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(54) Title: SAFINAMIDE IN THE TREATMENT OF DYSKINESIA

(57) Abstract: The present invention relates to the treatment and prophylaxis of dyskinesias, preferably dyskinesias associated with dopaminergic therapy.

Safinamide in the treatment of dyskinesia

Field of the Invention

The invention relates to the treatment and prophylaxis of dyskinesias, preferably dyskinesias associated with dopaminergic therapy.

Background of the Invention

Dyskinesias are characterized by the development in a subject of abnormal involuntary movements and may manifest as chorea (irregular, involuntary movements of the body, especially the face and extremities) or dystonia (disorder or lack of muscle tonicity). "dyskinesia" describes the occurrence of these abnormal involuntary movements in a subject. Such movements include ballistic movements and athetoid movements of the trunk, limbs and facial musculature.

One way in which dyskinesias may arise is as a side effect of dopamine replacement therapy for Parkinsonism or other basal ganglia-related movement disorders. Parkinsonism is a syndrome of symptoms characterised by slowness of movement (bradykinesia), rigidity and/or tremor. Parkinsonian symptoms are seen in a variety of conditions, most commonly in idiopathic parkinsonism (i.e. Parkinson's Disease) but also following treatment of schizophrenia, manganese poisoning, head injury and the like.

The use of dopamine-replacing agents, such as L-dopa and apomorphine, as symptomatic treatments for conditions such as Parkinson's disease has increased the quality of life of patients suffering from the conditions. However, dopamine-replacement therapy has limitations, especially following long-term treatment. Problems can include a wearing-off of the anti-parkinsonian efficacy of the treatment and in particular the appearance of a range of side effects or secondary effects. These effects may manifest as dyskinesias such as chorea and dystonia. Dyskinesia can be seen either when the patient is undergoing dopamine-replacement therapy (in the case of chorea and/or dystonia) or even when off therapy (when dystonia is prevalent). Ultimately, these effects severely limit the usefulness of dopaminergic treatments.

Many attempts have been made to develop agents that will prevent the development of, and/or treat, dyskinesias. For instance, attempts have been made to develop novel dopamine replacement therapies that will obviate or mitigate dyskinetic effects although such attempts have met with limited success. In other instances, combination treatments have been favoured.

Safinamide, 2(S)-(+)-2-[4-(3-Fluorobenzyloxy)benzylamino]propionamide, is an alpha-aminoamide derivative that is preferably orally formulated and used in form of its methanesulfonate (1:1 salt, molecular weight 398.4527), is currently being developed as an add-on treatment, preferably with dopaminergic therapy, such as L-dopa, for patients with Parkinson's disease. Also, an effect of safinamide on diskinesia has been described e.g. by Stocchi in Neurology 2006; 67(Suppl 2):S24-S29.

Safinamide is believed to have a novel dual mechanism of action based on the enhancement of the dopaminergic function (through reversible inhibition of monoamine oxidase-B and dopamine uptake) and reduction of glutamatergic activity by inhibiting glutamate release (Drugs of the Future 2001, 26(8): 745 – 749, Expert Opin. Investig. Drugs, 2008, 17(7), 1115-1125).

WO2004089353 disclose the use of safinamide or its derivatives in the tretment of PD in various combinations with other agents, such as L-dopa/PDI. Safinamide or a derative thereof is generally described to be used in the treatment of PD in dosages of up to 700 mg per day, including 300 mg per day. Patients that have been treated according to the example of WO2004089353 were early stage parkinson's disease patients, not having been treated with L-dopa or having only recently been treated with L-dopa. These patients received significantly lower dosages (0.5 mg/kg and 1.0 mg/kg per day) than the broadly stated 700 mg or 300 mg in combination with a dopamine agonist. No effect has been reported in this prior art document as to diskinesia, as this symptom is typical only for late stage patients having been treated long term with L-dopa.

Early phase II dose-finding clinical studies showed that safinamide was safe and effective in the treatment of PD, without increasing dyskinesia (Stocchi, F., Arnold, G., Onofrj, M. et al. Improvement of motor function in early Parkinson disease by safinamide. Neurology 2004, 63(4): 746-8). A worldwide, double-

blind, placebo-controlled phase III study in patients with early-stage disease was conducted to assess the safety and efficacy of safinamide as adjunctive therapy to a dopamine agonist with the goal of delaying the need for addition of levodopa (Stocchi, F., Borgohain, R., Onofrj, M. et al. Safinamide a new anti-parkinson agent is effective and well-tolerated in early PD patients on a stable dose of a single DA-agonist: Results of a randomized, international, placebo-controlled, phase III trial. Neurology 2007, 68(Suppl. 1): Abst 20.001). This comparative dose study was conducted in 270 patients receiving a single dopamine agonist plus placebo, 50–100 mg/day safinamide or 150–200 mg/day safinamide. After 6 months, statistically significant benefits with safinamide at doses of 50 and 100 mg/day were observed on motor symptoms (UPDRS III, –6.0 ± 7.2 vs. 3.6 ± 7.1), ADLs (UPDRS II, –2.2 ± 3.8 vs. –1.2 ± 3.5), quality of life and Clinical Global Impression (CGI) of severity. At the higher daily dose of 150–200 mg/day, no incremental benefits were observed over the lower dose. The mean change from baseline in the UPDRS III was –4.7 in the 50–100 mg/day safinamide group compared to –1.95 in the placebo group (p = 0.019). The higher dosing range, however, did not yield any statistically significant benefit over dopamine agonist monotherapy.

Safinamide has also been used in healthy subjects in dosages up to 10 mg/kg per day, (Pharmacological Research 50, 2004, 77–85) and in epilepsy patients in dosages up to 300 mg per day (Epilepsy Research 61, 2004, 1–48).

A significant reduction of dyskinesia was observed at 100 mg and 150 mg safinamide per day, when added to a stable dose of L-dopa (Stocchi, Neurology 2006; 67(Suppl 2):S24-S29). However, it is also reported in the same document, that there is no further improvement achieved at a higher dosage, i.e. 200 mg per day.

Therefore, it appears that safinamide is useful in the treatment of dyskinesias in parkinson's disease. However due to the reported limitation of its effects, particularly in dosages higher than 150 mg per day, there is still a need to develop ways by which dyskinesias may be treated more effectively.

Summary of the invention

Contrary to what is taught by the prior art, it has now been found that safinamide when given to a human patient in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate, is particularly effective and useful for the treatment of dyskinesias. Specifically, it is found that a higher dosage higher than 200 mg per day leads to improved treatment results. Dyskinesias (e. g. chorea and dystonia) are at least reduced, when safinamide is given in these high dosages to PD patients on dopamine-replacement therapy, particularly to late-stage PD patients, having been treated with L-dopa.

