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EXPERT OPINION

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Safinamide for the treatment of Parkinson's disease

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Introduction: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta. Non-dopaminergic neurotransmitter systems are also involved in its pathomechanism. The aim of the treatment is to improve the dopamine-deficient state and to alleviate the motor and the non-motor symptoms. Safinamide is an α-aminoamide derivative with a combined, dopaminergic and non-dopaminergic mode of action. Phase III clinical trials with safinamide, as add-on therapy to a dopamine agonist (DAA) and to levodopa (LD) in early and advanced stage PD, respectively, demonstrated an improvement of the motor symptoms.
Areas covered: The review discusses the pharmacokinetic and pharmacodynamic properties of safinamide and provides an overview of the clinical trials conducted with safinamide in PD. A literature search was made in PubMed for safinamide, safinamide pharmacokinetics, PD treatment and monoamine oxidase-B inhibitors, and in PubMed and on the ClinicalTrials.gov site for clinical trials with safinamide in PD.
Expert opinion: The place of safinamide in the therapy of PD is yet to be determined. However, the authors believe that safinamide is a valuable drug in the treatment of PD treatment with favorable pharmacokinetic and side-effect profiles. Data so far suggest that it can be used beneficially as add-on therapy both to DAAs in early PD and to LD in the later stages of the disease.

Keywords: dopaminergic, monoamine oxidase-B inhibitors, non-dopaminergic, Parkinson's disease, safinamide

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a frequency that increases with age. The cause of the neurodegenerative process in PD is not known; several mechanisms are involved in its development, including oxidative stress, inflammatory changes, proteosomal dysfunction and mitochondrial dysfunction [1-3]. The pathogenetic changes include the loss of dopaminergic neurons in the substantia nigra (SN) pars compacta and the appearance of Lewy bodies within the pigmented neurons of the SN. It is presumed that motor symptoms occur at a loss of about 60 – 80% of the dopaminergic neurons in the SN. Non-dopaminergic neurotransmitter systems, such as the serotonergic, the cholinergic, the adrenergic and glutamatergic, are also involved in the pathomechanism of the disease [4]. Besides the motor symptoms related to the dopamine-deficient state, non-motor symptoms can occur, even in the early stages of the disease, and impair the quality of life of the patients [5]. PD symptoms are summarized in **Table 1**.

2. Treatment approaches in PD

The treatments available at present mainly improve the motor symptoms caused by the dopaminergic loss. This can be achieved by supplying the dopamine precursor

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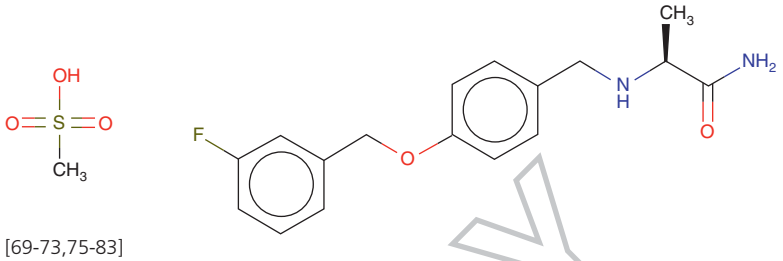
Box 1. Drug summary.

Drug name	Safinamide
Phase	Pre-registration
Indication	Parkinson's disease
Pharmacology description	Monoamine oxidase B inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	[69-73,75-83]

levodopa (LD) to increase the synthesis of dopamine, by stimulating the dopamine receptors or by acting on the metabolism of dopamine. As a result of the improving understanding of the complex pathomechanism of the disease, treatment has recently focused on non-dopaminergic medication for the treatment of the motor and non-motor symptoms and for alleviation of the dyskinesia. Effective neuroprotective therapy that is capable of halting the disease progression is not available [1,6,7].

The gold standard of the symptomatic treatment of the disease is LD therapy. LD, a dopamine precursor capable of crossing the blood–brain barrier, is taken up by the dopaminergic neurons and is decarboxylated to dopamine presynaptically in the basal ganglia. The peripheral metabolism responsible for the side effects is reduced by a peripheral decarboxylase inhibitor. In the first few months or years of LD therapy, a stable improvement of the motor symptoms can be seen. In time, however, the effect of LD wears off a few hours after LD intake. Later, *on* and *off* motor fluctuations occur, related to the fluctuations of the peripheral LD concentration but not correlated to the medication intake in the late stages of the disease. The progressive decrease in the number of dopaminergic neurons in the SN results in an inability of the striatum to buffer the variability in the brain dopamine concentrations caused by a short-acting dopaminergic agent. Oral substitution therapy is considered to cause a pulsatile stimulation of the dopamine receptors, which in turn is considered to underlie the development of motor fluctuations and LD-induced dyskinesia (LID). A continuous stimulation of the dopaminergic receptors presumably causes less fluctuation and dyskinesia [8,9]. The dopamine agonists (DAAs) have longer half-lives than that of LD but provide less symptomatic effect. The catechol-*O*-methyl transferase (COMT) inhibitors and the monoamine oxidase (MAO) inhibitors are dopaminergic agents which inhibit the dopamine metabolizing enzymes. The COMT inhibitors increase the bioavailability and the half-life of LD and reduce the fluctuations of plasma LD. COMT inhibitors are recommended for patients who exhibit the *wearing-off* phenomenon [5], as they improve and may also prevent the onset of *wearing-off*. In the STRIDE-PD study, the addition of the COMT inhibitor entacapone to LD resulted in earlier and more dyskinesia as compared with LD/carbidopa alone [10].

Although LD has a short half-life, in the early stages of disease, the presynaptic terminals are capable of storing dopamine and releasing it in a physiological manner. In advanced disease stages, the dopamine release becomes synchronous with the peripheral LD bioavailability and plasma levels and leads to a pulsatile stimulation presumably underlying motor complications. The LD/carbidopa intraintestinal gel (LCIG) therapy bypasses the gastric emptying, provides a continuous LD delivery and a smoother plasma LD level with less fluctuations [11-13]. The coefficient of variation for the plasma concentration of LD is decreased by LCIG therapy as compared with oral therapy [11]. Dyskinesias are presumably diminished as a result of an effect on the central therapeutic window and not by a reduction of the LD concentration, since the daily total dose is not reduced as compared with the previous oral dose [14]. Clinical trials have shown the efficacy of LCIG therapy in reducing dyskinesias, motor fluctuations [15] and off-time [16-21]. Improvements were revealed in gait disorder [22,23] and some of the non-motor features of PD, such as sleep, fatigue, attention, memory and cardiovascular, gastrointestinal and urinary functions [17,22,23]. Non-motor symptoms, such as neuropsychiatric symptoms, sleep disturbances, autonomic symptoms and sensory symptoms, can occur at any stage of the disease and affect the quality of life. The role of dopaminergic pathology in the development of the non-motor symptoms has been revealed [24]. Some of the non-motor symptoms, such as depression, anhedonia,

Table 1. Symptoms of Parkinson's disease.

