimen to patients. Patients will be instructed to continue dosing every 12 hours at times that are as consistent as possible. Patients will be told that they must NOT make up for missed doses.

[00129] NOTE: The last dose of investigational drug will be administered by the site staff at Visit 3, immediately after the completion of the first T25FW assessment (scheduled to occur approximately 12 hours after the prior dose of investigational drug, to correspond to trough plasma concentration of dalfampridine). The patient's typical dosing schedule should be monitored by the site to ensure the proper timing of assessments at Visit 3.

[00130] If a patient's dosing schedule results in Visit 3 occurring at an inconvenient time for the site, (e.g. patients on a 6 AM and 6 PM dosing schedule would require that Visit 3 begin at 5 AM), patients should be instructed to shift their dosing schedule during the week prior to Visit 3. Patients should shift no more than one hour per dose over 3-4 days to meet Visit 3 scheduling requirements.

[00131] The site staff must call the patient the week before Visit 3 as a reminder.

[00132] At study end (Visit 3) or early termination, all remaining DER will be collected and no further medication will be dispensed.

6.1.7.2. Method of Assigning Patients to Treatment Groups

[00133] Patients will be assigned at Visit 1 to one of three treatments: dalfampridine 10 mg ER, 5 mg ER, or matching placebo by Interactive Voice Response System (IVRS). Treatment will be randomly assigned in a 1:1:1 ratio according to a computer-generated randomization scheme created prior to the start of the study.
6.1.7.3. Concomitant Medications

[00134] The following medications are excluded for the duration of the study for the purpose of maintaining stable MS symptoms:

- Corticosteroids (also excluded 30 days prior to the Screening Visit)
- Botulinum toxin in the lower extremities (also excluded six months prior to the Screening Visit)
- Cyclophosphamide (also excluded six months prior to the Screening Visit)
- Mitoxantrone (also excluded six months prior to the Screening Visit)

[00135] The following medications may be given during the duration of the trial only if they have been started at least 90 days prior to the Screening visit and the treatment regimen has been stable for a minimum of 30 days prior to the Screening visit. The treatment regimen for these medications should remain stable for the duration of the trial.

- Betaseron®
- Extavia®
- Avonex®
- Copaxone®
- Rebif®
- Tysabri®
- Gilenya®

[00136] All prescription and over-the-counter (OTC) medications taken by the patient during the four weeks before screening and through the duration of the study will be recorded in the CRF. Any additions, deletions, or changes in the dose of these medications during the study will be entered in the CRF.

[00137] If the administration of any other concomitant treatment becomes necessary, it must be reported in the CRF and in the patient's medical records. As far as possible, no changes should be made to the concomitant treatment during the study.

6.1.7.4. Treatment Compliance

[00138] If at any time personnel engaged in the study judge that a patient has not complied with the dosing schedule, the patient will be reminded of the importance of
accurate compliance and will be encouraged to continue in the study, taking all doses as prescribed. If non-compliance continues and causes a concern for safety, the Investigator and/or Sponsor may discontinue the patient from the study. The lack of compliance should be recorded on the relevant drug accountability CRF for that patient.

6.1.7.5. Blinding

[00139] Drug administration will be double-blind, meaning that the treatment (dalfampridine 10 mg ER, 5 mg ER, or placebo) administered to each patient will not be known to the patients or the study personnel at the clinical site.

6.1.7.6. Unblinding in the Event of an Emergency

[00140] During an emergency or life threatening situation when knowledge of the assigned treatment is essential for immediate medical management, the Principal Investigator or designee may unblind the patient's treatment assignment. The Principal Investigator or designee should make every attempt to contact Acorda or designee as outlined in the protocol prior to unblinding. However, if not possible, Acorda or designee must be contacted immediately after the unblinding. The justification and process of unblinding should be appropriately documented in the Investigator File. Refer to the Site Instruction Manual for details on the unblinding procedure.

6.1.8 INVESTIGATIONAL DRUG MATERIALS AND MANAGEMENT

6.1.8.1. Description of Investigational Drug

[00141] Active: Dalfampridine-ER will be supplied as an unmarked, film coated, white to off-white, biconvex, oval shaped, non-scored tablet with a flat edge, containing 5 or 10 mg of the drug. Inactive ingredients consist of colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

[00142] Placebo: The placebo tablets will be identical in appearance to the dalfampridine-ER tablets, and contain the same inactive ingredients.
6.1.8.2. **Investigational Drug Storage**

Investigational drug must be maintained in a safe, secure and dry place (double locked, or stored at the central pharmacy) at controlled room temperature (77°F or 25°C: with brief excursions of 59°-86°F or 15-30°C) at the clinical site. Access should be restricted to study personnel and the Site Monitor only.

6.1.9 **STUDY PROCEDURES**

6.1.9.1. **Efficacy, Safety and Other Measurements**

6.1.9.1.1 **Efficacy Measurements**

The following section describes the efficacy measurements that will be obtained during the study. Every effort should be made to maintain the room temperature between 68° and 72° F during the assessment period; deviations will be noted. Every effort should be made to maintain stable concomitant therapy regimens (such as physical therapy) throughout the study.

(A) **Timed 25 Foot Walk Test (T25FW)**

For the purpose of maintaining the integrity of the blinded study, a blinded Evaluator will be responsible for carrying out T25FW (and the 6MW, see Section 6.1.7.1.B) throughout the study. The blinded Evaluator is blinded to the patient's overall safety and clinical assessments, including patient self-report questionnaire results. To ensure consistency throughout the study, the same blinded Evaluator should perform the T25FW at each visit whenever possible.

The T25FW test is a quantitative measure of ambulatory function that is widely used by MS specialists to assess the global impact of the disease and its progression on the patient's physical disability. It will be performed according to the detailed instructions provided in the Administration and Scoring Manual published by the National Multiple Sclerosis Society (the instruction booklet will be provided to all centers), and as summarized here. If required, the patient may use an appropriate assistive device to walk as quickly as
he/she can from one end to the other end of a clearly marked, unobstructed, 25-foot course. Every effort should be made to use the same testing room and the same designated area for the T25FW at every visit. Potential for external distractions should be kept to a minimum as much as possible.

[00147] A patient will stand with the toes of his/her shoes on the starting line (identified by a taped mark on the floor) and timing will begin when any part of the patient’s foot crosses the tape. Timing will end when any part of the patient’s foot crosses the finish line (identified by a taped mark on the floor). Time will be recorded in seconds and rounded to the nearest tenth of a second using a stopwatch provided for this study. The task is immediately administered again (a maximum five-minute rest period is allowed between trials) by having the patient walk back the same distance. The blinded evaluator must record each time and calculate and record the average of the two trials at the Screening Visit only, in order to determine patient eligibility; at all other visits, both times are to be recorded individually. Each patient must be instructed to maintain his/her normal activities without rehearsal or practice measures to unfairly improve their performance scores between visits.

[00148] The two back-to-back trials of the T25FW will be performed once at every study visit, except for Visit 3. There will be two assessment time points for the T25FW at this visit. The first will be scheduled to occur at approximately 12 hours post the prior dose of dalfampridine-ER, to correspond to trough plasma concentration of dalfampridine. The patient will then take his/her last dose of investigational drug and a second assessment of the T25FW will be performed 3-4 hours following this dose, to correspond to approximate peak plasma concentration of dalfampridine. The time of the administration of each walk must be exactly recorded on the CRF.

(B) Six Minute Walk Test (6MW)

[00149] The Six-Minute Walk, 5,6 a test of endurance, measures the distance that a patient can walk in a period of 6 minutes. It will be performed only at selected centers which have the facilities and capability to perform the test.

[00150] Six-minute walk distance will be reported in feet. This test will be performed after the T25FW, and after a sufficient period of rest (at least 10 minutes), at Visits 1 and 2. Refer to the Site Instruction Manual for details of administration. This test
will be administered by a blinded evaluator (see Section 6.1.7.1.1 A).

(C) 12-Item MS Walking Scale (MSWS-12)

[00151] The 12-Item MS Walking Scale (see Section 6.1.13.2) is a self-report questionnaire that asks patients to rate limitations of their mobility due to MS during the preceding two weeks on a 5-point scale (from 1 = not at all to 5 = extremely). It will be administered by site study personnel and completed by the patient as the first scheduled assessment at Visits 1, 2, and 3.

(D) EQ-5D™ Health Questionnaire

[00152] At Visits 1 and 3, patients will be asked to complete a short, generic health status questionnaire: the EuroQol Group EQ-5D™ Health Questionnaire (see Section 6.1.1 1.2.2).

6.1.9.1.2 Safety and Other Measurements

(A) Medical History/Prior and Current Concomitant Medications and Therapies

[00153] A complete medical history will be obtained including a history of the patient's MS diagnosis type and duration of disease, and a review of all prior medications and therapies. All current or recently used medications (within four weeks of the Screening Visit) will be recorded in the CRF. All current therapies will be recorded on the Concomitant Therapies page of the CRF. Every effort should be made to maintain a stable concomitant medication and therapy regimen for the duration of the study. Any new medications or deletions or changes in the dose of current medications during the course of the study will be entered in the CRF. The medical history and concomitant medication/therapy history will be obtained at the Screening Visit.

(B) Electrocardiogram (ECG)

[00154] A standard, resting 12-lead electrocardiogram (ECG) will be obtained for each patient at the Screening Visit. It is also acceptable to use results from a non-study ECG,
if available, as long as the ECG was performed and reported within 60 days prior to the Screening Visit, and a copy of that report is available to be filed with the source documents.