Detailed Description of the Invention

The present invention which is based on the finding that the use of safinamide in human patients in dosages higher than 200 mg per day may be used to treat many types of dyskinesia. For instance safinamide may be used according to the invention to treat dyskinesia associated with Huntington's disease, idiopathic torsion dystonia, tardive dyskinesia or off-dystonia in Parkinson's disease and most particularly for dyskinesia associated with parkinsonism, e. g. idiopathic Parkinson's disease, post-encephalitic parkinsonism or parkinsonism resulting from head injury.

Throughout the specification parkinsonism, PD, parkinson and parkinson's disease are used interchangeably.

Preferably, the term "dosages higher than 200 mg per day" is defined as "dosages equal to or higher than about 240 mg per day, more preferably equal to or higher than about 270 mg per day, equal to or higher than about 290 mg per day, equal to or higher than about 300 mg per day, equal to or higher than about 330 mg per day, equal to or higher than about 370 mg per day, equal to or higher than about 400 mg per day. The term "dosages higher than 200 mg per day" includes dosages between about 240 mg per day and about 1000 mg per day, preferably dosages between about 270 mg per day and about 700 mg per day,

more preferably dosages between about 290 mg per day and about 400 mg per day. Even more preferably, the term "dosages higher than 200 mg per day" is to mean about 240 mg per day, about 250 mg per day, about 260 mg per day, about 270 mg per day, about 280 mg per day, about 290 mg per day, about 300 mg per day, about 310 mg per day, about 320 mg per day, about 330 mg per day, about 340 mg per day, about 350 mg per day, about 360 mg per day or about 370 mg per day.

Most preferably, the term "dosages higher than 200 mg per day" is defined as "a dosage of about 300 mg per day".

The present invention also relates to the treatment of dyskinesias which manifest as hyperkinetic activity (e. g. Tourette's syndrome).

The present invention also relates to the treatment of dyskinesias which arise as a side or secondary effect of other therapeutic agents. For instance, the present invention relates to the treatment of dyskinesia associated with ropinirole, pramipexole, cabergoline, bromcriptine, lisuride, pergolide, L-DOPA or apomorphine treatment. Safinamide is preferably used according to the invention for the treatment of dyskinesia associated with L- DOPA or apomorphine treatment.

L-dopa (Levodopa ((-)-L-alpha-amino-beta- (3, 4-dihydroxybenzene) propanoic acid) increases dopamine concentration in the stratum, especially when its peripheral metabolism is inhibited by a peripheral decarboxylase inhibitor (PDI). L-dopa/PDI (i.e. the combination of L-dopa and PDI) therapy is widely used for symptomatic therapy for Parkinson's disease, such as combinations with L-dopa, with carbidopa ((-)-L-alpha-hydrazino-alpha-methyl-beta- (3, 4-dihydroxybenzene) propanoic acid monohydrate), such as SINEMET ; L-dopa and controlled release carbidopa (SINEMET-CR (g)), L-dopa and benserazide (MADOPAR (g), Prolopa), L-dopa plus controlled release benserazide (2-Amino-3-hydroxy-propionic acid N'- (2, 3,4-trihydroxy- benzyl)-hydrazide), MADOPAR-HBS.

The present invention particularly relates to the treatment of dyskinesia caused by agents used to treat PD. In this respect a preferred embodiment is the

treatment of dyskinetic side-effects or secondary effects associated with L-DOPA or apomorphine therapy for parkinsonism.

Safinamide may be used according to the present invention to treat dyskinesia as a monotherapy (i. e. use of the compound alone); as an adjunct to medicaments e.g. to prevent dyskinetic effects caused by the medicament. The medicaments are e. g. L-dopa or apomorphine or dopamine agonists given to treat parkinsonian patients or alternatively safinamide may be given in combination with other compounds or treatments which also reduce dyskinesia, e. g. p-opioid receptor antagonists, a2-adrenoreceptor-antagonists, cannabinoid CB 1-antagonists, NMDA receptor-antagonists, Biperiden, Orphenadrine, Diphenhydramine, Procyclidine, Trihexyphenidyl, Benztropine.

In one embodiment, the method and combination therapies according to the invention include one or more of levodopa/PDIs, dopamine agonists, amantidine and catechol-O-methyltransferase (COMT) inhibitors.

In a preferred embodiment, safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, may be combinded with levodopa/PDI and may also include additional Parkinson's Disease agents such as COMT inhibitors, amantidine and/or dopamine agonists. One combination which can be used in the pharmaceutical compositions, methods and combination therapies of the invention includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, and levodopa/PDI. Another combination which can be used in the pharmaceutical compositions, methods and combination therapies of the invention includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, , levodopa/PDI, and a COMT inhibitor. Another combination which can be used in the pharmaceutical compositions, methods and combination therapies of the invention includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, , levodopa/PDI, and a dopamine agonist. Another combination which can be used in the pharmaceutical compositions, methods and combination therapies of the invention includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, levodopa/PDI, a COMT inhibitor, and a dopamine agonist.

In one aspect, a combination therapy for PD includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, and a dopamine agonist. In one embodiment, a combination therapy for PD includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, and one or more of bromocriptine, cabergoline, lisuride, pergolide, ropinirole, apomorphine, sumanirole, rotigotine, talipexole, dihydroergocriptine, and pramipexole, for treating a patient in need of PD treatment.

In another aspect, a combination therapy for PD includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, and levodopa/PDI. In one embodiment a combination therapy for PD includes safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, and one or more of levodopa/PDIs such as levodopa plus carbidopa (SINEMET) levodopa plus controlled release carbidopa (SINEMET-CR (g)), levodopa plus benserazide (MADOPAR, levodopa plus controlled release benserazide (MADOPAR-HBS) for treating a patient in need of PD treatment.

COMT (catechol-O-methyltransferase) inhibitors enhance L-dopa treatment as they inhibit L-dopa's metabolism, enhancing its bioavailability and thereby making more of the drug available in the synaptic cleft for a longer period of time. Examples of COMT inhibitors include tolcapone (3, 4-dihydroxy-4'-methyl-5-nitrobenzophenone) and entacapone ((E)-2- cyano-3- (3, 4-dihydroxy-5-nitrophenyl)-N, N-diethyl-2-propenamide

Preferably, according to the present invention, safinamide is combined with at least one of L-dopa, PDI, dopamine agonists, such as pramipexole, ropinerole, COMT.

Therefore, the present invention relates to a method for treating dyskinesias associated with dopaminergic therapy which comprises administering safinamide in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate, to a patient in need thereof.

The term "an equivalent dosage of any pharmaceutically acceptable salt thereof" relates to the dosage calculated based on the molecular weight of the respective

salt. E.g., if the methansulfonate is used, an equivalent dosage to 300 mg safinamide would be 395.28 mg safinamide methansulfonate.

Safinamide is preferably used in form of its methansulfonate (1:1 salt).

Treatment of dyskinesias includes both reduction of dyskinesias and prophylactic treatment to prevent or ameliorate increased dyskinesias due to other therapy, for example dopaminergic therapy.