Motor symptoms
Bradykinesia/akinesia
Hypokinesia
Tremor
Postural instability
Gait disorder
Non-motor symptoms
Neuropsychiatric symptoms
Psychosis
Hallucinations
Delusions/illusions
Depression
Apathy
Fatigue
Anxiety
Cognitive impairment/dementia
Sleep disorders
REM sleep behavior disorder
RLS
Vivid dreaming
Insomnia
Excessive daytime somnolence
Autonomic symptoms
Drooling
Increased sweating
Gastrointestinal dysfunction
Delayed gastric emptying
Constipation
Bladder dysfunction
Urgency
Frequency
Orthostatic hypotension
Sexual dysfunction
Sensory symptoms
Anosmia
Pain
Paresthesia

REM: Rapid eye movement, RLS: Restless legs syndrome.

panic attacks related to *off* periods, restless legs syndrome, urinary urgency, nocturia, erectile impotence, constipation, fatigue and pain related to PD, are improved by the dopaminergic therapy, although most of the non-motor symptoms are unresponsive, exacerbated or induced by PD therapy [25]. The pulsatile dopaminergic stimulation is presumed to be responsible for the development of non-motor fluctuations, and a continuous dopaminergic stimulation might improve non-motor fluctuations [26].

Other drugs used in the treatment of PD are amantadine, which is valuable in the treatment of LID, and anticholinergics, which are beneficial in the treatment of PD-related tremor, but whose use is limited by their side effects [7].

3. MAO-B inhibitors

MAO-B is a key enzyme in the metabolism of dopamine in the brain. MAO-B inhibitors can be used as monotherapy in the earlier stages of the disease or as add-on therapy to LD in the more advanced stages. There is evidence of the role of a mitochondrial dysfunction and oxidative stress in the pathomechanism of genetic and sporadic forms of PD. A deficiency of complex I of the mitochondrial electron transport chain has been revealed in PD. The mitochondrial dysfunction is accompanied by the oxidative stress caused by reactive metabolites of dopamine and alterations in the levels of glutathione and iron in the SN [27]. The action of MAO-B is central to the processes involved in oxidative stress and oxidative damage in PD. MAO-B activates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to MPP+, enzymatically converts dopamine to hydrogen peroxide and activates other potential toxins, such as isoquinolines and β-carbolines. In animal models, MAO-B inhibitors prevent the formation of free radicals and prevent the oxidation of MPTP to MPP+ and thereby its neurotoxic effect, but no disease-modifying effect has been demonstrated for these compounds to date [28,29]. MAO-B inhibitors may protect against the generation of free radicals formed from the oxidation of dopamine. Selegiline may increase neurotrophic factor activity and may upregulate molecules which protect against oxidative stress and exerts an anti-apoptotic role, such as glutathione, superoxide dismutase, catalase and B-cell lymphoma-2 protein [30-32].

The selective irreversible MAO-B inhibitors selegiline and rasagiline reduce LD breakdown. A recent study evaluated the effect of long-term MAO-B inhibitor treatment with selegiline or rasagiline on MAO-A activity. Plasma samples were taken from PD patients on MAO-B inhibitor therapy, from PD patients without MAO-B inhibitor treatment and from healthy controls. A 70% reduction in MAO-A activity was detected *ex vivo* in PD patients on MAO-B inhibitor therapy as compared with the other two groups. No difference was detected between PD patients taking selegiline and rasagiline. The effect of selegiline on MAO-A activity *in vitro* was also evaluated by incubating human control standardized plasma samples with selegiline; the IC_{50} of selegiline was determined as 44 μM for MAO-A. The results were partially explained by pharmacokinetic considerations. About 4 h after the last medication intake, the plasma concentrations of selegiline and rasagiline were high enough to inhibit MAO-A activity. Long-term treatment with selegiline has previously been revealed to increase its $t_{1/2}$ and keep the concentration in a range high enough to inhibit MAO-A. The loss of specificity for MAO-B at higher concentrations and the inhibition of both isoenzymes may affect both the peripheral and the brain MAO. This results in a reduced breakdown of the neurotransmitter amines and might also reduce the synthesis of reactive oxygen species and other toxic compounds, but the role of the MAO-B/MAO-A interaction in the pathomechanism of PD and the possible neuroprotective effect of MAO-B inhibitors necessitate further investigations [33].

A large, multicenter, randomized, double-blind, placebo-controlled trial (DATATOP) proved that selegiline delayed the need for LD therapy in early PD [34], suggesting a

neuroprotective effect. The *post-hoc* analysis revealed the symptomatic effects of selegiline responsible for some of the beneficial effects and the long-term follow up of the patients showed that selegiline does not stop the disease progression [1]. The delayed start studies TEMPO and ADAGIO (a randomized, double-blind, placebo-controlled, delayed-start study to assess rasagiline as a disease modifying therapy in Parkinson's disease) showed that an early initiation of rasagiline therapy for early stage PD patients had a beneficial effect on the motor symptoms, which was preserved during the long-term follow up. In the ADAGIO study, patients were randomized to 1 or 2 mg/day of rasagiline or placebo for 9 months. In the second part of the study, all patients were treated with active medication for another 9 months. Patients originally randomized to rasagiline 1 mg/day demonstrated less progression of the clinical disability than those randomized to rasagiline after a delay of 9 months. The benefit was significant for the 1 mg/day dose but not for the 2 m/day dose [35-37].

In the LARGO and PRESTO trials for advanced-stage disease, the patients who received rasagiline exhibited a reduction of the *off* time, and significant improvements in the activities of daily living (ADL), and the motor subscores of the Unified Parkinson's Disease Rating Scale (UPDRS) and in the clinical global impression (CGI) scale score. A reduction of the daily dose of LD could also be achieved [38-40]. In a trial on early PD patients, rasagiline monotherapy provided benefits in the treatment of some of the non-motor symptoms [41]. A meta-analysis of the *Medline* and the *Cochrane Library* database showed that rasagiline as monotherapy reduces the motor scores in early PD, whereas as add-on therapy to LD, it reduces the *off* time in the more advanced stages of the disease [42].

4. Safinamide

Safinamide ((S)-(+)-2-[4-(fluorobenzyl) oxybenzyl]aminopropan amide methanesulfonate) is a water-soluble enantiomeric α-aminoamide derivative with a combined dopaminergic and non-dopaminergic mode of action (**Box 1**, for the chemical structure). It has been developed as antiepileptic medication. Milacemide was first shown to exhibit weak anticonvulsant activity and inhibition of MAO-A and -B [43-45]. New α-aminoamides have been developed, among which safinamide has been further investigated. Safinamide displays MAO-B inhibitory activity and a voltage-sensitive channel-blocking activity; its neuroprotective and neurorescuing properties have also been investigated. It can be used as add-on treatment to LD or a DAA and can improve motor symptoms [46,47] and some of the non-motor symptoms of PD [48]. Safinamide has completed the Phase III development program as add-on therapy to DAAs and to LD in patients with early and mid-to-late stage PD, respectively, and its beneficial effect on the motor symptoms of PD has been confirmed [49]. **Table 2** highlights the place of safinamide in the therapeutic spectrum of PD and **Table 3** presents some of the clinical trials conducted with safinamide in PD patients.

5. Pharmacokinetics of safinamide

Orally administered safinamide displays favorable pharmacokinetic properties, which are linearly and proportionally related to the administered dose [50]. The absorption is complete and reliable and is not appreciably influenced by food. The absolute bioavailability is high, at 95%. The pharmacokinetics is dose-proportional across the therapeutic dose range, with low intersubject variability. In a study of the pharmacokinetics of safinamide, administered as a single dose of 400 mg [^{14}C] safinamide methanesulfonate to healthy volunteers, maximum concentration was achieved at 1 h for the parent drug, at 7 h for the plasma and at 1.5 h for the whole-blood [^{14}C] radioactivity [51]. Its extravascular distribution is extensive, corresponding to the high lipophilicity. The plasma protein binding (92%) is apparently lower than the extravascular tissue binding [50,52]. Safinamide reaches high concentrations in the CNS [47].