[00155] The ECG report obtained at the Screening Visit must be reviewed and signed by the Investigator prior to final determination of the patient’s eligibility to enroll. Patients with abnormal clinically significant ECGs at screening as determined by the Investigator may not be enrolled into the study.

(C) Physical Examination

[00156] A full physical examination will be performed at the Screening Visit. A brief physical examination will be performed at each subsequent visit and documented in the patient’s medical record. Unfavorable changes in the patient's health status since the Screening Visit noted during the brief physical exam will be recorded on the Adverse Event page of the CRF.

(D) Vital Signs Measurements

[00157] Blood pressure, pulse, respiration rate, body temperature, and weight will be measured at the Screening Visit and at each subsequent visit. Height will be measured only at the Screening Visit. Vital sign measurements should be made by letting the patient rest supine for five minutes, recording blood pressure, temperature, respiratory rate and pulse, then raising the patient to the sitting position and repeating the measurement of blood pressure and pulse after one minute.

(E) Expanded Disability Status Scale (EDSS)

[00158] Each patient will be assessed and scored on the Expanded Disability Status Scale (EDSS) at the Screening Visit. The definition for each of the numerical scores of this scale appears in Section 6.1.13.3. The score will be used only as a baseline characterization.

(F) Clinical Laboratory Evaluations

[00159] At the Screening Visit only, a sample will be taken for blood chemistry
screening (calculated creatinine clearance and SMA-12: see analytes to be measured below). Blood samples should be collected after the completion of all functional assessments. If a test result is abnormal and determined by the Investigator as clinically significant, the site must contact Acorda or designee to discuss the patient's eligibility for this study.

At every visit, a urine sample (clean catch urine specimen) will be taken for microscopic urinalysis to detect laboratory evidence suggestive of urinary tract infection (UTI). If the patient has symptoms of a UTI, a urine culture must be performed in addition to the urinalysis for confirmation of the diagnosis. A urine culture should also be performed if the urinalysis is positive, even if the patient has no symptoms of UTI.

Laboratory evaluations may also be performed at any visit (including Unscheduled and Early Termination visits) if required for emergent adverse event investigation and follow-up, at any time during the study. Blood samples should be collected after the completion of all functional assessments. If a test result is clinically significant as determined by the Investigator, the site must contact Acorda or designee to discuss the patient's eligibility for this study.

A list of the clinical laboratory analytes for this study is provided in Table 5.

Table 5: Clinical Laboratory Analytes.

<table>
<thead>
<tr>
<th>SMA-12 + calculated creatinine clearance</th>
<th>Urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Blood</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>Glucose</td>
</tr>
<tr>
<td>AST</td>
<td>Ketones</td>
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<tr>
<td>Bilirubin (total)</td>
<td>pH</td>
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<tr>
<td>BUN</td>
<td>Protein</td>
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<tr>
<td>Calcium</td>
<td>Specific gravity</td>
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<td>Cholesterol</td>
<td>WBC</td>
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<tr>
<td>Creatinine</td>
<td>RBC</td>
</tr>
<tr>
<td>Calculated creatinine clearance (Screen only)</td>
<td>Hyaline Casts</td>
</tr>
<tr>
<td>Glucose</td>
<td>Granular Casts</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>Waxy Casts</td>
</tr>
<tr>
<td>Total Protein</td>
<td>WBC Casts</td>
</tr>
</tbody>
</table>
**SMA-12 + calculated creatinine clearance**

<table>
<thead>
<tr>
<th><strong>Urine Analysis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC Casts</td>
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<tr>
<td>Epithelial Cells</td>
</tr>
<tr>
<td>Crystals</td>
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<tr>
<td>Bacteria</td>
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<tr>
<td>Calcium Oxalate Crystals</td>
</tr>
<tr>
<td>Uric Acid Crystals</td>
</tr>
<tr>
<td>Triphosphate Crystals</td>
</tr>
</tbody>
</table>

**Pregnancy Test**

[00163] A urine pregnancy test will be performed for females of childbearing potential at the Screening Visit and at Visit 3 (last visit). It will also be obtained at the Early Termination Visit for patients who discontinue the study, and whenever needed.

**Plasma dalfampridine concentration**

[00164] Blood samples for determination of plasma dalfampridine concentration will be obtained Visit 1, Visit 2 and Visit 3. At Visit 3, blood samples will be obtained at two time points. The first sample will be taken immediately after the first assessment of the T25FW. The walks are scheduled to occur at approximately 12 hours after the prior dose of dalfampridine -EPv, to correspond to trough plasma concentration of dalfampridine. The patient will then take his/her last dose of investigational drug and a second assessment of the T25FW will be performed 3-4 hours following this dose, to correspond to approximate peak plasma concentration of dalfampridine. The second blood sample will be collected immediately after the second assessment of the T25FW. The time of each blood sampling and the time of the administration of the last dose of investigational drug must be exactly recorded on the Case Report Form (CRF).

[00165] A minimum of 7 mL of whole blood will be collected into an appropriately labeled heparin tube and kept cold (i.e., on wet ice) until centrifuged. Immediately after collection, the tube will be centrifuged at low speed and approximately 3 mL of plasma will be transferred from each sample into a labeled tube. The plasma should be stored at -20° C until the Sponsor or designee requests shipment to the central laboratory.
At that time, frozen plasma samples will be collected together and sent in an insulated container, on dry ice, overnight by express carrier to the designated central laboratory.

(I) Adverse Events

[00166] Monitoring of adverse events will be conducted throughout the study. Adverse events, including serious adverse events will be recorded in the CRFs. All adverse events should be monitored until its conclusion or up to the patient’s study completion/discontinuation, whichever comes first. Definitions, documentation, and reporting of adverse events and serious adverse events are described in detail in Section 6.1.8.

(J) Concomitant Medications/Therapies

[00167] All medications and therapies or procedures that are administered during the study must be recorded in the patient’s CRF and in the source documents. Every effort should be made to maintain a stable concomitant medication and therapy regimen for the duration of the study, however, concomitant medications/therapies for medical conditions are permitted as clinically indicated.

6.1.9.2. Study Sequence

[00168] The following sections describe the schedule of assessments to be performed during the study. If they qualify for the study, patients will be randomized and receive investigational drug at the baseline visit (Visit 1).

6.1.9.2.1 Screening Visit

[00169] The Investigator will assess eligibility after the following procedures have been performed:

• Obtain signed informed consent
• Assign patient number
• Obtain medical history, including demographic information, and MS History (diagnosis type and date of onset)
• Review of concomitant medications and therapies (record all medications taken within three weeks of Screening Visit).
• Patient must complete one set (two trials) of the T25FW, administered by the blinded Evaluator. Time of walk to be recorded exactly.
• EDSS
• Complete full physical examination
• Vital sign measurements and height and weight
• Perform 12-Lead ECG
• Laboratory evaluations (SMA-12, calculated creatinine clearance, urinalysis, and urine pregnancy test for females of childbearing potential). If abnormal, and determined by the Investigator as clinically significant, the site MUST contact Acorda or designee to discuss the patient's eligibility for this study.
• If found eligible, schedule a date and time for the next visit to occur in one week (+/- 1 day)

6.1.9.2.2 Visit 1 (Baseline and Randomization)

[00170] The following procedures should be performed at Visit 1, the start of the double-blind treatment period:
• Administer the MSWS-12
• Patient to complete one set (two trials) of the T25FW, administered by the blinded Evaluator. Time of walk to be recorded exactly.
• Take blood sample for plasma dalfampridine concentration
• Perform a brief physical examination and vital sign measurements
• Administer the EQ-5D™ health questionnaire
• Six-Minute Walk test (to be performed after a sufficient rest period—at least 10 minutes)
• Collect urine sample for urinalysis (confirmatory culture for UTI diagnosis, if needed)
• Record any changes in concomitant medications/therapies
• Review and record any adverse events over the past week
• Randomize patient to one of the three treatment arms (dalfampridine 10 mg ER twice daily, 5 mg ER twice daily, or placebo), and dispense a two-week supply of double-blind investigational drug
• Schedule a date and time for the next visit to occur in two weeks (+/- two days)

6.1.9.2.3 Visit 2

[00171] The following procedures should be performed at Visit 2 (the start of the third week of the double-blind treatment period):

• Administer the MSWS-12
• Patient to complete one set (two trials) of the T25FW, administered by the blinded Evaluator. Time of walk to be recorded exactly.
• Take blood sample for plasma dalfampridine concentration
• Perform a brief physical examination and vital sign measurements
• Six-Minute Walk test (to be performed after a sufficient rest period—at least 10 minutes)
• Collect urine sample for urinalysis (confirmatory culture for UTI diagnosis, if needed)
• Record any changes in concomitant medications/therapies
• Review and record any adverse events over the past two weeks
• Perform investigational drug accountability
• Dispense a two-week supply of double-blind investigational drug
• Schedule a date and time for the next visit to occur in two weeks (+/- two days)

6.1.9.2.4 Telephone Contact
[00172] The site must call the patient one week before Visit 3 as a reminder to shift the dosing schedule (if needed) to meet Visit 3 scheduling requirements (see Section 6.1.5.1).

6.1.9.2.5 Visit 3 (Final Visit)

[00173] Visit 3 should be scheduled approximately 11 hours after the patient's last dose of investigational drug. The following procedures should be performed at Visit 3 (study completion for the patient).