Conventional treatment of Parkinson's Disease includes treatment with L-dopa and with related drugs such as dopaminergic agents. L-dopa and related drugs give rise to L-dopa-induced dyskinesia; the familiar motor function problems that are observed in patients suffering from Parkinson's Disease. Treatment with safinamide according to the present invention will suppress the symptoms of Parkinson's Disease and will attenuate L-dopa-induced dyskinetic movements.

This allows the dosage of dopaminergic agents, for example L-dopa, to be increased without the complicating side-effects normally observed with higher dosages.

The invention is particularly useful, in cases where L-dopa therapy should not or cannot be discontinued or reduced.

Safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof may be used according to the invention in pharmaceutical compositions as the sole active ingredient or may be contained in a pharmaceutical composition together with one or more other active ingredients, or it may be co-administered with one or more known drugs.

Dopaminergic agents typically may be administered according to methods known in the art for such agents, in dosage forms, at unit doses and at frequencies as determined by the skilled medical practitioner. For example L-dopa typically may be administered orally from one to four times a day with a total daily dosage of 200mg to 1200 mg dependent on the patient's condition, body weight and other factors.

Administration of the therapies and combination therapies of the invention may be orally, topically, subcutaneously, intramuscularly, or intravenously.

The invention further relates to kits for treating patients having Parkinson's Disease.

Such kits include safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, in a dosage according to the present invention and a therapeutically effective dose of an agent for treating or at least partially alleviating the symptoms of Parkinson's Disease (e. g., levodopa plus carbidopa (SINEMET (g)), levodopa plus controlled release carbidopa (SINEMET-CR, levodopa plus benserazide), levodopa plus controlled release benserazide (MADOPAR- HBS), bromocriptine, pergolide, ropinirole, pramipexole, lisuride, cabergoline, apomorphine, sumanirole, rotigotine, talipexole, dihydroergocriptine, entacapone, tolcapone, amantidine) selegiline, rasagiline, lazabemide, or caroxazone, either in the same or separate packaging, and instructions for its use.

Administration may be, e. g. , intralesional, intraperitoneal, intramuscular or intravenous injection; infusion ; or topical, transdermal, transcutaneous, nasal, oral, ocular or otic delivery. A particularly convenient frequency for the administration of the combination is once a day.

As noted above, combination therapies and/or co-adinistration are part of the invention. The combination therapies and/or co-adinistration of the invention may be administered in any suitable fashion to obtain the desired treatment of PD in the patient. One way in which this may be achieved is to prescribe a regimen of safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, so as to pre-treat the patient to obtain the effects of safinamide then follow with the PD agent as part of a specific treatment regimen, e. g., a standard administration of levodopa/PDI (with or without a COMT inhibitor and/or amantidine) and/or a dopamine agonist, to provide the benefit of the co-action of the therapeutic agents.

Combination therapies and/or co-adinistration of the invention include this sequential administration, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner.

Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule, pill, or injection having a fixed ratio of safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, and, e. g., a dopamine agonist, or in multiple, single capsules or injections. The components of the combination therapies and/or co-adinistration, as noted above, can be administered by the same route or by different routes. For example, safinamide, the safinamide base or any other pharmaceutically acceptable salt thereof, may be administered by orally, while the other PD agent may be administered intramuscularly or subcutaneously ; or all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not believed to be critical.

Administration of the therapies and combination therapies of the invention may be administered (both or individually) orally, topically, subcutaneously, intramuscularly, or intravenously.

The preparation of pharmaceutical or pharmacological compositions will be known to those of skill in the art in light of the present disclosure. Typically, such compositions may be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid prior to injection; as tablets or other solids for oral administration; as time release capsules; liposome formulations ; or in any other form currently used, including suppositories, creams, lotions, mouthwashes, inhalants and the like.

The compositions and combination therapies of the invention may be administered in combination with a variety of pharmaceutical excipients, including stabilizing agents, carriers and/or encapsulation formulations as described herein. Compositions of the invention may be administered to a PD patient as pharmaceutically acceptable salts and/or in a pharmaceutically acceptable carrier."Pharmaceutically"or"pharmacologically acceptable" include molecular entities and compositions that do not produce an adverse, allergic or other untoward reaction when administered to an animal, or a human, as appropriate.

Pharmaceutically acceptable carrier include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like.

Pharmaceutically acceptable salts include acid addition salts and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders.

In certain defined embodiments, oral pharmaceutical compositions will comprise an inert diluent or assimilable edible carrier, or they may be enclosed in hard or soft shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0. 1 % of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 75% of the weight of the unit, or preferably between 25-60%. The amount of active compounds in such therapeutically useful compositions is such that a suitable dosage will be obtained.

The tablets, troches, pills, capsules and the like may also contain the following: a binder, as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a

flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compounds sucrose as a sweetening agent methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor.

The compositions and combination therapies of the invention can be formulated for parenteral administration, e. g., formulated for injection via the intravenous, intramuscular, subcutaneous, intralesional, or even intraperitoneal routes. The preparation of an aqueous composition that contains a composition of the invention or an active component or ingredient will be known to those of skill in the art in light of the present disclosure.

Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for using to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and the preparations can also be emulsified.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions ; formulations including sesame oil, peanut oil or aqueous propylene glycol ; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

The pharmaceutical composition of the present invention for treating and/or preventing PD can be provided in any and all dosage forms that can be administered to patients by the oral route, such as tablets, fine granules, capsules, and granules, and others.

Preferred forms are tablets.

Further preferred embodiments of the invention are described in the following:

Embodiment 1:
A method for treating dyskinesias which comprises administering safinamide to a human patient in need thereof in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 2:
A method for treating dyskinesias which comprises administering safinamide to a human parkinson disease patient, in need thereof in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 3:
A method for treating dyskinesias resulting from dopaminergic therapy which comprises administering safinamide to a human patient in need thereof in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 4:
A method for treating dyskinesias resulting from L-dopa therapy which is administered to alleviate symptoms of parkinson's disease, which method comprises administering safinamide to a human patient in need thereof in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 5:
A method for treating dyskinesias in a human parkinson's disease patient in need thereof which comprises co-administering to said patient safinamide in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate, and a dopaminergic agent, preferably in an amount that is effective to provide greater efficacy than provided by administering said dopaminergic agent alone.

Embodiment 6:

A method according to foregoing embodiment, wherein the dose of dopaminergic agent is greater than that administered to said patient in the absence of safinamide or in the presence of safinamide in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 7:
A method according to the foregoing embodiment 6, wherein the dose of dopaminergic agent is at least 20%, preferably at least 50%, more preferably at least 70% and most preferably at least 100% greater.

Embodiment 8:
A method according to any of the foregoing embodiments, wherein the patient has been treated with a lower dosage, before being treated with safinamide in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 9:
A method according to any of the foregoing embodiments, wherein the patient is not sufficiently responding to a lower dosage of safinamide or a lower equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 10:
A method according to any of the foregoing embodiments, wherein the patient is a late-stage parkinson patient.