The biotransformation of safinamide is considerable. About 1.5 and 7% is excreted in unchanged form in the feces and urine, respectively [52], which is indicative of the practically complete absorption of the drug and very little biliary excretion. The metabolism of safinamide has two principal routes. One metabolic route leads to a carboxylic acid metabolite (NW-1689) and presumably involves several enzymes, such as CYP enzymes, MAO-A and the aldehyde dehydrogenases. A CYP3A4 inhibitor (troleandromycin) exerted only a minimal effect on the clearance of safinamide *in vitro*. An investigation of the effects of another CYP3A4 inhibitor, ketoconazole, on the metabolic clearance of safinamide in healthy individuals in a monocentric, open-label, randomized, two-period crossover clinical trial showed that the CYP3A4--mediated metabolism did not significantly contribute to the metabolic clearance of safinamide *in vivo* [53]. The results also revealed that safinamide can be coadministered with potent CYP3A4 inhibitors without a requirement for dose adjustment. The other metabolic route is the direct amide hydrolysis of safinamide by amidases, leading to the metabolite safinamide acid (NW-1153). *In vivo* animal studies on rats, and *in vitro* studies on rat and human hepatocytes, suggested that NW-1153 is not a metabolic end product, but an intermediate converted to NW-1689.

The main circulating plasma metabolite of safinamide is NW-1689, which undergoes glucuronidation to become NW-1689 acyl glucuronide. The deaminated acid and the N-dealkylated acid have been identified as major metabolites in the plasma and urine. Other urinary metabolites identified in a more recent study are the β-glucuronide of the N-dealkylated acid, monohydroxy safinamide and minor urinary metabolites such as the glycine conjugate of the N-dealkylated acid and 2-(4-hydroxybenzylamino) propanamide [51].

Table 2. The place of safinamide in the treatment approaches of Parkinson's disease.

Dopaminergic therapy	Non-dopaminergic therapy
Levodopa	Anticholinergics
LCIG therapy	Benztropine
Dopamine agonists	Trihexyphenidyl
Pramipexole	Ethopromazine
Ropinirole	Antiglutamatergic agents
Apomorphine pump	Amantadine
MAO-B inhibitors	**Surgical approaches**
Rasagiline	DBS
Selegiline	Ablative surgery
Safinamide	Neural transplantation and gene therapy
Drugs tested for symptomatic, antidyskinetic and neuroprotective properties	
Adenosine A2A receptor antagonists	Istradefylline
Glutamate antagonists	Amantadine, kynurenines, safinamide
Glutamate receptor-related compounds	MGluR5 antagonists, MGluR4 agonists
Antiepileptic drugs with complex mechanism of action	Safinamide, zonisamide, levetiracetam
Vitamins	Folic acid, vitamin D
Antioxidants, scavenger of free radicals, compounds acting on mitochondria	Coenzyme Q10, creatine, inosine, vitamin E
Catecholamine reuptake inhibitor	
α2-adrenergic receptor antagonists	
Nicotine receptor agonist	
Serotonin modulators	
L-type Ca^{++} channel blocker	

DBS: Deep brain stimulation; LCIG: Levodopa-carbidopa intraintestinal gel; MAO: Monoamine oxidase.

The systemic clearance of safinamide is low and its terminal half-life is about 26 h [54]. In the case of the administration of radioactively labeled safinamide, the terminal half-life was 22 h for the unchanged drug and 80 h for the radioactivity. This permits a once-daily administration. A steady-state concentration is achieved on day 5 of the once-daily dosing treatment regimen [51].

Safinamide has proved to be safe and well tolerated. The vital signs and the biochemical analysis of the blood and urine showed no differences as compared with placebo. No difference in the pressor response to intravenous administration of safinamide was encountered in healthy volunteers relative to placebo administration [55,56].

6. Pharmacodynamics of safinamide

The precise mechanism through which safinamide improves the symptoms of PD is uncertain (**Figure 1**, for the effect of safinamide in PD). As mentioned earlier, safinamide has a combined dopaminergic and non-dopaminergic mechanism of action, including the selective and reversible inhibition of MAO-B, activity-dependent sodium channel antagonism and inhibition of glutamate release *in vitro*. The dopaminergic mode of action is through potent and highly selective reversible MAO-B inhibition, thereby enhancing the brain dopamine concentration [47,57].

The selectivity of safinamide for MAO-B has been shown to be 1000 times higher as compared with placebo. The selectivity of MAO-B over MAO-A is greater than in the cases of selegiline and rasagiline [47,50,52,58-60]. In the event of unspecific MAO inhibition, dietary amines enter the circulation, induce noradrenaline release from peripheral adrenergic neurons and cause a hypertensive response, the *cheese effect*. The high selectivity of safinamide for MAO-B makes no dietary restrictions necessary. Reversibility explained by noncovalent binding to the core of the enzyme has been demonstrated in *in vitro* experiments [61]. The reversibility of safinamide avoids potential drug interactions [56].

Studies of the pharmacokinetics and pharmacodynamics of safinamide in healthy volunteers showed that a relevant inhibition of MAO-B starts at a dose of 25 μg/kg and is dose-dependent and progressive, with full inhibition observed at a single dose > 600 μg/kg. No inhibition of MAO-A was observed. The inhibition of MAO-B was effective in a dose-related manner in the microgram per kilogram range and complete in the milligram/kilogram range. Safinamide inhibits the inactivation of both exogenous dopamine formed from LD and endogenous dopamine [50].

In clinical studies, elevation of the dose of safinamide administered above the dose providing complete MAO-B inhibition provides a further clinical improvement, suggesting that, besides MAO-B inhibition, safinamide also exhibits other modes of action. The non-dopaminergic mode of action occurs through the inhibition of glutamate release by blocking the activity of the voltage-dependent sodium channels [47,62,63]. Safinamide displays high affinity for sodium channel binding site II. Inhibition of the fast sodium channel is concentration- and state-dependent. Safinamide is more potent at depolarized membrane potentials, when most of the channels are inactivated, as compared with the resting potential, suggesting

Table 3. Clinical trials with safinamide.

Definition	Phase/type	Duration (months)	N	S dose (mg/day)	Characteristics	Outcome measures	Results (where available)
Safety and efficacy on motor function (Study 009) [69]	Phase III PC	3	172	70 (median)	Early PD: compared to placebo	Responder rate (responders: > 30% improvement in the UPDRS motor subscore compared to baseline) Decrease in UPDRS motor score Safety	37.5 versus 21.4% in the P group 3.3.
Efficacy and safety (Study 015, NCT00643045) [70,71]	Phase III PC	24 weeks	269	150 – 200 50 – 100	Early PD: add-on therapy to DA	Change in the UPDRS motor scores as compared to baseline	Improvement
Long-term efficacy and safety (Study 017, NCT00642889) [70,71]	Phase III R, DB, PC, preplanned	12	227	100 200	Early PD: Add-on therapy to a single stable dose of DA Extension of Study 015	The time from baseline to intervention (intervention: an increase in the DA dose, addition of another DA, addition of LD or other PD treatment or the discontinuation due to lack of efficacy) Intervention rate UPDRS motor scores Quality of life scores Safety	With 100 mg S: a delay in median time to intervention of 9 days (*post-hoc* analysis). The difference between the two S groups was not significant Significantly lower compared to P improvement No difference in the occurrence of adverse events between the active and the P groups.
MOTION (NCT00605683) [72]	Phase III R, DB, PC	24 weeks	679	50 100	Early PD: add-on therapy to DA	Change in mean UPDRS-section III value compared to baseline Change from baseline in the ADL, cognition, global clinical status, responder rates in motor function, health-related quality of life Safety	Significant improvement with 100 mg S Significant improvement S was well tolerated
Extension study (NCT01028586) [73]		78 weeks	507	50 100	Early PD: add-on therapy to DA	Time to intervention Intervention rate The change in UPDRS motor scores, ADL scores, the change in CGI, a change in quality of life and cognitive measures	Improvement
S-LID (NCT01113320) [75]	Phase II DB, PC, parallel-group, dose-escalation	10 weeks	26		Late PD: antidyskinetic effect	The maximum reduction in UDysRS compared to baseline The total *on* and *off* time as evaluated by the patient diaries The change in UPDRS scale and subscale values The change in the CGI	

See also text for references.