- Administer the MSWS-12
- Patient to complete one set (two trials) of the T25FW, administered by the blinded Evaluator. Schedule T25FW to occur approx. 12 hours after last dose. Time of walk to be recorded exactly.
- Take blood sample for plasma dalfampridine concentration immediately after second trial of timed walk (time of draw to be recorded exactly)
- Dispense one blinded tablet (last dose of investigational drug) and record time exactly. Schedule second set of T25FW to occur 3 to 4 hours post-dose.
- Collect urine sample for urinalysis (confirmatory culture for UTI diagnosis, if needed)
- Urine pregnancy test for females of childbearing potential
- Perform a brief physical examination and vital sign measurements
- Record any changes in concomitant medications/therapies
- Review and record any adverse events over the past two weeks
- Patient to complete another set (two trials) of the T25FW test 3 to 4 hours post-dose, administered by the blinded Evaluator. Time of walk to be recorded exactly.
- Record time of last meal.
- Take blood sample for plasma dalfampridine concentration immediately after second trial of timed walk (time of draw to be recorded exactly)
- Administer the EQ-5D™ health questionnaire
- Perform investigational drug accountability
- Complete a final status assessment

6.1.9.2.6 Unscheduled Visits

[00174] All Unscheduled Visit information shall be documented in the source documentation and CRFs. When indicated, unscheduled visits may include any of the following safety assessments:

- Laboratory (SMA-12/urinalysis/urine pregnancy test) if needed to follow-up an adverse event or clinically significant abnormal value at the previous visit, or if pregnancy is suspected.
- Urine culture to confirm diagnosis of urinary tract infection
- Brief physical examination and measurement of vital signs
- Record any change in concomitant medications/therapies
- Review and record any adverse events since the last visit
- Drug accountability if applicable
- Complete a final status assessment if visit is for early termination

6.1.9.2.7 Early Termination Visit

[00175] Discontinued patients or patients who wish to withdraw early should be encouraged to return to the clinic for early termination procedures (same as Unscheduled Visit).

6.1.10 ADVERSE EVENTS

6.1.10.1. Adverse Events

[00176] Definition: An adverse event (AE) is any new, undesirable medical occurrence or change of an existing condition in a patient that occurs during the study period, whether or not it is related to the investigational drug.

[00177] Abnormal laboratory findings considered by the Principal Investigator to be clinically significant, for example, those that are unusual or unusually severe for the population being studied, will also be considered adverse events.
For the purposes of this study any exacerbation of the patient's underlying multiple sclerosis is to be considered an adverse event and documented as such.

Identifying Adverse Events: At each study visit, patients should voluntarily report any AEs in response to general non-leading questions (e.g., "how have you been feeling since your last visit?").

Documenting Adverse Events: All adverse events reported by the patient or observed by the study personnel from the Screening Visit up to the patient's study completion/discontinuation will be recorded on the Adverse Event Case Report Form, whether or not the event is considered by the Investigator to be related to the investigational drug. The information collected will include the diagnosis, duration, severity, seriousness, study discontinuation information, action taken with investigational drug, relationship to investigational drug and outcome. Whenever possible, the Investigator should group together, into a single term, signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis, and sneezing might be grouped together as "upper respiratory infection."

Severity: Every adverse event should be graded for severity. The severity categories of mild, moderate or severe, are defined below:

- Mild is defined as causing no limitation of usual activities
- Moderate is defined as causing some limitation of usual activities
- Severe is defined as causing inability to carry out usual activities

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Relationship to Investigational drug: The Investigator will be asked to document his/her opinion of the relationship of the adverse event to the investigational drug as follows:

- Not related - the event can be readily explained by the patient's underlying medical condition or concomitant therapy; and no relationship exists between the investigational drug and the event.
- Unlikely - the temporal relationship between the event and the administration of the investigational drug is uncertain; and the event can most likely be explained by the patient's medical condition or other therapies.
- Possibly - there is some logical temporal relationship between the event and the
administration of the investigational drug; and the event is unlikely to be explained by the patient's medical condition or other therapies.

- Related - the temporal relationship is compelling between the administration of the investigational drug; and the event cannot be explained by the patient's medical condition or other therapies.

[00184] Action taken with Investigational drug: Every adverse event should have the action taken with investigational drug documented. The following options are allowed:

- Dose not changed
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

[00185] Outcome: Every adverse event should have the outcome documented. The following options are allowed:

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

[00186] Follow-up: Each adverse event should be followed until its resolution or up to the patient's study completion/discontinuation, whichever comes first.

6.1.10.2. Serious Adverse Events

[00187] Definition: A serious adverse event (SAE) is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the Investigator's or Sponsor's opinion on the relationship to the investigational drug. This includes but is not limited to an event that:

- Is fatal
- Is life threatening (places the patient at immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Is a persistent or significant disability/incapacity
- Causes a congenital anomaly/birth defect

[00188] Important medical events that may not be immediately life threatening or result in death or hospitalization but that jeopardize the patient or require intervention to prevent one of the outcomes listed above, or require urgent investigation, may be considered serious.

[00189] Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the study or before the investigational drug was given, are not to be considered SAE’s unless they occur at a time other than the planned date.

[00190] For the purposes of this study, seizures are to be considered serious adverse events and be reported as such.

[00191] Reporting: All SAEs that occur during the course of the study from the Screening Visit up to the patient’s study completion/discontinuation must be reported by the Investigator to United BioSource Corporation (UBC), the sponsor's safety reporting group, whether or not the event is considered causally related to the investigational drug. Acorda SAE Report forms will be provided to each investigational center.

[00192] If there are serious, unexpected adverse drug reactions associated with the use of the investigational drug, Acorda Therapeutics will notify the appropriate regulatory agencies and all participating investigators in accordance with IND Safety reporting regulations. It is the responsibility of the Investigator to promptly notify the IRB of all unexpected serious adverse drug reactions involving risk to human patients. An unexpected event is one that is not reported in or more severe or specific than what is found in the Investigator's Brochure. Although reported in the Investigator's Brochure, for the purpose of this study, seizures will be submitted to the appropriate regulatory agencies and all participating investigators on an expedited basis, and should be reported to the IRB by the Investigator.

[00193] Follow-up: Each SAE should be followed until its resolution or up to the
patient's study completion/discontinuation, whichever comes first.

The Investigator must determine whether the clinical seriousness of the event warrants removal of the patient from the study. He/she should, in any case, institute appropriate diagnostic and therapeutic measures and keep the patient under observation for as long as is medically indicated.

For study related questions (including medical monitoring questions), please refer to the Site Instruction Manual for contact information.

6.1.11 STATISTICS

This section outlines the nature of and rationale for the statistical methods to be used for the analysis of data from the study. A separate Statistical Analysis Plan (SAP), which must be documented as completed prior to unblinding the study, will describe data handling and statistical techniques in full detail.

All computations will be performed using SAS® Version 8 or above. Statistically significant treatment differences will be declared if the resulting p-value is 0.05 or less. All tests will be two-sided. No interim analysis is planned.

6.1.11.1. Assessment of Treatment Group Comparability

6.1.11.1.1 Demographic, Background and Baseline Variables

Key demographic, background, and baseline variables include:

- Demographics: gender, age, and race
- MS diagnosis type
- Duration of disease
- EDSS score
- Baseline efficacy measures: walking speed, MSWS-12 Score, six-minute walk distance, and EQ-5D™ scores.

Other background variables include:

- Medications both prior and current
- Medical conditions at screening
- Physical exam abnormalities at screening
• Baseline Safety Measures: screening vital signs, screening chemistry (SMA-12 only), pre-treatment adverse events and pre-treatment urinalysis.

6.1.11.1.2 Computational Details

(A) Derived Endpoints and Data Handling

[00200] Age and duration of disease will be computed based on age and duration at screening. The derivation of baseline efficacy measures is addressed in the efficacy section.

[00201] All medications (prior and current) will be coded using the most current version of the World Health Organization Anatomical Therapeutic Chemical (WHO ATC) Classification System with WHO-DRUG.

(B) Statistical Summaries and Analysis

[00202] A series of statistical tests will be performed to assess the treatment group comparability in key demographic, background, and baseline variables. Variables with continuous distributions (e.g., baseline walking speed) will be analyzed via analysis of variance (ANOVA) with effects for treatment. Nominal categorical data (e.g., gender and race) will be analyzed via the Cochran-Mantel-Haenszel (CMH) test, controlling for baseline.

[00203] For each analysis, a corresponding sensitivity analysis will be performed with center as the additional control variable. Small sites will be combined together to form a center whenever applicable.

[00204] Other background variables will be summarized for each treatment group by presenting the number and percentage of subjects in each category.

6.1.11.2. Evaluation of Efficacy

6.1.11.2.1 Efficacy Variables

[00205] The computational details for the derivation of all applicable variables in this section can be found in Section 6.1.9.2.2(A) 'Derived Endpoints and Data Handling.'

(A) Primary Efficacy Variable

[00206] The primary efficacy variable will be change from baseline in walking
speed (T25FW) at approximately 3-4 hours post dose at Visit 3 (i.e. near the $C_{\text{max}}$ for dalfampridine-ER at the end of double-blind week 4).

(B) Secondary Efficacy Variables

[00207] The key secondary efficacy variables are:

1. Change from baseline in walking speed (T25FW) at approximately 12 hours post dose at Visit 3 (i.e. near the $C_{\text{max}}$ for dalfampridine-ER at the end of double-blind week 4).