Embodiment 11:
A method according to any of the foregoing embodiments, wherein the patient is an advanced idiopathic parkinson patient, suffering from L-dopa induced dyskinesia, particularly peak-dose dyskinesia.

Embodiment 12:
A method according to any of the foregoing embodiments, wherein the patient is an advanced idiopathic parkinson patient. Such patient has preferably a Hoehn and Yahr disease staging of II to IV.

Embodiment 13:
A method according to any of the foregoing embodiments, and embodiment 7 in particular, wherein the dopaminergic agent is L-dopa and/or the dopaminergic treatment comprises administration of L-dopa.

Embodiment 14:
A method according to any of the foregoing embodiments, wherein in addition to safinamide and the dopaminergic agent, a peripheral decarboxylase inhibitor (PDI) is administered.

Embodiment 15:

A method according to any of the foregoing embodiments, wherein the dopaminergic agent is L-dopa and carbidopa.

Embodiment 16:
A method according to any of the foregoing embodiments, wherein the method also comprises administration of dopamine agonists, preferably ropinerole and/or pramipexole.

Embodiment 17:

Pharmaceutical unit dosage form containing more than 200 mg or equivalent amounts of safinamide or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate, preferably together with pharmaceutical excipients. Most preferably, the unit dosage form contains about 300 mg of safinamide.

Embodiment 18
A method according to any of the foregoing embodiments, wherein the dose of safinamide is preferably higher than 250 mg per day, more preferably higher than 270 mg, higher than 290 mg higher than or about 300 mg.

Embodiment 19

A method according to any of the foregoing embodiments, wherein safinamide or any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate, are adminstered orally, preferably once daily.

Embodiment 20:
A solid oral dosage form, preferably a tablet, containing 250 mg to 400 mg, preferably, 250 mg, 270 mg, 275 mg, 290 mg, 300 mg, 330 mg or 350 mg Safinamide or equivalent amounts of in a dosage higher than 200 mg per day or an equivalent dosage of any pharmaceutically acceptable salt thereof, such as safinamide methanesulfonate.

Embodiment 21:
Use of safinamide for the preparation of a medicament for treating dyskinesias which comprises administering safinamide to a human patient, in need thereof in dosages higher than 200 mg per day.

Embodiment 22:
Use of safinamide for the preparation of a medicament for treating dyskinesias resulting from L-dopa therapy which is administered to alleviate symptoms of parkinson's disease, which method comprises administering safinamide to a human patient in need thereof in dosages higher than 200 mg per day.

Embodiment 23:
Use of safinamide for the preparation of a medicament for treating dyskinesias in a human parkinson's disease patient in need thereof which comprises co-administering to said patient safinamide in dosages higher than 200 mg per day and a dopaminergic agent.

Embodiment 24:
Use of safinamide according to any of the foregoing embodiments, wherein the patient is not sufficiently responding to a lower dosage of safinamide.

Embodiment 25:

Use of safinamide according to any of the foregoing embodiments, wherein the patient is a late-stage parkinson patient.

Embodiment 26:
Use of safinamide according to any of the foregoing embodiments, wherein the patient is an advanced idiopathic parkinson patient, suffering from L-dopa induced dyskinesia.

Embodiment 27:
Use of safinamide according to any of the foregoing embodiments, wherein the dopaminergic agent is L-dopa and/or the dopaminergic treatment comprises administration of L-dopa.

Embodiment 28:
Use of safinamide according to any of the foregoing embodiments, wherein in addition to safinamide and the dopaminergic agent, a peripheral decarboxylase inhibitor (PDI) is administered.

Embodiment 29:

Use of safinamide according to any of the foregoing embodiments, wherein the dopaminergic agent is L-dopa and carbidopa.

Embodiment 30:

Use of safinamide according to any of the foregoing embodiments, wherein the method also comprises administration of one or more dopamine agonists.

Embodiment 31:
An oral pharmaceutical dosage form containing more than 200 mg safinamide or any pharmaceutically acceptable salt thereof.

Embodiment 32:

An oral pharmaceutical dosage form containing about 300 mg safinamide or any pharmaceutically acceptable salt thereof.

Embodiment 33:
Use of safinamide according to any of the foregoing embodiments, wherein the dose of safinamide is equal to or higher than about 240 mg per day.

Embodiment 34:
Use of safinamide according to any of the foregoing embodiments, wherein the dose of safinamide is about 300 mg per day.

Embodiment 35:
Use of safinamide according to any of the foregoing claims, wherein safinamide is used in equivalent dosages of its methansulfonate 1:1 salt.

Throughout the specification, the abbreviations used have the following meaning:

γGT	Gamma-glutamyl transferase
1st Q	First quarter
5-HT1A and 5-HT2A	5-hydroxy tryptamine subtypes 1A and 2A
ADL	Activities of daily living
AE	Adverse Event
AIMS	Abnormal involuntary movement scale
ALT	Alanine transaminase
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
ANCOVA	Analysis of covariance

AP	Alkaline phosphatase
AREDS	Age-Related Eye Disease Study
AST	Aspartate aminotransferase
BL	Baseline
BUN	Blood urea nitrogen
BW	Body weight
CFR	Code of Federal Regulations (USA)
CGI	Clinician based Global Impression
CGI-C	Clinician based Global Impression of Change
CI	Confidence interval
COMT	c-ortho methyl transferase
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
DAT	Dopamine transporter
Decr	Decrease
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EoS	End of Study
EU	European Union
EEA	European Economic Area
EMEA	European Medicine Evaluation Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDL	High density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IF	Investigator file
IMP	Investigational Medicinal Product
Incr	Increase
IRB	Institutional Review Board
ISMB	Independent Safety Monitoring Board
ITT	Intent to Treat
IUD	Intrauterine device
IVRS	Interactive Voice Response System
LC/MS/MS	Liquid chromatography / Mass spectroscopy / Mass spectroscopy
LDH	Lactic dehydrogenase
LDL	Low density lipoprotein
LID	L-dopa-indiced dyskinesia
LLQ	Lower limit of quantification
LPLV	Last patient last visit
LSmean	Least squares mean
MAO-B	Mono amine oxidase type B
MDS-UPDRS	Movement Disorder Society Sponsored revised Unified Parkinson's Disease Rating scale
Mg /d	Milligrams per day

Mg/kg	Milligrams per kilogram
mg	Milligrams
ml	Millilitres
MoCA	Montreal Cognitive Assessment Test
MOP	Manual of Operations
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NA	Not applicable
Na^+	Sodium
Neurol	Neurological
NMDA	n-methyl d-aspartate
OCT	Optical coherence tomography
PD	Parkinson Disease
PDYS-26	Parkinson Disease Dyskinesia Scale – 26 items
PGI	Patient based Global Impression
PGI-C	Patient based Global Impression of Change
PGx	Pharmacogenetics/Pharmacogenomics
PK	Pharmacokinetics
p.o.	per os (oral)
PoC	Proof of Concept
QAM	Every morning
QTc	Corrected QT interval
RBC	Red blood cell
RDRS	Rush dyskinesia rating scale
SAE	Serious Adverse Event
Scr	Screening