ADL: Activities of daily living; CGI: Clinical global impression; DA: Dopamine agonist; DB: Double-blind; DRS: Dyskinesia Rating Scale; LD: Levodopa; LID: Levodopa-induced dyskinesia; N: Number of patients enrolled; P: Placebo; PC: Placebo-controlled; PD: Parkinson's disease; R: Randomized; S: Safinamide; UDysRS: Unified Dyskinesia Rating Score; UPDRS: Unified Parkinson's Disease Rating Scale.

Table 3. Clinical trials with safinamide (continued).

Definition	Phase/type	Duration (months)	N	S dose (mg/day)	Characteristics	Outcome measures	Results (where available)
Short-term safety and efficacy of S (Study 016, NCT01187966) [76]	Phase III	6	669	50 100	Mid-to-late stage PD: add-on therapy to LD	Motor function The average amount of the *on* time with no dyskinesia or with minor dyskinesia The average duration of the *off* time compared to P	Significant improvement Increased Decreased
Long-term safety and efficacy of S. Extension of Study 016 (Study 018, NCT01286935) [76-79].	Phase III	18	544	50 100	Mid-to-late stage PD: add-on therapy to LD	The degree of improvement in the DRS scores during *on* time compared to the baseline values Patient diary analysis Duration of daily *on* time with no/minor dyskinesia Duration of the daily *off* time Motor scores, ADL scores and clinical status Safety	Significant improvement in patients with severe dyskinesia with 100 mg S (*post-hoc* analysis) Long-term improvement Increased Decreased Greater improvement in the 100 mg/day S group. Reduction of LD dose possible Few dropouts and no safety concerns
SETTLE efficacy and safety of S (NCT00627640) [80,81]	Phase III PC	24 weeks	549	50 100	Advanced PD: add-on therapy to a stable dose of LD and other antiparkinsonian drugs	Increase in mean *on* time without troublesome dyskinesia (patient diaries) Motor symptoms Decrease in *off* time, quality of life measures and CGI The *off*-time after the morning dose of LD Tolerability, safety	Significant improvement for both doses A significant improvement of > 30% Good
Long-term safety and tolerability of S (NCT00865579) [82]	Phase III, open-label	3 years			PD patients that have already completed a study with S	The physical and neurological condition Other safety parameters Quality of life measures	
Cognitive impairment associated with PD (NCT01211587) [83]	Phase II DB, PC, R, parallel group	24 weeks	103		Cognitively impaired, but non-demented PD patients	PD Cognitive Rating Scale and subscale scores Dementia Rating Scale-2 and subscale scores The CGI, the change in cognitive dysfunction Grid-Hamilton Depression Rating scale PD sleep scale apathy scale	

See also text for references.

ADL: Activities of daily living; CGI: Clinical global impression; DA: Dopamine agonist; DB: Double-blind; DRS: Dyskinesia Rating Scale; LD: Levodopa; LID: Levodopa-induced dyskinesia; N: Number of patients enrolled; P: Placebo; PC: Placebo-controlled; PD: Parkinson's disease; R: Randomized; S: Safinamide; UDysRS: Unified Dyskinesia Rating Score; UPDRS: Unified Parkinson's Disease Rating Scale.

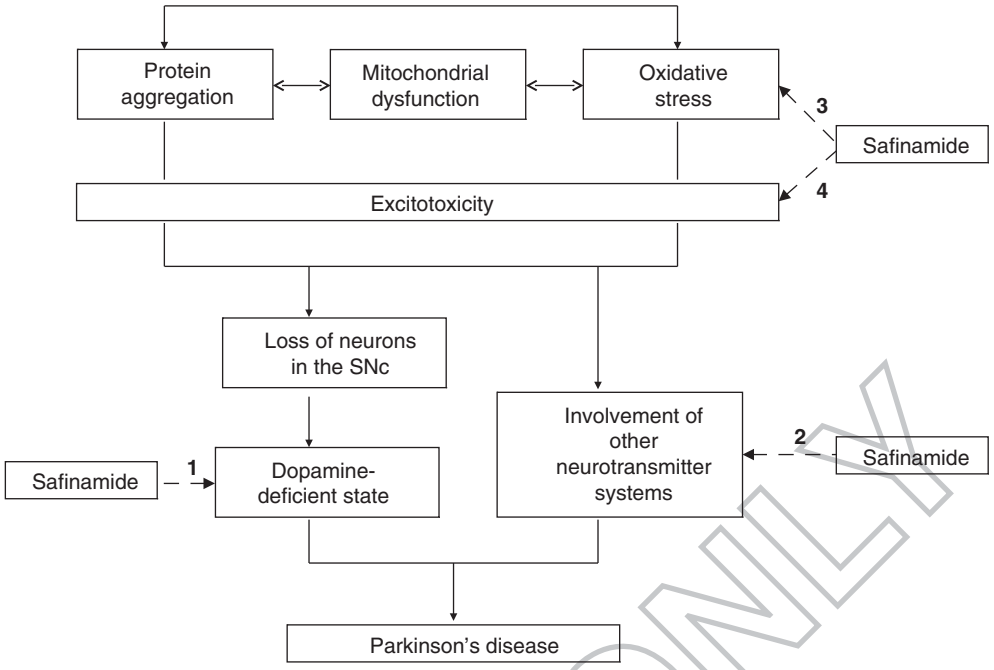


Figure 1. The effect of safinamide in the pathomechanism of PD is shown. Protein aggregation, oxidative stress, mitochondrial dysfunction and presumably the glutamate-induced excitotoxicity are major factors contributing to the pathology of PD. These factors cause the loss of pigmented neurons of the substantia nigra pars compacta leading to a dopamine-deficient state. The dopamine-deficient state, combined with the involvement of other neurotransmitter systems, is responsible for the development of the motor and non-motor symptoms of the disease. Safinamide improves the dopamine-deficient state through MAO-B inhibition (1) and improves the motor symptoms. It also exhibits an antiglutamatergic effect (2), which may be beneficial in the treatment of dyskinesia. Safinamide might also have a neuroprotective role; it may possibly also lower oxidative stress through MAO-B inhibition (3) and exert an anti-excitotoxic effect through glutamate inhibition (4).

PD: Parkinson's disease; MAO: Monoamine oxidase.

that safinamide preferentially interacts with the inactivated sodium channel. Safinamide keeps the sodium channels in an inactivated state and prevents their activation. The blockade is enhanced during high-frequency stimulation, when the channels are in an inactivated state. This suggests that safinamide leaves the physiological activity unaffected and depresses abnormal activity [47].