2. Change from baseline in MSWS-12 at Visit 3.

[00208] Other secondary efficacy variables will include:

- Changes from baseline in MSWS-12 at Visit 2
- Change from baseline in walking speed (T25FW) at Visit 2
- Change from baseline in Six-Minute Walk distance (feet) at Visit 2
- Changes from baseline in 5 specific dimensional scores, average scores across 5 dimensions and visual analogue self-rating (VAS) scores of EQ-5D™ at Visit 3

6.1.11.2.2 Computational Details

(A) Derived Endpoints and Data Handling

[00209] **Walking Speed:** At each visit time point, there will be two trials of the T25FW. All visits, other than Visit 3, have one time point. There will be two time points for the T25FW at Visit 3:

- The first scheduled T25FW test at Visit 3 to occur at approximately 12 hours post the prior dose
- The second scheduled T25FW test at Visit 3 to occur at approximately 3-4 hours after taking the last dose of investigational drug at the investigational site.

[00210] Walking speed for an individual trial will be derived (in feet per second) by multiplying the reciprocal of the time to complete the walk (in seconds) by 25 (feet). The walking speed for a particular study visit time point will be derived by calculating the average of the walking speeds for Trial 1 and Trial 2 of that visit time point. If either trial is missed, then the walking speed for that visit time point will be the walking speed from the
non-missing trial.

[00211] **Six-Minute Walk Distance:** The (modified) Six-Minute Walk (6MW) test measures the distance that a patient can walk back and forth in a 100-foot hallway over a period of 6 minutes. Total 6MW distance will be reported in feet. This test will be completed by only selected centers which have the facilities and capability to perform the test.

[00212] **MSWS-12 Score:** The MSWS-12 is a 12-question questionnaire that asks patients to rate limitations of their mobility due to MS during the preceding two weeks on a 5-point scale (from 1= not at all to 5=extremely). For each visit, the MSWS-12 score will be calculated by summing the 12 components and transforming into a scale with a range of 0 to 100.

\[ \text{MSWS-12 Score} = 100 \times \left( \frac{\text{Sum of Items 1-12} - 12}{48} \right) \]

[00213] For a visit in which at least 50% of the component questions are answered but at least one is not, scores from the unanswered component questions will be imputed using the respondent's specific mean score. For a visit in which more than 50% of the component questions are not answered, the MSWS-12 score will be considered missing (see below for imputation of missing values).

[00214] **EQ-5D™ Health Questionnaire:** The EQ-5D™ is a brief questionnaire that asks patients to rate their health status in 5 specific dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression: one question per dimension) and to rate their general state of health on a visual analog scale (VAS). It will be administered at both Visit 1 (baseline) and Visit 3. Results of the EQ-5D™ changes from baseline will be summarized using descriptive statistics. Each question will have three distinguishable choices that can be analyzed using a 3-point scale (i.e. 1 = no problem, 2 = some problems and 3 = extreme problems). For each visit, the average score of 5 dimensions will be calculated by averaging the scores of 5 dimensions. For a visit in which at least three questions are checked but at least one is not, scores from the unanswered component questions will be imputed using the respondent's specific mean score. For a visit in which more than 3 questions are not answered, the average overall score will be considered missing.

[00215] **Imputation for Missing Values:** If after the above computations, a value is missing for a particular parameter at a scheduled visit time point, then the missing value will be imputed using the last observation carried forward (LOCF) principle as follows:
• a missing Visit 1 value would be imputed with the screening value
• a missing Visit 2 value would be imputed with the Visit 1 value
• a missing Visit 3 value would be imputed with the Visit 2 value

[00216] If two consecutive visits are missing, then a missing value will be assigned to the third visit.

[00217] **Analysis Variables**: At all applicable scheduled visit time points, analysis variables based on changes from baseline will be computed for walking speed, MSWS-12 score, and six-minute walking distance. For a particular efficacy variable (e.g., walking speed) changes from baseline at each post-baseline visit time point will be derived by subtracting the baseline value from the post-baseline value. For walking speed, the baseline will be derived by calculating the average among all the visits prior to taking double-blind medication for which data is available (e.g., if a visit before initiation of double-blind treatment is missed, then the unmissed visit will be the baseline value). MSWS-12 and Six-Minute Walk Test are assessed pre-treatment at Visit 1 only; thus the measurements at Visit 1 will serve as the baseline.

(B) **Statistical Analysis**

[00218] **Treatment Comparison of Efficacy Variable**: Treatment differences (dalfampridine 10 mg ER twice daily vs. placebo and dalfampridine 5 mg ER twice daily vs. placebo) for the following continuous variables will be analyzed via analysis of variance with effects for treatment and corresponding baseline.

1. (Primary Efficacy Variable) Change from baseline in walking speed (T25FW) at approximately 3-4 hours post dose at Visit 3 (i.e. near $C_{\text{max,ss}}$ for dalfampridine-ER at the end of double-blind week 4)

[00219] The key secondary efficacy variables:

2. Change from baseline in walking speed (T25FW) at approximately 12 hours post dose at Visit 3 (i.e. near $C_{\text{m,ss}}$ for dalfampridine-ER at the end of double-blind week 4)

3. Change from baseline in MSWS-12 at Visit 3

[00220] Other secondary efficacy variables:

• Change from baseline in MSWS-12 at Visit 2
• Change from baseline in walking speed (T25FW) at Visit 2
• Change from baseline in Six-Minute Walk distance (feet) at Visit 2
• Changes from baseline in VAS scores of EQ-5D™ at Visit 3

[00221] Treatment differences for the following categorical variables will be analyzed via Cochran-Mantel-Haenszel (CMH) test, controlling for baseline score:
• Changes from baseline in 5 specific dimensional scores of EQ-5D™ at Visit 3
• Changes from baseline in average scores across 5 specific dimension of EQ-5D™ at Visit 3

[00222] For each analysis above, a corresponding sensitivity analysis will be performed with center as the additional control variable. Small sites will be combined together to form a center whenever applicable.

[00223] **Plasma Concentration Response Analysis**: To analyze the plasma concentration response relationship, four variables of interest are as follows:
• Change in walking speed from baseline at C_{max} at Visit 3
• Change in walking speed from baseline at C_{mi} at Visit 3
• Observed plasma concentration level at C_{max} at Visit 3
• Observed plasma concentration level at C_{mi} at Visit 3

[00224] A linear regression analysis will be performed using the observed plasma concentration level as an explanatory variable and the change in walking speed from baseline as a response variable. A test of the slope will indicate if the plasma concentration response exists.

(C) Protection for Multiple Comparisons

[00225] This study was powered to detect differences between dalfampridine 10 mg ER and placebo on change from baseline in walking speed at approximately C_{max} (Visit 3). No other comparisons were powered for this study. As such, to demonstrate study sensitivity with respect to efficacy and maintain an overall alpha level less than or equal to 0.05, the following stepwise procedures will be performed. If statistical significance is not achieved at a particular step, no subsequent comparisons will be eligible to be declared statistically significant.
Study-Sensitivity Steps (dalfampridine 10 mg ER twice daily vs. placebo twice daily):

1. Change from baseline in walking speed at approximately $C_{\text{max,ss}}^{\text{ss}}$ at Visit 3.
2. Change from baseline in walking speed at approximately $C_{\text{m,k,ss}}^{\text{ss}}$ at Visit 3.
3. Change from baseline in MSWS-12 for dalfampridine-ER at Visit 3.

Efficacy Evaluation of 5 mg (dalfampridine 5 mg ER twice daily vs. placebo twice daily):

4. Change from baseline in walking speed at approximately $C_{\text{max,ss}}^{\text{ss}}$ at Visit 3.
5. Change from baseline in walking speed at approximately $C_{\text{m,k,ss}}^{\text{ss}}$ at Visit 3.
6. Change from baseline in MSWS-12 at Visit 3.

The above protections for multiplicity pertain to the primary and key secondary efficacy endpoints. Regardless of the outcome of these comparisons, the comparisons for other secondary efficacy endpoints will be performed and nominal p-values will be reported to complete the full clinical picture.

6.1.11.2.3 Efficacy Populations

The primary efficacy analysis will be based on the intention-to-treat principle (i.e., on the initial treatment intent, not on the treatment eventually administered). According to ICHE9 (Statistical Principles for Clinical Trials), there are a limited number of circumstances that might lead to excluding randomized patients from analyses such as: 1) the failure to take at least one dose of trial medication or 2) the lack of any data post randomization. The Full Analysis Population (FAP) will be the basis of the primary efficacy analysis and will include all randomized patients who took at least one dose of double-blind investigational drug and who have a baseline T25FW assessment and at least one post-baseline T25FW assessment. The justification for excluding patients with no baseline value and at least one post-baseline T25FW assessment from the FAP is that there would be no reasonable imputation for the primary efficacy variable (Change from baseline in walking speed at approximately 3-4 hours post dose at Visit 3).

If warranted, secondary efficacy analyses will be performed on a Per-Protocol Population (PPP). A PPP is a subpopulation of the FAP and will consist of all FAP patients with no major protocol violations.
6.1.11.2.4 Statistical Power

[00231] In the MS efficacy studies previously conducted by Acorda Therapeutics, the treatment difference of dalfampridine 10 mg ER bid vs. placebo in change-from-baseline walking speed is approximately 0.16 feet/second with a standard deviation of 0.367 feet/second. The standard deviation for the current study is expected to be larger compared to the corresponding value of earlier studies, in which the average of multiple time points were used in the calculation of change-from-baseline walking speed. Thus a slightly inflated common standard deviation of 0.400 feet/second was used in the sample size estimate based on a 0.050 two-sided significance level test.