SERT	Serotonin transporter
SNr	Substantia Nigra pars reticularis
SNRI	Serotonin norepinephrine reuptake inhibitor
SRB	Safety Review Board
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment emergent adverse event
TC	Telephone call
TMax	Time to Maximum plasma level
UDysRS	United Dyskinesia Rating Scale
UK	United Kingdom
ULN	Upper limit of normal
VLDL	Very low density lipoprotein
vs	versus
WBC	White blood cell

Example

The following study confirms that safinamide, when used in high dosages according to the present invention, can attenuate l-dopa induced dyskinesia in Parkinson's disease, which is expressed e.g. by the maximum reduction in Unified Dyskinesia Rating Score (UDysRS) compared to baseline across all post-baseline dose visits. In particular, the study confirms that daily dosages of safinamide higher than 200 mg per day result in a significantly stronger attenuation of L-dopa induced dyskinesia, than lower dosages.

A dose range of safinamide 100 - 300 mg PO QAM compared to placebo is assessed in late-stage Parkinson's disease patients with l-dopa induced

dyskinesias, specifically advanced idiopathic PD patients treated with L-dopa and suffering from temporally predictable L-dopa induced peak-dose dyskinesia.

The assessment includes: evaluation of changes from baseline in motor fluctuations, motor function, activities of daily living, and change in global clinical status.incidences of treatment emergent adverse effects (TEAE) and clinically significant changes in laboratory safety tests, ECG morphology, vital signs, ophthalmological, and dermatological examinations.

The study is a prospective, randomized, double-blind, parallel-group, placebo-controlled, dose escalation trial, wherein 36 subject are randomized (2:1 randomization into active or placebo, i.e. 24 active and 12 placebo).

The study is based on a within subject dose escalation design. Across dose levels of main interest are steady-state evaluations after administration of safinamide 100 mg/d, 200 mg/d, and 300 mg/d, all administered p.o. QAM.

Each subject starts with 100 mg/d safinamide, followed by 150 mg/d, 200 mg/d, 250 mg/d, and finally 300 mg/d, or corresponding placebo.

Safinamide is provided in form of tablets at dosage strength of 50 mg (small – 7 mm tablets) and matching placebo tablets in blisters. Dosing is achieved using appropriate multiples of these tablet strengths

The pharmaceutical tablet formulation used contains in addition to safinamide the following ingredients (white film tablets):

Composition of Safinamide 50 mg DC Tablets

Ingredient	Unit Formula (mg/tablet)	Function	Quality Reference
Active Ingredient			
Safinamide methanesulfonate	65.88[a]		In-house monograph
Excipients			
Microcrystalline cellulose	50.12	Diluent-binder	Ph. Eur. / USP
Crospovidone	6.25	Binding agent	Ph. Eur.
Magnesium stearate	2.50	Lubricant	Ph. Eur. / USP

Colloidal Silicon Dioxide	0.25	Glidant	Ph. Eur. / USP
Core tablet weight	125.00		
Hypromellose*	3.50	Film former	Ph. Eur. / USP
Titanium dioxide*	1.00	Pigment	Ph. Eur.
Polyethyleneglycole 6000*	0.50	Plasticizer	Ph. Eur.
Coated tablet weight	130.00		

[a] Equivalent to 50 mg free base
* either used as single ingredients or as ready-to-use mixture

The trial medication is administered orally, once per day, in the morning with breakfast, in addition to the morning dose of the first L-dopa dose. The trial medication consists of a combination of tablets needed to achieve the desired daily dose for their assigned treatment group.

The trial medication is applied in a dose escalation scheme. The subject starts with 100 mg/day and escalates up to 300 mg/day. A summary of the titration scheme is shown in Table 1 below:

Table 1: Dose titration schedule

Trial Day	**Dose Type**	**Treatment Group Safinamide mg/day**	**Placebo Group Placebo**	**Number of Tablets**
1	Starting	100 mg	Placebo	2
9	Dose increase	150 mg	Placebo	3
12	Dose increase	200 mg	Placebo	4
23	Dose Increase	250 mg	Placebo	5
26	Target	300 mg	Placebo	6

The use of L-dopa is a prerequisite for entering the trial. L-dopa is given as combination of L-dopa with an aromatic amino acid decarboxylase inhibitor, i.e. carbidopa or benserazide. The dose of L-dopa treatment remains constant during the course of the trial.

The trial starts with a screening visit (Visit 1) approximately 2 weeks (+/-3 days) before the baseline visit. There is a baseline assessment (Visit 2) prior to treatment and an initial efficacy assessment 2-3 hours after the first administered safinamide dose (100 mg at Trial Day 1). At the next visit at Trial Day 8 (Visit 3), clinical assessments for safety and efficacy is performed, then the safinamide dose is increased to the next level (150 mg/d administered for the next 3 days; Trial Day 9-11) and then to 200 mg/d administered from Trial Days 12 -21. Efficacy and safety assessments are performed on Trial Day 22 (Visit 4) followed by dose escalation to 250 mg/d for trial days 23 – 25, and a final dose escalation to a dose of 300 mg/d at Trial Day 26. An assessment of safety and efficacy is performed on Trial Day 36 (Visit 5) and on Trial Day 66 at the end of the treatment phase (Visit 6).

Subjects have their safinamide dose tapered over the ensuing week, and return at Trial Day 101 for a final safety and clinical assessment (Visit 7).

The duration of controlled treatment for each subject is 10 to 11 weeks, including a wash-out interval (taper phase) of 1 week and a safety evaluation four weeks after the last dose.

The assessments and activities that are carried out at the Screening Visit are provided in Table 2.

Table 2 Overview of Assessments to be Carried Out at Screening

Activity	Includes
Informed consent	• Written informed consent for participation in the trial
Registration	• Collection of demographic data • Inclusion/exclusion criteria review
Relevant medical history	• Previous treatments, concomitant disease other than PD
Physical examination	• General appearance, head/neck, pulmonary cardiovascular, gastrointestinal, genitourinary, lymphatic, musculoskeletal system, extremities, ears, nose, and throat
Neurological examination	
Dedicated safety checks	• Dermatological assessment • Ophthalmological safety assessment • 12-lead ECG • Vital signs
Hematology/Clinical chemistry	• Hematology: red blood cells, white blood cells, platelets, hemoglobin, hematocrit • Biochemistry: creatinine, sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, total bilirubin, triglycerides, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γGT, total cholesterol, HDL, LDL, VLDL, CPK,
Virology tests	• Hepatitis B antibody (core and surface) and surface antigen, and

Activity	Includes
	hepatitis C antibody screens
Urine tests	• pH, specific gravity, protein, glucose, ketones, RBC, WBC, casts, bilirubin, nitrites
Pregnancy test	• Serum pregnancy test for women of childbearing potential
Exclusion of dementia	• MoCA < 26 points
Diary cards	• Training on the proper use of diary cards • Issuing of diary cards for dyskinesia recording
Assessment of PD/LID	• Video recording of LID (habituation to procedure for UDysRS) • MDS-UPDRS

Subjects at Baseline and visits after randomization undergo the following assessments as outlined in Table 3.