In rat cortical neurons, safinamide modulates N-type calcium channels and might therefore inhibit presynaptic neurotransmitter release. Safinamide inhibits glutamate release in animal models [47]. At high doses, safinamide inhibits dopamine uptake [52,64] and might also inhibit dopamine reuptake and enhance dopamine release [65]. Diminution of glutamate release may have a neuroprotective property [62].

The neuroprotective effect has been studied both in cell cultures and in animal models [58]. Safinamide prevents *in vitro* veratridine-induced neuronal cell death and protects the hippocampal neurons in rat from kainic acid-induced neuronal loss [47]. In MPTP-lesioned mice, pretreatment with safinamide prevented the forebrain dopamine depletion and neuronal death in the SN, an effect also exhibited by selegiline and rasagiline [66]. Treatment with safinamide after MPTP administration to black C57 mice led to a dose-dependent sparing of the dopaminergic neurons relative to the control [47]. In another experiment, safinamide administered 30 min prior to and after bilateral carotid artery occlusion in Mongolian gerbils resulted in complete prevention of the hippocampal neuronal damage [58].

The antidyskinetic effect of safinamide has been tested in MPTP-lesioned dyskinetic macaque monkey, in comparison with and in combination with amantadine. LID and Parkinsonian symptoms were measured and plasma levels of safinamide were monitored during the experiments. Two acute and one semi-chronic experiment were conducted. Safinamide pretreatment dose-dependently reduced the duration and the intensity of dyskinesia measured by the LID scores. An inverse correlation was found between the LID and the safinamide blood levels. Safinamide also prolonged the duration of the effect of LD as compared with amantadine, which, although reducing LID, also reduced the duration of the antiparkinsonian response to LD. When amantadine was added to safinamide, only a modest additional antidyskinetic effect was achieved and no reduction in the duration of the antiparkinsonian effect of LD was seen [67].

The tremorolytic action of safinamide has been investigated in animal models. Safinamide significantly reduced the tremulous jaw movements induced in rats by pilocarpine, pimozide and galantamine, supporting the efficacy of safinamide in Parkinsonian tremor [68].

7. Clinical trials with safinamide in PD

7.1 Clinical efficacy of safinamide as compared with placebo

The safety and efficacy of different doses of safinamide (0.5 or 1 mg/kg) on motor function were investigated in a 3-month placebo-controlled study (Study 009) on 172 early stage PD patients [69]. Those patients with a > 30% improvement in the UPDRS motor subscore relative to the baseline were defined as responders. The responder rate in the group on high-dose safinamide (median 70 mg/day) was 37.5%, which was significantly higher than that in the placebo group (21.4%). The decrease in UPDRS motor score was 3.3. The study also proved the safety of safinamide [70].

7.2 Safinamide as adjunct therapy to a DAA

Safinamide was the first medication tested in clinical trials as an adjunct to DAAs. In the subgroup of the patients enrolled in the above study who were on a stable dose of a single DAA, the patients receiving safinamide as an adjunct to a DAA exhibited a significantly better response as compared with placebo. A small open-label study led to the same result [65,70].

The efficacy and safety of a high (150 – 200 mg) and a low (50 – 100 mg) dose range of safinamide as add-on therapy to a single stable dose of DAA were evaluated in comparison with placebo in a study enrolling 269 patients (Study 015, NCT00643045). The primary end point was the change in the UPDRS motor scores relative to the baseline. The extension study (Study 017, NCT00642889) was a 12-month, randomized, double-blind, placebo-controlled preplanned study to evaluate the long-term efficacy and safety of safinamide as add-on therapy for early stage PD. A total of 227 patients were randomized to 100 or 200 mg/day safinamide or to placebo added to a DAA. The primary efficacy end point was the time from baseline to an increase in the DAA dose, addition of another DAA, addition of LD or other PD treatment (defined as intervention) or discontinuation due to the lack of efficacy. The treatment was well tolerated, with no difference in the occurrence of adverse events between the safinamide and the placebo groups. The median time to intervention for the pooled safinamide groups was 559 days, whereas in the placebo group it was 466 days, although the difference between the two groups did not reach statistical significance. Patients receiving 100 mg safinamide exhibited an intervention rate that was significantly lower than that of the placebo group and a delay of 9 days in the median time to intervention, as revealed by the *post-hoc* analysis [71]. The lower dose of safinamide added to the DAA resulted in a statistically significant improvement in UPDRS motor scores over the placebo group. A statistically significant improvement was also measured in the quality of life scores in the pooled dose group and in the individual dose groups [70].

MOTION (NCT00605683) was a 24-week, randomized, double-blind, placebo-controlled international Phase III clinical trial that investigated safinamide in early idiopathic PD as add-on therapy to a DAA. A total of 679 patients with a disease duration of < 5 years who had been on a stable dose of a single DAA for at least 4 weeks prior to enrolment were randomized to receive either 50 mg of safinamide, 100 mg of safinamide or placebo as add-on therapy. The primary end point was the change in the mean UPDRS-section III value relative to the baseline. The secondary outcome measures were the change from baseline to week 24 in the ADL, cognition, the health-related quality of life, the change in global clinical status and the responder rates in the motor function evaluation [72]. Safinamide was well tolerated, with adverse events such as nausea, dizziness, somnolence, headache and back pain reported. The dropout rate was about 11%, with 607 patients completing the trial. Safinamide 100 mg/day as add-on to DAA therapy significantly improved the UPDRS motor score and certain quality of life measures as compared with the placebo. The extension study (NCT01028586) enrolled 507 patients receiving 50 or 100 mg of safinamide or placebo for 78 weeks. The primary end point was the time to intervention, whereas the secondary end points were the proportion of patients requiring intervention, the change in UPDRS motor scores, the ADL scores, a change in the CGI and quality of life and cognitive measures [73].

Rasagiline was also investigated as add-on therapy to DAAs in early stage PD patients. ANDANTE was a Phase IV, 18-week, placebo-controlled, randomized, double-blind study (NCT01049984) to assess the efficacy and safety of rasagiline as add-on therapy to a single stable dose of a DAA (6 mg/day of ropinirole or 1 mg/day of pramipexole) in early stage PD patients, suboptimally controlled by the DAA. The primary outcome measure was a change in the total UPDRS score value, whereas the secondary outcome measures were the UPDRS subscore values and the CGI-I values. Of the 328 patients randomized, 321 were included in the analysis of the clinical efficacy. The results were presented at the MDS Congress in 2013; significant improvements in the UPDRS total score and motor subscore values were reported as compared with the placebo arm. No significant differences in the occurrence of adverse events were seen in the two study arms and only a few patients needed LD rescue therapy. The addition of rasagiline to a DAA significantly improves the motor function with a favorable adverse event profile [74].

7.3 Safinamide as adjunct therapy to LD

The potential antidyskinetic properties of safinamide were explored in clinical trials on PD patients suffering from LID. A total of 26 patients were enrolled in a Phase II, double-blind, placebo-controlled, parallel-group, dose-escalation

trial (Safinamide-LID, NCT01113320). The primary outcome measure was the maximum reduction in Unified Dyskinesia Rating Score compared to the baseline. Secondary end points were the total *on* and *off* times as evaluated by the patient diaries and the changes in the UPDRS scale and subscale scores and in the CGI [75].