[00232] Considering these assumptions, a sample size of 135 patients in each group is expected to provide approximately 90% power to detect the treatment difference of 0.16 feet/second between dalfampridine 10 mg ER bid vs. placebo in change-from-baseline walking speed at \( C_{\text{max} \text{ss}} \).

6.1.11.2.5 Plasma Concentrations

[00233] Dalfampridine plasma concentration levels will be summarized at each scheduled visit time point using descriptive statistics (n, mean, standard error of the mean [SEM], standard deviation [SD], median, minimum and maximum). Additional analyses comparing efficacy data to plasma concentrations may be specified in the SAP.

6.1.11.3 Evaluation of Safety

6.1.11.3.1 Safety Variables

[00234] Key safety variables are:

- Adverse Events (AEs)
- Urinalysis results for the evaluation of the frequency of urinary tract infection
- The secondary safety variables include vital signs, physical exam and SMA-12 measures.

6.1.11.3.2 Computational Variables
(A) Derived Endpoints and Data Handling

[00235] All AEs will be coded using the most current version of the Medical Dictionary of Regulatory Activities (MedDRA), and will be classified by MedDRA system organ class (SOC) and preferred term. Treatment-emergent AEs will be defined as AEs reported in the clinical database with a date of onset (or worsening) on or after the start date of double-blind treatment.

[00236] For each patient, the baseline urinalysis will be the maximum white blood cell count among the Screening Visit and Visit 1.

(B) Statistical Summaries

[00237] The following will be presented for the key safety variables:

- Pre-treatment AEs by system organ class (SOC) and preferred term
- An overall summary of treatment emergent adverse events (including deaths, serious AEs, related AEs, maximum severity, and withdrawals due to AEs)
- Treatment-emergent AEs by SOC and preferred term
- Treatment-emergent AEs by preferred term in descending frequency (based on the overall dalfampridine rate)
- Treatment-emergent AEs by maximum severity, SOC, and preferred term
- Drug-related treatment-emergent AEs by SOC and preferred term
- Serious treatment-emergent AEs by SOC, and preferred term
- Treatment-emergent AEs leading to withdrawal by SOC preferred term
- Shifts in urinalysis results

[00238] The secondary safety variables may be summarized. Descriptive statistics (n, mean, standard error of the mean [SEM], standard deviation [SD], median, minimum and maximum) will be calculated for continuous variables. Frequencies and percentages will be tabulated for categorical variables. Percentages will be based on the total number of non-missing values. If there are missing values, the number missing will be presented, but without a percentage.

[00239] Additional exploratory analyses comparing safety data to plasma
concentrations may be specified in the SAP.

6.1.11.3.3 The Safety Population

[00240] All safety analyses will be based on the safety population, defined as all randomized patients treated with at least one dose of double-blind investigational drug.

6.1.12 REFERENCES


6.1.13 APPENDICES

6.1.13.1. McDonald Criteria For Diagnosis And Classification Of Multiple Sclerosis
I. Diagnostic Criteria for Multiple Sclerosis (Revised, 2005)\textsuperscript{3}

Table 6:

<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>ADDITIONAL DATA NEEDED FOR MS DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 or more attacks; objective clinical evidence of 2 or more lesions</td>
<td>None</td>
</tr>
</tbody>
</table>
| 2 or more attacks; objective clinical evidence of 1 lesion | Dissemination in space, demonstrated by:  
- MRI  
- 2 or more MRI detected lesions consistent with MS plus positive CSF  
OR  
- Await further clinical attack implicating a different site |
| 1 attack; objective clinical evidence of 2 or more lesions | Dissemination in time, demonstrated by:  
- MRI  
OR  
- Second clinical attack |
| 1 attack; objective clinical evidence of 1 lesion  
(monosymptomatic presentation; clinically isolated syndrome) | Dissemination in space, demonstrated by:  
- MRI  
OR  
- 2 or more MRI-detected lesions consistent with MS plus positive CSF  
AND  
- Dissemination in time, demonstrated by:  
- MRI  
OR  
- Second clinical attack |
| Insidious neurological progression suggestive of MS | One year of disease progression (retrospectively or prospectively determined)  
AND  
- Two out of three of the following:  
a. Positive brain MRI (9 T2 lesions or 4 or more T2 lesions with positive visual evoked potentials;  
b. Positive spinal cord MRI (two or more focal T2 lesions);  
c. Positive CSF |
II. Definitions of Terms Used in Diagnostic Criteria

Table 7:

<table>
<thead>
<tr>
<th>What Is An Attack?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neurological disturbance of kind seen in MS</td>
</tr>
<tr>
<td>• Subjective report or objective observation</td>
</tr>
<tr>
<td>• 24 hours duration, minimum</td>
</tr>
<tr>
<td>• Excludes pseudoattacks, single paroxysmal episodes</td>
</tr>
</tbody>
</table>

Determining Time Between Attacks

• 30 days between onset of event 1 and onset of event 2

<table>
<thead>
<tr>
<th>What is a Positive MRI²,³</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 out of 4 of the following:</td>
</tr>
<tr>
<td>• 1 Gd-enhancing brain or cord lesion or 9 T2 hyperintense brain and/or cord lesions if there is no Gd-enhancing lesion</td>
</tr>
<tr>
<td>• 1 or more brain inf atentorial or cord lesion</td>
</tr>
<tr>
<td>• 1 or more juxtacortical lesion</td>
</tr>
<tr>
<td>• 3 or more periventricular lesions</td>
</tr>
</tbody>
</table>

Note: individual cord lesions can contribute along with individual brain lesions to reach required number of T2 lesions

<table>
<thead>
<tr>
<th>What Provides MSI Evidence of Dissemination in Time?</th>
</tr>
</thead>
<tbody>
<tr>
<td>• A Gd-enhancing lesion detected in a scan done at least 3 months after onset of initial clinical event at a site different from the initial event</td>
</tr>
</tbody>
</table>

or

• A new T2 lesion detected in a scan done at any time compared to a reference scan done at least 30 days after initial clinical event

<table>
<thead>
<tr>
<th>What is Positive CSF?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoclonal IgG bands in CSF (and not serum) or elevated IgG index</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What is Positive VEF?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed but well-preserved wave form</td>
</tr>
</tbody>
</table>

75
III. Clinical Course Definitions for Multiple Sclerosis

**Relapsing remitting MS:** Clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression.

**Secondary progressive MS:** Initial relapsing-remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus.

**Primary progressive MS:** Disease progression from onset with occasional plateaus and temporary minor improvements allowed.

**Progressive relapsing MS:** Disease progression from onset with subsequent superimposed relapses.
### 6.1.13.2. The 12-Item Walking Scale

Table 8:

**Multiple Sclerosis Walking Scale (MSWS-12)**

**Instructions:**
- These questions ask about *limitations to your walking due to MS during the past 2 weeks.*
- For each statement, please *circle the one number that best describes your degree of limitation.*
- Please answer all *questions even if some seem rather similar to others, or seem irrelevant to you.*
- *If you cannot walk at all, please tick this box.* □

<table>
<thead>
<tr>
<th>In the past two weeks, how much has your MS...</th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Limited your ability to walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Limited your ability to run?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Limited your ability to climb up and down stairs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Made standing when doing things more difficult?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Limited your balance when standing or walking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. Limited how far you are able to walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Increased the effort needed for you to walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. Made it necessary for you to use support when walking indoors (e.g., holding on to Furniture, using a stick, etc.)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. Made it necessary for you to use support when walking outdoors (e.g., using a stick, a frame, etc.)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Slowed down your walking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. Affected how smoothly you walk?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. Made you concentrate on your walking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
6.1.13.3. Expanded Disability Status Score (EDSS)

KURTZKE EXPANDED DISABILITY STATUS SCALE (EDSS)

0-Normal neurologic exam.

1.0-No disability, minimal signs on one FS.

1.5-No disability minimal signs on >1 FS.

2.0-Minimal disability in 1 FS.

2.5-Minimal disability in 2 FS.

3.0-Moderate disability in 1 FS; or mild disability in 3-4 FS, though fully ambulatory.

3.5-Fully ambulatory but with moderate disability in 1 grade 3 FS and 1-2 grade 2 FS; or 2 grade 3 FS or 5 grade 2 FS.

4.0-Fully ambulatory without aid, up and about 12hrs/day despite relatively severe disability. Able to walk without aid or rest some 500 meters.

4.5-Fully ambulatory without aid, up and about much of day, able to work a full day, may otherwise have some limitations of full activity or require minimal assistance. Relatively severe disability. Able to walk without aid or rest some 300 meters.

5.0-Ambulatory without aid for about 200 m. Disability impairs full daily activities.

5.5-Ambulatory for 100 m, disability precludes full daily activities.

6.0-Intermittent or unilateral constant assistance required to walk 100 m with or without resting.

6.5-Constant bilateral support required to walk 20 m without resting.

7.0-Unable to walk beyond 5 m even with aid, essentially restricted to wheelchair, wheels self, transfers alone.

7.5-Unable to take more than a few steps, restricted to wheelchair, any need aid in transfer, wheels self but may require motorized chair for full day's activities.

8.0-Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed much of day, retains self care functions, generally effective use of arms.

8.5-Essentially restricted to bed much of day, some effective use of arms, some self care functions.

9.0-Helpless bed patient, can communicate and eat.

9.5-Totally helpless bed patient; unable to communicate effectively or eat/swallow.

10.0-Death.
6.1.14 RESULTS

[00241] The protocol set forth above in Sections 6.1.1 to 6.1.13 was carried out essentially as described. A summary of the results and a detailed description of the results are presented below.