Table 3: Overview of Assessments at Baseline and After Randomization

Activity	Includes	Frequency (+/- 2 days)
Dyskinesia assessment	• UDysRS • Video recording of peak LIDs • Patient diary • PDYS-26 • Global Impression (CGI, PGI)	• Each trial visit
PD assessment	• MDS-UPDRS	• Each trial visit

Activity	Includes	Frequency (+/- 2 days)
Vital signs/Cardiac assessment	• Vital signs • 12-lead ECG	• Each trial visit after completion of all efficacy assessments.
Laboratory tests	• Hematology: red blood cells, white blood cells, platelets, hemoglobin, hematocrit • Biochemistry: creatinine, sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, total bilirubin, triglycerides, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γGT, total cholesterol, HDL, LDL, VLDL, CPK,	• Each trial visit after completion of all efficacy assessments.
Urine test	• pH, specific gravity, protein, glucose, ketones, RBC, WBC, casts, bilirubin, nitrites	• Each trial visit after completion of all efficacy assessments.
Urine pregnancy test		• At baseline - In countries where this is mandated by local regulations, more frequent pregnancy testing will be

Activity	Includes	Frequency (+/- 2 days)
		performed as required.
PK sampling	• Safinamide plasma concentrations	• Each trial visit after completion of all efficacy assessments.
Safety assessment	• AEs/SAEs • Concomitant medication	• Each trial visit after completion of all efficacy assessments.

Subjects at end of trial undergo the following assessments as outlined in Table 4.

Table 4: Overview of Assessments at End of Trial

Activity	Includes
Physical examination	• General appearance, head/neck, pulmonary cardiovascular, gastrointestinal, genitourinary, lymphatic, musculoskeletal system, extremities, ears, nose, and throat, after completion of all efficacy assessments.
Neurological examination	(After completion of all efficacy assessments.)
Dedicated safety checks	• Dermatological assessment • Ophthalmological safety assessment • 12-lead ECG • Vital signs (After completion of all efficacy assessments.)
Hematology/Clinical chemistry	• Hematology: red blood cells, white

Activity	Includes
	blood cells, platelets, hemoglobin, hematocrit • Biochemistry: creatinine, sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, total bilirubin, triglycerides, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γGT, total cholesterol, HDL, LDL, VLDL, CPK, (After completion of all efficacy assessments.)
Urine tests	• pH, specific gravity, protein, glucose, ketones, RBC, WBC, casts, bilirubin, nitrites (After completion of all efficacy assessments.)
Dyskinesia assessment	• UDysRS • Video recording of peak LIDs • Patient diary • PDYS-26 • Global Impression (CGI, PGI)
PD assessment	• MDS-UPDRS
Safety assessment	• AEs/SAEs • Concomitant medication

Subjects in this trial are advanced idiopathic PD patients treated with L-dopa and suffering from temporally predictable L-dopa induced peak-dose dyskinesia. They also fulfill all of the following inclusion criteria:

1. The subject presents with a diagnosis of idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria.
2. The subject is an out-patient aged 30 years or above.
3. PD subjects with a Hoehn and Yahr disease staging of II-IV.
4. PD subjects experiencing L-dopa induced dyskinesias, specifically predictable peak-dose dyskinesia.
5. Peak-dose dyskinesia must be considered by the subject to be problematic and/or disabling.
6. Peak-dose dyskinesia must warrant medical treatment in the Investigator's opinion.
7. The subject has participated successfully in a diary-card training session.
8. In the judgment of the Investigator based on the subject's history, previous treatments, and the clinical presentation, the subject is considered as being optimally treated at the present time (i.e., further adjustments of current medication are not expected to further improve the subject's symptoms of Parkinson's disease).
9. Stable dose of all PD drugs for at least 4 weeks before Screening Visit. This may include: L-dopa dopamine agonists, COMT inhibitors, anticholinergics, and budipine.
10. The dose of L-dopa and all PD drugs used during the trial remain unchanged throughout the trial.
11. Female subjects must be neither pregnant or breast-feeding and must lack child-bearing potential.
12. The subject shows adequate compliance with the schedule for intake of trial medication and the completion of the diaries.

Subjects furthermore do not fulfill any of the following exclusion criteria:

1. The subject has participated in any safinamide clinical trial before.
2. The subject is experiencing diphasic, off state, myoclonic, dystonic, or akathetic dyskinesias.
3. (For female subjects) The subject is pregnant or lactating.
4. Treatment with a MAO-B inhibitor within the eight weeks prior to the screening visit.
5. Treatment with amantadine in the eight weeks prior to the screening visit.
6. Treatment with opioids (e.g., tramadol, meperidine derivatives), SNRIs (e.g. venlafaxine, duloxetine), tri- or tetra-cyclic antidepressants, in the 8 weeks prior to the screening visit. Dextromethorphan will be permitted if used for treating cough.
7. The subject has received neurosurgical intervention related to PD (e.g. deep brain stimulation, thalamotomy etc.) or is scheduled to do so during the trial period.
8. Current clinically significant gastro-intestinal, renal, hepatic, endocrine, pulmonary or cardiovascular disease, including acute gastric ulcer, hypertension that is not well controlled, asthma, chronic obstructive pulmonary disease (COPD), and Type I diabetes. Subjects with a history of gastric ulcer who have not had a recent episode of acute gastritis and are not currently experiencing gastric pain will be eligible for inclusion.
9. Diagnosis of HIV, or positive test for Hepatitis C antibodies, or Hepatitis B surface antigen.
10. Concomitant disease likely to interfere with trial medication (e.g. capable of altering absorption, metabolism, or elimination of the trial drug).
11. The subject has any clinically significant illness that might interfere with the subject's ability to participate in the trial.
12. Second- or third-degree atrio-ventricular block or sick sinus syndrome, uncontrolled atrial fibrillation, severe or unstable angina, congestive heart failure, myocardial infarction within 3 months of the screening visit, or a significant ECG abnormality, including QTc – 450 msec (males) or – 470 msec (females), where QTc is based on Bazett's correction method.

13. Ophthalmologic history including any of the following conditions: albino subjects, family history of hereditary retinal disease, progressive and/or severe diminution of visual acuity (i.e., 20/70), retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), or diabetic retinopathy
14. The subject is suffering from dementia or other severe neuropsychiatric illness that prevents him/her from giving informed consent, or has a total score on the MoCA <26 points.
15. Signs and symptoms suggestive of transmissible spongiform encephalopathy, or family members who suffer(ed) from such.
16. Known hypersensitivity to the trial treatment(s), including placebo or other comparator drug(s).