Study 016 (NCT01187966) and its extension study (Study 018, NCT01286935) evaluated the short- and the long-term safety and efficacy of safinamide as add-on therapy to LD in patients with mid-to-late stage PD. The 24-month data were presented in 2011 at the poster session of the AAN meeting [76]. In Study 016, 669 patients with idiopathic PD on a stable dose of LD therapy were randomized to receive 50 mg/day of safinamide (223 patients), 100 mg/day of safinamide (224 patients) or placebo (222 patients) for 6 months. The 6-month treatment with safinamide (50 or 100 mg/day) significantly improved the motor function, increased the average duration of the *on* time with no dyskinesia or with minor dyskinesia and decreased the average duration of the *off* time relative to the placebo. Patients who completed the 24-week trial could continue the treatment in the extension study (544 patients). Changes in the LD dose and treatment with other PD medication except a MAO-B inhibitor, were allowed. The primary end point was the degree of improvement in the Dyskinesia Rating Scale (DRS) scores during the *on* time as compared with the baseline value. At 2 years, the differences seen in the DRS scores for the 50 mg/day and the 100 mg/day safinamide groups were not significant, but the *post-hoc* analysis of the 100 mg/day safinamide subgroup with severe dyskinesia (DRS scores > 4 at baseline) demonstrated a significant improvement in the DRS scores ($p = 0.03$). Patient diary analysis showed that the improvement reported at 6 months was still present after 2 years of therapy. An increase in the daily *on* time with no/minor dyskinesia and a decrease in the daily *off* time were reported. Overall, the improvement was greater in the 100 mg/day safinamide group for the motor scores, ADL scores and clinical status. These patients were more likely to achieve a reduced LD dose than the patients from the other groups. There were few dropouts and no safety concerns emerged [76-79].

The SETTLE trial (NCT00627640) evaluated the efficacy and safety of two different doses of safinamide (50 – 100 mg) as compared with placebo as add-on therapy to a stable dose of LD and other anti-Parkinson drugs (DAAs, anticholinergics, amantadine and/or COMT inhibitors) over 24 weeks in 549 subjects with advanced PD. The principal end point was the increase in mean *on* time without troublesome dyskinesia, as recorded in the patient diaries. A significant benefit of both doses of safinamide over placebo was revealed, with a significant improvement of > 1 h in the *on* time as reported by the patient diaries and the caregiver and a 30% or more improvement in the motor symptoms ($p = 0.018$). Benefits were observed in the *off* time, in the quality of life measures (39-Item Parkinson's Disease Questionnaire [PDQ-39] and EQ-5D), in the CGI of severity and change and also in the *off* time after the morning dose of LD. The onset of the effect was rapid: improvements in both the *on* time and the *off* time were observed from week 2 onward. Tolerability was good and 484 patients completed the trial. No relevant changes were detected in vital signs, laboratory results, ECG or ophthalmological examinations. Adverse events such as nausea, urinary tract infections, falls, back pain and dyskinesia were reported. Transient mild dyskinesia occurred more frequently with safinamide but did not lead to discontinuation of the study. No increase in troublesome dyskinesia was observed [80,81].

An open-label trial (NCT00865579) is currently evaluating the long-term safety and tolerability of safinamide in PD patients who have already completed a previous study with safinamide. The physical and neurological condition together with other safety parameters, such as vital signs, laboratory evaluations, ECG and quality of life measures were compared at different visits with the baseline [82].

7.4 Safinamide for PD-associated cognitive impairment

In order to explore the potential benefit of safinamide on cognitive impairment associated with PD 103, cognitively impaired, but non-demented PD patients were enrolled in a double-blind, randomized, placebo-controlled, parallel group Phase II clinical trial (NCT01211587). The primary outcome measures were the PD Cognitive Rating Scale and subscale scores, DRS-2 and subscale scores, the CGI change in cognitive dysfunction, the Grid-Hamilton Depression Rating scale, the PD sleep scale and the apathy scale scores [83].

8. Safety and tolerability issues

In the clinical studies detailed above, the tolerability proved to be good. The clinical trials were accompanied by a dropout rate of only about 11%. No relevant changes in vital signs, laboratory results, ECG or other examinations occurred. Adverse events such as nausea, dizziness, falls, somnolence, headache, back pain, urinary tract infections and transient mild dyskinesia were reported [73,80,81].

9. Regulatory affairs

The results of the SETTLE and MOTION trials were presented at the AAN, MDPD and MDS conferences. The Newron Company has started meetings with the European health authorities to discuss the results of the preclinical and clinical trials in order to achieve support for the registration of safinamide as an add-on therapy to DAAs in early stage PD and to LD in advanced stage PD. Additional discussions with European health authorities, EMA and FDA for European and US approval and the regulatory submission were planned for QIV/2013 [84].

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10. Conclusion

The α-aminoamide derivative safinamide exhibits both a dopaminergic and a non-dopaminergic mode of action. It is a potent selective and reversible MAO-B inhibitor, a sodium-channel antagonist and an inhibitor of glutamate release. Safinamide has a dose-dependent, dose-proportional and linear favorable pharmacokinetic profile. Its biotransformation is extensive. It does not interact with CYP. Safinamide is well tolerated, with few side effects.

Safinamide was investigated in Phase III clinical trials as adjunct therapy to DAAs for patients with early stage PD and to LD therapy for patients in the mid-to-late stages of PD. The results from the MOTION and SETTLE studies confirmed that safinamide comprises effective add-on therapy to DAAs in early stage PD patients and to LD in mid-to-late stage PD. Safinamide significantly improved the motor function, as assessed by the UPDRS motor score in the MOTION study and improved the motor fluctuation assessed by the *on* time without troublesome dyskinesia in mid-to-late stage PD patients in the SETTLE study. In the Phase III trials, significant improvements in the quality of life, assessed by the PDQ-39 test and/or by the EQ-5D scale were seen. **Box 1** presents the main characteristics of safinamide.

11. Expert opinion

The cause of PD is multifactorial and the pathomechanism of the disease is not completely understood. There are many unmet needs of PD patients, such as the suitable treatment of many of the non-motor symptoms and a neuroprotective therapy capable of protecting the dopaminergic neurons from premature death. LD is still the best symptomatic treatment available, capable of alleviating the motor symptoms of the disease. The MAO-B inhibitors provide a lower symptomatic effect on motor symptoms as compared with LD. Besides an effect on motor symptoms, the delayed-start studies suggest disease-modifying properties of the MAO-B inhibitors. As compared with the other compounds in this class of medication, safinamide bears a more favorable pharmacokinetic profile and complex pharmacodynamic properties.

Safinamide is a unique compound exhibiting a combined non-dopaminergic and dopaminergic mode of action. It is a reversible MAO-B inhibitor, with a higher selectivity for MAO-B than for MAO-A, this selectivity being greater than in the cases of the other compounds available in this class of medications. It also inhibits the voltage-sensitive sodium channels and modulates the N-type calcium channels.

The symptomatic effect of safinamide has not yet been compared with those of other MAO-B inhibitors. The MOTION study that investigated safinamide as an add-on therapy to DAAs in early stage PD patients revealed positive outcomes in the *post-hoc* analysis for those patients taking 100 mg of safinamide. Rasagiline as add-on therapy to DAAs (ropinirole or pramipexole) showed more pronounced outcomes in the ANDANTE study. However, the results cannot be compared, due to the different inclusion criteria. The results suggest that the combination of a DAA with a MAO-B inhibitor delays the need for LD. Besides the symptomatic effect on the motor function, already confirmed in clinical trials, a tremorolytic, an antidyskinetic and presumably a neuroprotective effect could be further explored. Further trials are needed to assess the effects of safinamide on LD-induced fluctuations and dyskinesias as compared with placebo, amantadine and COMT inhibitors. In view of the various mechanisms involved in PD pathology, a compound combining favorable effects on dopaminergic and non-dopaminergic, glutamatergic neurotransmission might well have manifold effects in the treatment of PD.