6.1.14.1. SUMMARY OF THE RESULTS

[00242] This study evaluated a 5 mg dose of dalfampridine-ER to improve walking in people with multiple sclerosis (MS). The study failed to confirm efficacy of the 5 mg dose.

[00243] The study randomized 430 participants across three treatment arms: placebo, 5 mg or the currently marketed dose of 10 mg of dalfampridine-ER, twice daily. Baseline characteristics were measured at a single visit after randomization, following a qualifying screening visit. Study drug was then given for 4 weeks. Participants returned after 2 weeks on study drug for interim measurements (Visit 2), and again at 4 weeks (Visit 3). The primary outcome was the change in walking speed (feet/second) on the Timed 25- Foot Walk (T25FW) test at Visit 3, measured at the time of peak plasma drug concentration, versus baseline.

[00244] Improvements in the primary outcome for the 5 mg dose (0.423 ft/sec, p=0.457) and the 10 mg dose (0.478 ft/sec, p=0.107) at Visit 3 were not statistically significant compared to placebo (0.363 ft/sec). The AMPYRA® (dalfampridine) Extended Release Tablets, 10 mg registration studies used a consistent response analysis to allow for the variability in MS-related symptoms, including walking ability. The design of the current study required a single endpoint analysis that had not been used previously in the AMPYRA® development program. In a post-hoc analysis, T25FW data were analyzed with methods similar to those used in the pivotal studies, combining all measures prior to treatment as the baseline and all measures on treatment as the on-drug value. The average change from baseline in walking speed was significantly greater for the 10 mg group compared to placebo (0.443 vs. 0.303 ft/sec, p=0.014) but not for the 5 mg group (0.366 vs. 0.303 ft/sec, p=0.292).

[00245] In addition, using a responder definition of average improvement in walking speed of at least 20% from baseline, similar to an analysis presented in the AMPYRA® prescribing information, the 10 mg group showed significantly more responders
than the placebo group (44% vs. 27%, p=0.004). The 5 mg group did not show a significant increase in response over placebo (32% vs. 27%, p=0.366).

A planned secondary outcome measure of improvement in walking, the 6-Minute Walk Test, was applied at Visit 2 in a subset of the study participants (approximately 50 randomized per treatment arm). The 10 mg dose, but not the 5 mg dose, showed a significant improvement compared to placebo (10 mg +129 ft vs. placebo +42 ft, p=0.014; 5 mg +77 ft vs. placebo +42 ft, p=0.308).

Changes in perceived effect of MS on walking-related activities, as measured by the self reported 12-Item MS Walking Scale (MSWS-12), showed improvements for the 10 mg and 5 mg groups that were not significant compared to placebo (10 mg -11.1, p=0.286; 5 mg -9.7, p=0.866; placebo -8.4). A negative change represents reduced perceived disability.

The current study, together with the AMPYRA® registration studies, continue to show that 10 mg twice daily is the appropriate, safe and effective dose. The 5 mg twice daily dose of dalfampridine-ER failed to show efficacy over placebo on the primary or secondary measures. The 10 mg twice daily dose, which has consistently shown efficacy in our well-controlled clinical trials, did not meet the previously untested primary outcome measure selected for this study. We believe that this was due to increased patient variability, related to the study design. However, the 10 mg dose showed significant improvements in the 6-Minute Walk and in responder analyses of the Timed 25-Foot Walk.

No new safety signals were observed in this study. No seizures were reported. Two participants experienced serious adverse events in each of the 5 mg and the 10 mg treatment groups, including loss of consciousness in one patient in the 10 mg group who had discontinued dalfampridine-ER four days prior to the event. Adverse events that occurred in the combined dalfampridine-ER group at a rate of at least 2% greater than the placebo group included: urinary tract infection (8.0%> vs. 5.6%> placebo), nausea (7.7% vs. 3.5% placebo), dizziness (7.7% vs. 2.1% placebo), insomnia (6.3% vs. 4.2% placebo) and upper respiratory tract infection (2.8% vs. 0.7% placebo). Overall, adverse events were consistent with the U.S. Food and Drug Administration (FDA)-approved product labeling.

6.1.14.2. DETAILED DESCRIPTION OF RESULTS
6.1.14.2.1 STUDY OVERVIEW

Figure 2 presents an agenda/outline of the figures discussed hereinbelow. See Figure 3 for a summary of the study overview. This study was a post-marketing commitment requested by the FDA at the time that AMPYRA® was approved. The goal of the study was to determine whether a 5 mg dose twice daily of dalfampridine-ER was effective in improving walking in people with MS. The 5 mg dose failed to show efficacy over placebo on the primary outcome measure or in any of the secondary outcome measures in this study. The study's primary outcome measure was the change in walking speed on the Timed 25-Foot Walk test at the end of week 4 versus baseline, measured at the time of peak plasma drug concentration. The Primary Outcome measure in this study had not previously been used in any of Acorda Therapeutics’ Phase 2 or Phase 3 clinical trials. Neither the 10 mg nor the 5 mg dose achieved statistical significance on this outcome. However, the 10 mg dose showed significant improvement on a responder analysis of walking speed, whereas the 5 mg did not. This responder analysis is consistent with an analysis that was used in AMPYRA®’s Phase 3 registration studies and which is also represented in AMPYRA®’s prescribing information. In addition, when the average walking speed on all on-drug visits was compared to the average of both pre-treatment visits, 10 mg showed a significant improvement, whereas 5 mg did not. The 10 mg dose showed a significant improvement on the 6 Minute Walk Test, which marks the first time that AMPYRA®’s effects had been evaluated with this endpoint. With regard to safety, no seizures were reported and the safety data overall were consistent with AMPYRA®’s prescribing information. In summary, the totality of the evidence in this study continues to indicate that the 10 mg twice daily is the appropriate, safe and effective dose, as was demonstrated in the Phase 3 registration studies. This study also showed that the 5 mg dose did not demonstrate efficacy over placebo on either the primary or secondary outcome measures.

6.1.14.2.2 STUDY DESIGN AND BASELINE DEMOGRAPHICS

Figure 5 shows a summary of the study design. A multicenter, randomized, double blind, placebo-controlled, parallel group, 4 week in duration study in patients with MS was conducted to assess whether a lower dose of dalfampridine-ER, 5 mg, is efficacious...
for treating of MS-related walking impairment. The study was carried out in 64 centers, all located in the United States (U.S.). Participants were screened for eligibility based on key inclusion criteria, which were: diagnosis of Multiple Sclerosis, ages between of 18 and 70 years old who had MS related walking impairment as determined by the investigator through the patient's history and/or clinical assessment. At Baseline, Visit 1, participants were randomized to one of three treatment groups: dalfampridine-ER 5 mg twice daily, 10 mg twice daily, or matching placebo. The randomization was carried out in a 1:1:1 ratio.

Figure 6 shows an abbreviated schedule focusing on key study events at the various Visits. The top row of the table in Figure 6 shows the visit schedule. Visit 2 occurred at day 15th (2 weeks), and Visit 3 at day 29th (4 weeks) of the study. Patients with a successful screening, were randomized at Visit 1 into one of the treatment groups, and had each of the assessments shown in the grids at subsequent Visits 2 and 3. At Visit 3, in order to measure walking speed at the time of highest and lowest plasma concentrations, the participants were brought to the clinic approximately 12 hours after their last dose, given the Timed 25 Foot Walk (T25FW) test, dosed with study medication, and then required to wait 3-4 hours for another Timed 25-Foot Walk test. The 6 Minute Walk Test (6MWT) was only done at baseline and Visit 2. The purpose of the 6MWT is to assess how far a patient can walk within six minutes. The Multiple Sclerosis Walking Scale (MSWS-12), which is a 12 item patient questionnaire used to assess the impact of MS on various aspects of walking ability, was done at Baseline and the two on-drug Visits, 2 and 3. Blood samples were collected at all 3 visits for determination of dalfampridine concentrations.

The Planned Analysis for the Study is shown in Figure 7. The Primary Efficacy Variable was the change from baseline in walking speed using T25FW at 3 to 4 hours after dosing with dalfampridine-ER at Visit 3, which is estimated to be the time of peak plasma concentration at steady state. A Key Secondary variable was the change from baseline in the walking speed using T25FW approximately 12 hours after the last dalfampridine-ER dose prior to Visit 3, which is estimated to be the time of lowest plasma concentration at steady state. Other secondary variables in the study included the change from baseline in the MSWS-12 at Visits 2 and 3, the T25FW at Visit 2, and the 6 MWT at Visit 2.

The baseline demographics for this study are summarized in Figure 8. In
this study a total of 430 patients was randomized across all three groups fairly equally: 143 into the Placebo group, 144 into the dalfampridine-ER 5 mg group and 144 into the 10 mg group. The gender distribution of this study mirrors the gender distribution of Multiple Sclerosis, with 70% of the participants being women. The average age of the study participants was approximately 54 years. The average walking speed as determined by the Baseline Visit T25FW was 2.75 feet per second; and the average distance walked on the 6-MWT was 850 feet. The average score in the MSWS-12 was 62.3, where zero is the best score and 100 being the worse.

[00255] The baseline demographics and physical characteristics of the patients who completed the Six-Minute Walk Test are presented by treatment group in Table 9.

Table 9: Baseline Demographics and Physical Characteristics for Patients who Completed the Six Minute Walk Test (FAP)
### Full Analysis Population (FAP): All FAP subjects who completed the six-minute walk test at Visit 2.