Primary endpoint

The primary endpoint is the patient maximum reduction in Unified Dyskinesia Rating Scale (UDysRS) (total score) from baseline (Visit 2) to post-baseline visits (Visit 3, Visit 4, Visit 5, and Visit 6). The primary endpoint is evaluated for each patient and then summarized using descriptive statistics by treatment group (safinamide vs placebo). In addition, an exploratory analysis is conducted using an analysis of covariance (ANCOVA) model with treatment as a factor and baseline score as the covariate.

Secondary endpoint(s)

Other efficacy variables from baseline to all post-baseline dose visits.

- Complete new MDS-UPDRS and subscales,
- Patients diary (Hauser diary, all parts),
- PDYS-26 (dyskinesia specific questionnaire),

- CGI (dyskinesia specific)

- PGI (dyskinesia specific)

In addition, the following assessments are performed when the subject is in 'ON' phase: MDS-UPDRS (parts I-IV), UDysRS and CGI. All efficacy assessments are performed at approximately the same time of the day at each visit.

UdysRS (Primary efficacy variable)

The UdysRS has been developed by C. Goetz and colleagues (Goetz CG, Nutt JG, Steppins GT. The Unified Dyskinesia Rating Scale (UdysR): Presentation and Clinimetric Profile. Mov Disord 2008; 23: 2398-2403). The UDysRS is a composite four-part scale that assesses: I: Historical Disability (patient perceptions) of On-Dyskinesia impact (11 items, 1 with involvement of the rater to assist in obtaining the portion of the day the subject has dyskinesia and 10 answered by the patient/caregiver in the form of a questionnaire. This section is based on the Lang–Fahn Scale, but with significant modification); II: Historical Disability (patient perceptions) of Off-Dystonia impact (4 items, 1 with involvement of the rater to determine the hours per day with Off-dystonia and 3 answered by the patient/caregiver in the form of a questionnaire. This section is based on the MDS-UPDRS); III: Objective Impairment (Dyskinesia severity and anatomical distribution based on four activities observed or video-recorded). Seven anatomical areas are rated for severity of dyskinesia or dystonia on each task with the highest score for the four tasks recorded as the final score for each body region. This section is based on the AIMS; IV: Objective Disability (four items with ratings based on the same four activities in Part III. This section is based on the Rush Dyskinesia Rating Score); and finally V: Total Objective Score (sum of impairment and disability scores i.e. sum score of part I – IV). The scale extracted items and concepts from the following scales: Lang–Fahn questionnaire,11 MDS-UPDRS;19 AIMS; 9 and; 10 RDRS. Score ranges are 0 to 44 for Part I, 0 to 16 for Part II, 0 to 28 for Part III, and 0 to 16 for Part IV, with a total score range of 0 to 104.

Part III of the UDysRS is rated in real time by the Investigator. A video recording of part III is performed, but this is not considered for a central review by an independent reader. This video-recording is considered only as a back-up for exploratory analysis in case of unclear interpretation of real-time ratings. A practice session with the video recording is completed during screening to habituate subjects to the procedure.

The primary efficacy analysis is based on the change from baseline UDysRS (total) scores. More specifically, the patient maximum UDysRS (total) reduction across all post-baseline visits (measured at V3, V4, V5, or V6) from baseline (V2) is determined for each individual subject. The above-mentioned maximum UDysRS reduction score is then descriptively summarized with mean, SD, median, min, and max by treatment group (safinamide and placebo). In addition, an exploratory analysis is performed on the maximum UDysRS reduction score by using an analysis of covariance (ANCOVA) model including treatment (safinamide and placebo) as the factor and baseline score as the covariate. The LSmean of treatment difference (safinamide versus placebo) and the associated 95% CIs is derived from the above model for descriptive purposes only. Furthermore, the visit (V3, V4, V5, or V6) at which the subject first reaches the maximum UDysRS reduction is recorded and descriptively summarized by treatment group.

As a secondary analysis, the change from baseline in total UDysRS is descriptively summarised with mean, SD, median, min and max by treatment group (safinamide and placebo) at each individual post-dose visit (V3, V4, V5, and final visit V6). Also, an exploratory analysis using a repeated measurement ANCOVA model is applied to the change from baseline scores at all 4 post-dose visits, including treatment (safinamide, placebo), visit (V3, V4, V5, V6) and treatment by visit as factors and baseline score as the covariate. The LSmean difference (safinamide versus placebo) and the associated 95% CIs is derived from the above model for descriptive purposes only.

In addition to the total UDysRS score, the sub-total of Section I+II (Historical) and sub-total of III+IV (Objective) is also assessed in the same manner as above.

Patient's diary card

A home diary to assess functional status in PD patients with motor fluctuations and dyskinesia was published by Hauser et al.(Hauser RA, Friedlander J, Zesiewicz TA, et al. A home diary to assess functional astatus in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol 2000; 23: 75-81). This diary asks subjects to indicate their predominant status during half-hour intervals over a 24-hour period however in this study a truncated 18-hour version is used (06:00 to 24:00 hr) each day and includes the categories 'asleep', 'OFF', 'ON without dyskinesia', 'ON with non-troublesome dyskinesia' and 'ON with troublesome dyskinesia'. In general, the diaries are completed on the two consecutive days (2 x 24 hours) before each of the Visits 3, 4, 5, 6, and the Follow-up Visit (Visit 7). For Visit 2, it is five consecutive days.

For the filling-in of the diaries, the definitions as outlined in Table 5 apply.

Table 5: Definitions for diary recording

OFF:	Time when medication has worn off and is no longer providing benefit with regard to mobility, slowness and stiffness.
ON:	Time when medication is providing benefit with regard to mobility, slowness and stiffness.
Dyskinesia:	Involuntary twisting and turning movements (tremor is shaking back and forth and is not considered dyskinesia).
Non-troublesome dyskinesia:	Dyskinesia not interfering with function or causing meaningful discomfort.
Troublesome dyskinesia:	Dyskinesia interfering with function or causing meaningful discomfort.

In the diary, the function will be scored as follows:

- 'asleep' (the patient is asleep),
- 'OFF',
- 'ON without dyskinesia',
- 'ON with non-troublesome dyskinesia',
- 'ON with troublesome dyskinesia'.

The Hauser diary is a well accepted efficacy instrument in Parkinson's disease trials According to the EMEA "Guideline on Clinical Investigation of Medicinal Products in the Treatment of Parkinson's Disease" from July 2008, patient's diaries scoring the type of dyskinesias (disabling/non-disabling) over predefined periods on pre-specified days during the trial are recommended.

The change from baseline in the daily total "on" time (ON w/o dyskinesia, or ON with non-troublesome dyskinesia), and change from baseline in daily total "off" time as measured by the patients' diary are analysed in the same manner as described in the UDysRS secondary analysis.