The important roles played by glutamate in neurotoxicity and by glutamate antagonists in neuroprotection have been demonstrated in several animal models of PD and of other neurodegenerative disorders. Neuroactive kynurenines with an antiglutamatergic effect are also investigated in this respect [85-90]. Safinamide-induced neuroprotection has been investigated in animal models (MPTP-treated mice, a rat kainic acid model and a gerbil ischemia model) and neuroprotective and neurorescuing effects have been revealed. Further research is necessary to investigate the potential neuroprotective effect of safinamide in PD patients.

The place of safinamide in the therapy of PD is yet to be determined. The favorable pharmacokinetic and side-effect profile and the possibility that the LD dose can be reduced when safinamide is added together with the presumed neuroprotective properties outlined above suggest that safinamide is a valuable compound in the treatment of PD. It may serve as the first line of add-on therapy to DAA and LD in the early and the mid-to-late stage disease, respectively.

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Declaration of interest

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Drug Evaluation~~: US Spelling~~
neurology

Safinamide for the treatment of Parkinson's disease

Safinamide

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Introduction:

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta. Non-dopaminergic neurotransmitter systems are also involved in its pathomechanism. The aim of the treatment is to improve the dopamine-deficient state and to alleviate the motor and the non-motor symptoms. Safinamide is an α~~alfa~~-aminoamide derivative with a combined, dopaminergic and non-dopaminergic mode of action. Phase III clinical trials with safinamide, as add-on therapy to a dopamine agonist (DAA) and to levodopa (LD) in early and advanced- stage PD, respectively, demonstrated an improvement of the motor symptoms.

Areas covered:

The review discusses the pharmacokinetic and pharmacodynamic properties of safinamide and provides an overview of the clinical trials conducted with safinamide in PD. A literature search was made in PubMed for safinamide, safinamide pharmacokinetics, PD treatment and monoamine oxidase~~MAO~~-B inhibitors, and in PubMed and on the ClinicalTrials.gov site for clinical trials with safinamide in PD.

Expert opinion:

The place of safinamide in the therapy of PD is yet to be determined. However, the authors believe that safinamide is a valuable drug in the treatment of PD treatment with favorable pharmacokinetic and side-effect profiles. Data ~~suggests~~ so far suggest that it can be used beneficially as add-on therapy both to DAAs~~dopamine agonists~~ in early PD and to LD~~levodopa~~ in the later stages of the disease.

Keywords: dopaminergic, monoamine oxidase-B inhibitors, non-dopaminergic, Parkinson's disease, safinamide

ADAGIO a randomized, double-blind, placebo-controlled, delayed-start study to assess rasagiline as a disease modifying therapy in Parkinson's disease

ADL activities of daily living

ANDANTE Rasagiline as add-on to dopamine agonists in the treatment of Parkinson's Disease trial

BBB blood–brain barrier

CGI clinical global impression

COMT catechol-*O*-methyl transferase

CYP450 cytochrome P450

DA dopamine agonists

DRS Dyskinesia Rating Scale

EQ-5D European Quality of life scale (EuroQoL)

LARGO Lasting effect in Adjunct therapy with Rasagiline Given Once daily

LCIG levodopa-carbidopa intra-intestinal gel

LD levodopa

LID levodopa-induced dyskinesia

MAOB monoamine oxyidase B

MOTION SafinaMide add-On To dopamine agonist for early Idiopathic ParkinsON's disease with motor fluctuations

MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

PD Parkinson's disease

PDQ-39 39-Item Parkinson's Disease Questionnaire

PRESTO Parkinson's Rasagiline: Efficacy and Safety in the Treatment of "OFF"

REM rapid eye movement

RLS restless legs syndrome

ROS reactive oxygen species

SETTLE SafinamidE Treatment as add-on To LEvodopa in idiopathic Parkinson's disease with motor fluctuations

SN substantia nigra

TEMPO TVP-1012 (an early name for rasagiline) in Early Monotherapy for Parkinson's Disease Outpatients

UDysRS Unified Dyskinesia Rating Scale

UPDRS unified Parkinson's disease rating scale

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder with a frequency that increases with age. The cause of the neurodegenerative process in PD is not known; several mechanisms are involved in its development, including oxidative stress, inflammatory changes, proteosomal dysfunction and mitochondrial dysfunction [1,2,3]. The pathogenetic changes include the loss of dopaminergic neurons in the substantia nigra (SN) pars compacta and the appearance of Lewy bodies within the pigmented neurons of the SN~~substantia nigra~~. It is presumed that motor symptoms occur at a loss of about 60~~-~~ – 80% of the dopaminergic neurons ~~of~~ in the SN~~substantia nigra~~. Non-dopaminergic neurotransmitter systems, such as the serotonergic, the cholinergic, the adrenergic and glutamatergic, are also involved in the pathomechanism of the disease [4]. Besides the motor symptoms related to the dopamine-deficient state, non-motor symptoms can occur, even in the early stages of the disease, and impair the quality of life of the patients [5]. PD symptoms are summarized in Table 1.

2. Treatment approaches in PD

The treatments available at present mainly improve the motor symptoms caused by the dopaminergic loss. This can be achieved by supplying the dopamine precursor levodopa (LD) to increase the synthesis of dopamine, by stimulating the dopamine receptors or by acting on the metabolism of dopamine. As a result of the improving understanding[AuQ1] of the complex pathomechanism of the disease, treatment has ~~focused~~ recently focused on non-dopaminergic medication ~~investigated~~ for the treatment of the motor and non-motor symptoms and for alleviation of the dyskinesia. Effective neuroprotective therapy~~,~~ that is capable of halting the disease progression~~,~~ is not available [1,6,7].

The gold standard of the symptomatic treatment of the disease is LD~~levodopa~~ therapy. LD~~evodopa~~, a dopamine precursor capable of crossing the blood–brain barrier, is taken up by

the dopaminergic neurons and is decarboxylated to dopamine presynaptically in the basal ganglia. The peripheral metabolism responsible for the side- effects is reduced by a peripheral decarboxylase inhibitor. In the first few months or years of LD~~levodopa~~ therapy, a stable improvement of the motor symptoms can be seen. In time, however, the effect of LD~~levodopa~~ wears off a few hours after LD~~levodopa~~ intake. Later, *on* and *off* motor fluctuations occur, related to the fluctuations of the peripheral LD~~levodopa~~ concentration~~,~~ but not correlated to the medication intake in the late stages of the disease. The progressive decrease in the number of dopaminergic neurons in the SN~~substantia nigra~~ results in an inability of the striatum to buffer the variability in the brain dopamine concentrations caused by a short-acting dopaminergic agent. Oral substitution therapy is considered to cause a pulsatile stimulation of the dopamine receptors, which in turn is considered to underlie the development of motor fluctuations and ~~levodopa~~LD-induced dyskinesia (LID). A continuous stimulation of the dopaminergic receptors presumably causes less fluctuation and dyskinesia [8,9]. The dopamine agonists (DAAs) have longer half-lives than that of LD~~levodopa,~~ but provide less symptomatic effect. The cat~~h~~echol-*O*-methyl transferase (COMT) inhibitors and the monoamine- oxidase (MAO) inhibitors are dopaminergic agents which inhibit the dopamine metabolizing enzymes. The COMT inhibitors increase the bioavailability and the half-life of LD~~levodopa~~ and reduce the fluctuations of plasma LD~~levodopa~~. COMT inhibitors are recommended for patients who exhibit the *wearing-off* phenomenon [5], as they improve and may also prevent the onset of *wearing-off*. In the STRIDE-PD study, the addition of the COMT inhibitor entacapone to LD~~levodopa~~ resulted in earlier and more dyskinesia as compared with ~~levodopa~~LD/carbidopa alone [10].