**Abbreviations:** SD = Standard Deviation, SE = Standard Error

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=49</th>
<th>5 mg N=53</th>
<th>10 mg N=51</th>
<th>Total N=153</th>
<th>Treatment P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.147</td>
</tr>
<tr>
<td>Male</td>
<td>12 (24.5)</td>
<td>8 (15.1)</td>
<td>16 (31.4)</td>
<td>36 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>37 (75.5)</td>
<td>45 (84.9)</td>
<td>35 (68.6)</td>
<td>117 (76.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Age – (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.510</td>
</tr>
<tr>
<td>n</td>
<td>49</td>
<td>53</td>
<td>51</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>53.8 (1.27)</td>
<td>52.0 (1.32)</td>
<td>53.9 (1.30)</td>
<td>53.2 (0.75)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8.89</td>
<td>9.62</td>
<td>9.28</td>
<td>9.26</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56.0</td>
<td>53.0</td>
<td>56.0</td>
<td>55.0</td>
<td></td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(33, 69)</td>
<td>(32, 70)</td>
<td>(35, 70)</td>
<td>(32, 70)</td>
<td></td>
</tr>
<tr>
<td><strong>Age Group – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.589</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>44 (89.8)</td>
<td>49 (92.5)</td>
<td>44 (86.3)</td>
<td>137 (89.5)</td>
<td></td>
</tr>
<tr>
<td>≥65 years</td>
<td>5 (10.2)</td>
<td>4 (7.5)</td>
<td>7 (13.7)</td>
<td>16 (10.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Race – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>Black or African American</td>
<td>9 (18.4)</td>
<td>15 (28.3)</td>
<td>5 (9.8)</td>
<td>29 (19.0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (3.9)</td>
<td>2 (1.3)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40 (81.6)</td>
<td>38 (71.7)</td>
<td>44 (86.3)</td>
<td>122 (79.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.181</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>4 (8.2)</td>
<td>1 (1.9)</td>
<td>1 (2.0)</td>
<td>6 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>45 (91.8)</td>
<td>52 (98.1)</td>
<td>50 (98.0)</td>
<td>147 (96.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.287</td>
</tr>
<tr>
<td>n</td>
<td>49</td>
<td>53</td>
<td>51</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>166.96</td>
<td>166.64</td>
<td>169.46</td>
<td>167.68</td>
<td></td>
</tr>
<tr>
<td>(1.467)</td>
<td>(1.088)</td>
<td>(1.553)</td>
<td>(0.796)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>10.271</td>
<td>7.922</td>
<td>11.094</td>
<td>9.842</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>165.10</td>
<td>167.60</td>
<td>168.10</td>
<td>167.60</td>
<td></td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(152.0, 208.3)</td>
<td>(149.9, 182.9)</td>
<td>(137.2, 190.5)</td>
<td>(137.2, 208.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.154</td>
</tr>
<tr>
<td>n</td>
<td>49</td>
<td>53</td>
<td>51</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>77.98 (3.012)</td>
<td>76.95 (2.749)</td>
<td>84.44 (3.102)</td>
<td>79.78 (1.715)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>74.50</td>
<td>76.40</td>
<td>79.00</td>
<td>76.70</td>
<td></td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(47.2, 136.2)</td>
<td>(44.6, 142.7)</td>
<td>(50.8, 137.1)</td>
<td>(44.6, 142.7)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.398</td>
</tr>
<tr>
<td>n</td>
<td>49</td>
<td>53</td>
<td>51</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>27.81 (0.929)</td>
<td>27.59 (0.889)</td>
<td>29.17 (0.862)</td>
<td>28.19 (0.516)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>6.505</td>
<td>6.475</td>
<td>6.159</td>
<td>6.378</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>27.00</td>
<td>26.70</td>
<td>28.20</td>
<td>27.10</td>
<td></td>
</tr>
<tr>
<td>(Min, Max)</td>
<td>(17.9, 55.8)</td>
<td>(17.1, 46.4)</td>
<td>(20.3, 49.0)</td>
<td>(17.1, 55.8)</td>
<td></td>
</tr>
</tbody>
</table>
6.1.14.2.3 STUDY RESULTS

[00256] See Figures 9 to 14 for the Study Results. The primary endpoint for this trial was the change in walking speed from baseline, measured with the Timed 25 Foot Walk at the end of the 4 week treatment period and at 3-4 hours post dose to characterize the time of peak plasma concentration. The mean changes for the three treatment groups are shown in Figure 10, the placebo group increasing by 0.36 feet per second, the 5 mg group by 0.42 and the 10 mg group by 0.48. Neither of the planned comparisons between 5 mg and placebo and 10 mg and placebo was statistically significant, with p values of 0.457 and 0.107 respectively (see Figure 10). Nonetheless, the numerical difference between the 10 mg and placebo means is in a range consistent with the previous Phase 3 studies. The absolute values for change are somewhat higher than expected, and this is consistent with an enhanced placebo response that is often seen when testing drugs that are already approved. The lack of statistical significance for the differences was based on a markedly higher variability of the timed walk speeds for all groups at the 4 week visit than Acorda Therapeutics has seen before. This may be due to the prolonged and complex nature of that visit, where patients were required to wait for 3-4 hours for a second evaluation. This is unlike previous studies, where patients generally came for a single evaluation and this extra burden may have introduced significant additional variability.

[00257] An analysis more equivalent to the approach in previous studies, looking not at the difference between two single time points but at the totality of the timed walk data, was performed and results obtained are summarized in Figure 11. Taking the average of the two pre-treatment measurements of walking speed and the average of the three on-treatment assessments, the average change in walking speed was calculated, as shown in Figure 11. These average changes are not markedly different from the primary endpoint values, but now the difference between 10 mg and placebo has a p-value of 0.014, and the difference between 5 mg and placebo has a p-value of 0.292 (see Figure 11). This much lower p-value for the 10 mg comparison is a reflection of the fact that averaging across the multiple assessments, as was done in previous studies of Acorda Therapeutics, helps to reduce the effect of background variability on the statistical comparison of the group data.

[00258] The prior Phase 3 studies used a response analysis as part of the primary
endpoint, based on consistency of improvement in average walking speed. This trial had too few visits to apply a similar analysis, but the alternative response analysis that was also used before and which appears as part of the prescribing information or drug label was performed. The number of patients in each group who experienced a 20% or greater improvement in walking speed with treatment was assessed. The histogram shown in Figure 12 shows that there was a significantly greater response rate of 44% on this criterion for the 10 mg group compared to either placebo at 27% or 5 mg at 32%. Again, the difference in rate between 10 mg and placebo was in the range that would be expected from previous studies, though the response rates for all groups were higher than would have been expected, indicating a stronger placebo response overall in this study.

[00259] The 6-Minute Walk test was included in this study for a subset of randomized patients (see Figure 13). The 6-Minute Walk test is another objective measure of walking that involves measuring the distance that can be walked as fast as possible in a 6 minute period. This measure was included in Visit 2 to avoid even more patient burden in Visit 3. As shown in Figure 13, the 6 Minute Walk distance increased by 129 feet in the 10 mg group compared to 42 feet in the placebo group, with a p value of 0.014, whereas the 5 mg group increased walking distance by only 77 feet, with a p-value of 0.308 compared to placebo.

[00260] Another planned analysis of a secondary endpoint was the patient self-assessment tool, the 12-Item MS Walking scale, which was also used in AMPYRA®’s Phase 3 studies to show the clinical meaningfulness of the increase in walking speed. As shown in Figure 14, the 10 mg group showed the greatest improvement in self-assessed impact of MS on various walking-related activities, with a reduction in score of 11.1 points, compared to 8.4 points for placebo and 9.7 points for the 5 mg group. However, the p-values for these comparisons of 10 mg and 5 mg against placebo were 0.286 and 0.866 respectively, based on the high variability in this subjective measure (see Figure 14). The difference in average change between 10 mg and placebo groups is consistent with prior Phase 3 data, though there is once again both a higher placebo response reflected in the magnitude of change for all three groups and a greater variability of responses that adversely affects the statistical analysis.
6.1.14.2.4 SAFETY

[00261] As summarized in Figure 16, no new safety signals were observed in this study and no seizures were reported. Two participants experienced serious adverse events in each of the 5 mg and the 10 mg treatment groups, including loss of consciousness in one patient in the 10 mg group who had discontinued dalfampridine-ER four days prior to the event. Adverse events that occurred in the combined dalfampridine-ER group at a rate of at least 2% greater than the placebo group included: urinary tract infection, nausea, dizziness, insomnia and upper respiratory tract infection. The percentages are presented in Figure 16. Overall, adverse events were consistent with the FDA-approved product labeling.

6.1.14.2.5 STUDY CONCLUSIONS

[00262] See Figure 17 for a summary of the study conclusions. In summary, this study was a post-marketing commitment requested by the FDA at the time that AMPYRA® was approved. The goal of the study was to determine whether a 5 mg dose twice daily of dalfampridine-ER was effective in improving walking in people with MS. The 5 mg dose failed to show efficacy over placebo on the primary outcome measure or in any of the secondary outcome measures in this study. Although the previously untested primary outcome measure in this study was not met by the 10 mg twice daily dose, the totality of the evidence in this study continues to indicate that the 10 mg twice daily is the appropriate, safe and effective dose, as was demonstrated in the Phase 3 registration studies. This study is the first time that data on AMPYRA®’s effects have been assessed on the 6-Minute Walk Test.

Incorporation by reference

[00263] Various references such as patents, patent applications, and publications are cited herein, the disclosures of which are hereby incorporated by reference herein in their entireties.
WHAT IS CLAIMED IS:

1. A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has relapsing remitting multiple sclerosis.

2. A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has secondary progressive multiple sclerosis.

3. A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has primary progressive multiple sclerosis.

4. A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of an 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has progressive relapsing multiple sclerosis.