MDS-UPDRS

The MDS-UPDRS (Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Rating Results. Mov Disord 2008; 23: 2129-2170) is a revised version of the standard UPDRS that was in practice since its introduction in 1987 and became the most widely used clinical rating scale in PD. The major advantages of the MDS-UPDRS over the UPDRS are the more complete set of items and a better defined clinimetric profile. All parts of the MDS-UPDRS (Part I-IV) are analyzed separately and in total.

Change from baseline MDS-UPDRS total score and sub-section scores is summarized descriptively and analysed in the same manner as described in the UDysRS secondary analysis

PDYS-26

The PDYS-26 (Katzenschlager R, Schrag A, Evans A, et al. Quantifying the impact of dyskinesias in PD. The PDYS-26: a patient-based outcome measure. Neurology 2007; 69: 555 – 563) is a distinct dyskinesia-specific quality of life instrument addressing 26 questions on different daily activities. The PDYS-26 is a patient-based method for quantifying the impact of dyskinesias on activities of daily living in PD. It satisfies both new and traditional psychometric criteria for reliable and valid measurement, and provides information about dyskinesias from the patients' own perspective, which could complement existing clinician-based scales.

The PDYS-26 questionnaire includes 26 questions; each question has a possible answer in category from 'Not at All' up to 'Activity Impossible', or 'Not Applicable'. For each question, the patients' answers (in above category) is summarized descriptively with subject number and percentage by treatment (safinamide and placebo) at each visit (V2, V3, V4, V5, V6). In addition, a consolidated summary of all the 26 questions are provided as described as following. Each patient's

answer as Not at All, Mildly, Moderately, Severely, Activity Impossible, is scored by (0-4 scale) and the individual patient's average score across the 26 questions is derived. The patient PDYS-26 average score is summarized in the same manner as described in the UDysRS secondary analysis.

CGI / PGI

The CGI (Clinical Global Impression) (Guy W. Clinical Global Impressions. 1976. National Institute of Mental Health. ECDEU Assessment Manual for Psychopharmacology) is the general name for two scales, the CGI – Severity scale (CGI-S) and the CGI – Change scale (CGI-C).

The CGI-S scale measures global severity of illness at a given point in time. It is rated on a 7-point Likert-type scale ranging from 1 (normal, not ill at all) to 7 (among the most extremely ill subjects).

The CGI-C scale measures the change in the subject's clinical status form a specific point in time using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. In completing the CGI-C, the rater should review all efficacy-related data, and assess its clinical meaningfulness.

The CGI is from the clinician's perspective. The PGI (Patient Global Impression) is the same scale applied from the patient's perspective.

The PGI is the general name for two scales, the PGI – Severity scale (PGI-S) and the PGI – Change scale (PGI-C).

The PGI-S scale measures global severity of illness at a given point in time. It is rated on a 7-point Likert-type scale ranging from 1 (normal, not ill at all) to 7 (among the most extremely ill subjects).

The PGI-C scale measures the change in the subject's clinical status form a specific point in time using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change.

Claims

1. Safinamide for use in the treatment of dyskinesias which is to be administered to a human patient, in need thereof in dosages higher than 200 mg per day, wherein the patient is an advanced idiopathic parkinson patient, suffering from L-dopa induced dyskinesia, and/or a late-stage parkinson patient.

2. Safinamide for use in the treatment of dyskinesias resulting from L-dopa therapy which is administered to alleviate symptoms of parkinson's disease, wherein safinamide is to be administered to a human patient in need thereof in dosages higher than 200 mg per day, and wherein the patient is an advanced idiopathic parkinson patient, suffering from L-dopa induced dyskinesia, and/or a late-stage parkinson patient.

3. Safinamide for use in the treatment of dyskinesias in a human parkinson's disease patient in need thereof which is to be co-administered to said patient in dosages higher than 200 mg per day, with a dopaminergic agent, wherein the patient is an advanced idiopathic parkinson patient, suffering from L-dopa induced dyskinesia, and/or a late-stage parkinson patient.

4. Safinamide for use according to the foregoing claim, wherein the dopaminergic agent is L-dopa and/or the dopaminergic treatment comprises administration of L-dopa.

5. Safinamide for use according to any of the foregoing claims, wherein in addition to safinamide and the dopaminergic agent, a peripheral decarboxylase inhibitor (PDI) is administered.

6. Safinamide for use according to any of the foregoing claims, wherein the dopaminergic agent is L-dopa and carbidopa.

7. Safinamide for use according to any of the foregoing claims, wherein the method also comprises administration of one or more dopamine agonists.

8. Safinamide for use according to any of the foregoing claims, wherein the dyskinesia is L-dopa induced peak-dose dyskinesia.

9. Safinamide for use according to any of the foregoing claims, wherein the patient does not suffer from diphasic, off state, myoclonic, dystonic or akathetic dyskinesia.

10. Safinamide for use according to any of the foregoing claims, wherein the patient suffers from troublesome, problematic or disabling dyskinesia.

11. An oral pharmaceutical dosage form containing more than 200 mg safinamide or any pharmaceutically acceptable salt thereof.

12. An oral pharmaceutical dosage form containing about 300 mg safinamide or any pharmaceutically acceptable salt thereof.

13. Safinamide for use according to any of the foregoing claims, wherein the dose of safinamide is equal to or higher than about 240 mg per day.

14. Safinamide for use according to any of the foregoing claims, wherein the dose of safinamide is about 300 mg per day.

15. Safinamide for use according to any of the foregoing claims, wherein safinamide is used in equivalent dosages of its methansulfonate 1:1 salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/051836

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/165 A61P25/14 A61K45/06 A61K31/198
ADD.

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

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 practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/089353 A2 (NEWRON PHARMACEUTICALS INC [IT]; RUGGERO FARIELLO [IT]; CATTANEO CARLO) 21 October 2004 (2004-10-21) cited in the application page 10, lines 15-19 page 16, lines 9-13 page 19, lines 4-6 page 29, lines 16-18 page 30, line 6 page 33, lines 8-12 claims 2,11,13,14 ----- -/--	1-15

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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 document but published on or after the international filing date

"L" 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)

"O" 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

"T" 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

"X" 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.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2011	11/04/2011

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/051836

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	LEONETTI FRANCESCO ET AL: "Solid-phase synthesis and insights into structure-activity relationships of safinamide analogues as potent and selective inhibitors of type B monoamine oxidase", JOURNAL OF MEDICINAL CHEMISTRY, vol. 50, no. 20, October 2007 (2007-10), pages 4909-4916, XP002576709, ISSN: 0022-2623 abstract	15
A	EP 1 870 097 A1 (NEWRON PHARM SPA [IT]) 26 December 2007 (2007-12-26) paragraph [0013] paragraph [0054] paragraph [0025] paragraph [0070] - paragraph [0072]; example 2	1-15
A	US 2007/093495 A1 (RUGGERO FARIELLO [IT] ET AL) 26 April 2007 (2007-04-26) the whole document	1-15

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Information on patent family members

International application No
PCT/EP2011/051836

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