5. A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is Caucasian.

6. A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is African-American.
A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is Hispanic.

A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient is Asian.

A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein the patient has a body weight in the range of 40 kg to 150 kg.

The method of claim 9, wherein the patient has a body weight in the range of 40 kg to 110 kg.

The method of claim 9 or 10, wherein the patient has a body weight in the range of 40 kg to 80 kg.

The method of claim 9 or 10, wherein the patient has a body weight in the range of 50 kg to 90 kg.

The method of claim 9 or 10, wherein the patient has a body weight in the range of 60 kg to 100 kg.

The method of claim 9, wherein the patient has a body weight in the range of 70 kg to 120 kg.
15. A method for improving walking capacity in a patient with multiple sclerosis in need thereof, said method comprising orally administering to the patient 10 mg of 4-aminopyridine twice daily, wherein the 4-aminopyridine is in a sustained release composition, and wherein said administering step is performed over a period of time that is greater than 4 weeks.

16. The method of claim 15, wherein said administering step is performed over a period of time that is greater than 5 weeks.

17. The method of claim 15 or 16, wherein said administering step is performed over a period of time that is greater than 6 weeks.

18. The method of any one of claims 15 to 17, wherein said administering step is performed over a period of time that is greater than 2 months.

19. The method of any one of claims 15 to 18, wherein said administering step is performed over a period of time that is greater than 6 months.

20. The method of any one of claims 15 to 19, wherein said administering step is performed over a period of time that is greater than 1 year.

21. The method of any one of the preceding claims wherein the sustained release composition is in the form of a tablet or capsule.

22. The method of any one of the preceding claims, wherein the patient has a creatinine clearance rate of greater than 50 mL/min.

23. The method of any one of the preceding claims, further comprising measuring walking capacity of the patient by the 6 Minute Walk Test.
24. The method of claim 23, wherein the measuring of walking capacity by the 6 Minute Walk Test is prior to treatment with said 4-aminopyridine.

25. The method of claim 23, wherein the measuring of walking capacity by the 6 Minute Walk Test is during a treatment period with said 4-aminopyridine.

26. The method of claim 23, wherein the measuring of walking capacity by the 6 Minute Walk Test is after a treatment period with said 4-aminopyridine.

27. The method of claim 24, further comprising measuring walking capacity of the patient by the 6 Minute Walk Test during a treatment period with said 4-aminopyridine.

28. The method of any one of the preceding claims, wherein the patient exhibits an at least 20% improvement in walking speed as measured by the Timed 25 Foot Walk test relative to walking speed of the patient prior to treatment with said 4-aminopyridine.
Chemical name: 4-aminopyridine
USAN: dalfampridine
CAS registry number: 504-24-5
Chemical Structure:

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{N} \\
\text{NH}_2
\end{array}
\]

Molecular Formula: C₅H₆N₂
Relative molecular mass: 94.1
Appearance: White solid
Solubility: aqueous solubility ≥ 50mg/mL
Melting point: 157 to 162 °C
Study Overview
Design and Baseline Demographics
Analysis of Primary Endpoint
Analysis of Secondary Endpoints
Safety
Q&A
Study Overview

- Post-marketing commitment required by FDA
- 5 mg failed to show efficacy in primary or secondary endpoints
- 5 mg and 10 mg not statistically significant on primary outcome measure
- 10 mg showed significant effects using analysis methods consistent with registration studies and prescribing information
- 10 mg showed significant effect on 6-Minute Walk
- No new safety signal observed
- Study report to be provided to FDA

ACORDA®
Changing Tomorrows

Figure 3
Study Design and Baseline Demographics

Figure 4
Study Design

- A multi-center, randomized, double-blind, placebo-controlled, parallel group, 4-week study in patients with MS
- Participants were screened for eligibility and 1 week later returned for Baseline Visit 1
- Participants were randomized to one of three treatment groups: dalfampridine-ER 5 mg twice daily, 10 mg twice daily, or matching placebo, in a ratio of 1:1:1
<table>
<thead>
<tr>
<th>Visit</th>
<th>Baseline</th>
<th>Randomization</th>
<th>On-Drug visit</th>
<th>T25FW</th>
<th>MSWS-12</th>
<th>6-MWT</th>
<th>PK samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X A, B</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visit 2</td>
<td>2 Weeks</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Visit 3</td>
<td>4 weeks</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Abbreviations:
- A = Peak time
- B = Troueh time
- T25FW = Timed 25 Foot Walk
- MSWS-12 = 12 Minute Walk Test
- 6-MWT = 6 Minute Walk Test
- PK = Pharmacokinetic
DER-401 Planned Analyses

- Primary Efficacy Variable
  - Change from Baseline in Walking Speed using T25FW 3 to 4 hours after the last dose of dalfampridine-ER at Visit 3 (Week 4)

- Secondary Variables
  - Change from Baseline in:
    - Walking Speed using T25FW approximately 12 hours after dalfampridine-ER dose at Visit 3 (Week 4)
    - MSWS-12 at Visit 3 (Week 4)
    - MSWS-12 at Visit 2 (Week 2)
    - T25FW at Visit 2 (Week 2)
    - 6-Minute Walk Test at Visit 2 (Week 2)
Baseline Demographics

- 430 participants randomized
  - Placebo group = 143
  - DER 5 mg group = 144
  - DER 10 mg group = 143
- Gender distribution = 70% women & 30% men
- Average age = 53.6 yrs
- Average walking speed = 2.75 ft/sec
- Average MSWS-12 score = 62.3
- Average 6-MWT distance = 850 ft
Study Results
# Primary Endpoint - T25FW

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=136</th>
<th>DER 5mg N=143</th>
<th>DER 10 mg N=136</th>
<th>DER 5 mg vs PBO</th>
<th>DER 10 mg vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from Baseline in Walking Speed at T max at Visit 3 (ft/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.36</td>
<td>0.42</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.457</td>
<td>0.107</td>
</tr>
</tbody>
</table>

*Figure 10*
## Figure 11

### Average Change in T25FW

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average Change in Walking Speed Between Pre-Treatment and On-Treatment Periods (ft/sec)</th>
<th>Mean</th>
<th>P-value</th>
<th>Post hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo N=136</td>
<td>0.30</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>DER 5 mg N=143</td>
<td>0.37</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>DER 10 mg N=136</td>
<td>0.44</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>DER 10 mg vs PBO</td>
<td>0.014</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>DER 5 mg vs PBO</td>
<td>0.292</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Percent of participants who had an average $\geq 20\%$ improvement in walking speed

![Bar chart showing percentage of participants for placebo, 5 mg, and 10 mg treatment groups.](chart.png)

- Placebo: 25\%
- 5 mg: 40\%
- 10 mg: 50\%

Significance levels:
- $P = 0.004$
- $P = 0.040$
- $P = 0.366$

Figure 12
## 6-Minute Walk Test

### Average Change from Baseline in Six-Minute Walk Distance at Visit 2 (ft)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=49)</th>
<th>DER 5mg (N=53)</th>
<th>DER 10mg vs PBO (N=51)</th>
<th>DER 5mg vs PBO (N=53)</th>
<th>Mean</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpopulation of participants who performed 6-MWT at Visit 2 planned analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Mean values and p-values are provided for comparison between different treatment groups.
# Multiple Sclerosis Walking Scale-12

## Change from Baseline in MSWS-12 at Visit 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=136</th>
<th>DER 5mg N=143</th>
<th>DER 10 mg N=136</th>
<th>DER 5 mg vs PBO</th>
<th>DER 10 mg vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-8.4</td>
<td>-9.7</td>
<td>-11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>0.866</td>
<td>0.286</td>
</tr>
</tbody>
</table>

A negative change in score represents an improvement in function
Adverse Events

- No new safety signals
- Two participants experienced Serious AEs in both the dalfampridine-ER 5 mg & 10 mg groups
- No seizures observed

<table>
<thead>
<tr>
<th>Combined Dalfampridine Group Adverse Events ≥ 2% More Frequent than Placebo Group</th>
<th>Placebo N=143</th>
<th>Total Dalfampridine N=286</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>8 (5.6)</td>
<td>23 (8.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (3.5)</td>
<td>22 (7.7)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (2.1)</td>
<td>22 (7.7)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (4.2)</td>
<td>18 (6.3)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>1 (0.7)</td>
<td>8 (2.8)</td>
</tr>
</tbody>
</table>
Study Conclusions

- Post Marketing Commitment required by FDA
- 5mg failed to show efficacy in primary or secondary endpoints
- 10mg evaluated using previously untested endpoint
- 10mg showed significant effects using analysis methods consistent with registration studies and prescribing information
- No new safety signal observed
- Full data set to be presented in peer-review setting
- Study report to be provided to FDA
INTERNATIONAL SEARCH REPORT

According to International Patent Classification (IPC) or to both national classification and IPC

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4409 A61K9/20 A61P25/28

ADD.

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

Further special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"C" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"D" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"X" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"O" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"S" document member of the same patent family

Date of the actual completion of the international search

25 November 2013

Date of mailing of the international search report

04/12/2013

Name and mailing address of the ISA/Authorized officer

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Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Gradassi, Giulia
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
## INTERNATIONAL SEARCH REPORT

### International application No

PCT/US2013/054541

### Information on patent family members

**Patent document cited in search report** | **Publication date** | **Patent family member(s)** | **Publication date**  
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