Alt~~T~~hough LD~~levodopa~~ has a short half-life, in the early stages of disease, the presynaptic terminals are capable of storing dopamine and releasing it in a physiological manner. In advanced disease stages, the dopamine release becomes synchronous with the peripheral

LDlevodopa bioavailability and plasma levels and leads to a pulsatile stimulation presumably underlying motor complications. The levodopaLD/carbidopa intraintestinal gel (LCIG) therapy by-passes the gastric emptying, provides a continuous LDlevodopa delivery and a smoother plasma LDlevodopa level with less fluctuations [11,12,13]. The coefficient of variation for the plasma concentration of LDlevodopa is decreased by LCIG therapy as compared with oral therapy [11]. Dyskinesias are presumably diminished as a result of an effect on the central therapeutic window and not by a reduction of the LDlevodopa concentration, since the daily total dose is not reduced as compared with the previous oral dose [14]. Clinical trials have shown the efficacy of LCIG therapy in reducing dyskinesias, motor fluctuations [15] and off-time [16,17,18,19,20,21]. Improvements were revealed in gait disorder [22,23] and some of the non-motor features of PD, such as sleep, fatigue, attention, memory and cardiovascular, gastrointestinal and urinary functions [17,22,23]. Non-motor symptoms, such as neuropsychiatric symptoms, sleep disturbances, autonomic symptoms and sensory symptoms, can occur at any stage of the disease and affect the quality of life. The role of dopaminergic pathology in the development of the non-motor symptoms has been revealed [24]. Some of the non-motor symptoms, such as depression, anhedonia, panic attacks related to *off* periods, restless legs syndrome, urinary urgency, nocturia, erectile impotence, constipation, fatigue and pain related to PD, are improved by the dopaminergic therapy, although most of the non-motor symptoms are unresponsive, exacerbated or induced by PD therapy [25]. The pulsatile dopaminergic stimulation is presumed to be responsible for the development of non-motor fluctuations, and a continuous dopaminergic stimulation might improve non-motor fluctuations [26].

Other drugs used in the treatment of PD are amantadine, which is valuable in the treatment of LID, and anticholinergics, which are beneficial in the treatment of PD-related tremor, but whose use is limited by their side- effects [7].

3. MAO-B inhibitors

MAO-B is a key enzyme in the metabolism of dopamine in the brain. MAO-B inhibitors can be used as monotherapy in the earlier stages of the disease or as add-on therapy to LD~~levodopa~~ in the more advanced stages. There is evidence of the role of a mitochondrial dysfunction and oxidative stress in the pathomechanism of genetic and sporadic forms of PD. A deficiency of complex I of the mitochondrial electron transport chain has been revealed in PD. The mitochondrial dysfunction is accompanied by the oxidative stress caused by reactive metabolites of dopamine and alterations in the levels of glutathione and iron in the SN~~substantia nigra~~ [27]. The action of MAO-B is central to the processes involved in oxidative stress and oxidative damage in PD. MAO-B activates 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to MPP+, enzymatically converts dopamine to hydrogen peroxide and activates other potential toxins, such as isoquinolines and β~~beta~~-carbolines. In animal models, MAO-B inhibitors prevent the formation of free radicals~~,~~ and prevent the oxidation of ~~1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (~~MPTP~~)~~ to MPP+ and there~~fore~~by its neurotoxic effect, but no disease-modifying effect has been demonstrated for these compounds to date [28,29]. MAO-B inhibitors may protect against the generation of free radicals formed from the oxidation of dopamine. Selegiline may increase neurotrophic factor[AuQ2] activity and may upregulate molecules which protect against oxidative stress and exerts an anti-apoptotic role, such as glutathione, superoxide dismutase~~SOD~~, catalase~~,~~ and B-cell lymphoma~~CL~~-2 protein [30,31,32].

The selective irreversible MAO-B inhibitors selegiline and rasagiline reduce LDlevodopa breakdown. A recent study evaluated the effect of long-term MAO-B inhibitor treatment with selegiline or rasagiline on MAO-A activity. Plasma samples were taken from PD patients on MAO-B inhibitor therapy, from PD patients without MAO-B inhibitor treatment and from healthy controls. A 70% reduction in MAO-A activity was detected *ex vivo* in PD patients on MAO-B inhibitor therapy as compared with the other two groups. No difference was detected between PD patients taking selegiline and rasagiline. The effect of selegiline on MAO-A activity *in vitro* was also evaluated by incubating human control standardized plasma samples with selegiline; the IC_{50} of selegiline was determined as 44 µM for MAO-A. The results were partially explained by pharmacokinetic considerations. About 4 h after the last medication intake, the plasma concentrations of selegiline and rasagiline were high enough to inhibit MAO-A activity. Long-term treatment with selegiline has previously been revealed to increase its Tt$_{1/2}$ and keep the concentration in a range high enough to inhibit MAO-A. The loss of specificity for MAO-B at higher concentrations and the inhibition of both isoenzymes may affect both the peripheral and the brain MAO. This results in a reduced breakdown of the neurotransmitter amines and might also reduce the synthesis of reactive oxygen speciesROS and other toxic compounds, but the role of the MAO-B/MAO-A interaction in the pathomechanism of PD and the possible neuroprotective effect of MAO-B inhibitors neceessitate further investigations 33.

A large, multicenter, randomized, double-blind, placebo-controlled trial (DATATOP) proved that selegiline delayed the need for LDlevodopa therapy in early PD 34, suggesting a neuroprotective effect. The *post–hoc* analysis revealed the symptomatic effects of selegiline responsible for some of the beneficial effects and the long-term follow- up of the patients showed that selegiline does not stop the disease progression 1. The delayed start studies TEMPO and ADAGIO (a randomized, double-blind, placebo-controlled, delayed-start study

to assess rasagiline as a disease modifying therapy in Parkinson's disease) showed that an early initiation of rasagiline therapy for early- stage PD patients had a beneficial effect on the motor symptoms, which was preserved during the long-term follow- up. In the ADAGIO study, patients were randomized to 1 or 2 mg/day of rasagiline or placebo for 9 months. In the second part of the study, all patients were treated with active medication for another 9 months. Patients originally randomized to rasagiline 1 mg/day demonstrated less progression of the clinical disability than those randomized to rasagiline after a delay of 9 months. The benefit was significant for the 1 mg/day dose, but not for the 2 m/day dose [35,36,37].

In the LARGO and PRESTO trials for advanced-stage disease, the patients who received rasagiline exhibited a reduction of the *off* time, and significant improvements in the activities of daily living (ADL), and the motor subscores of the Unified Parkinson's dDisease rRating sScale (UPDRS) and in the clinical global impression (CGI) scale score. A reduction of the daily dose of LDlevodopa could also be achieved [38,39,40]. In a trial on early PD patients, rasagiline monotherapy provided benefits in the treatment of some of the non-motor symptoms [41]. A meta-analysis of the *Medline* and the *Cochrane Library* database showed that rasagiline as monotherapy reduces the motor scores in early PD, whereasile as add-on therapy to LDlevodopa, it reduces the *off* time in the more advanced stages of the disease [42].

4. Safinamide

Safinamide ((S)-(+)-2-[4-(fluorobenzyl) oxybenzyl]aminopropan amide methanesulfonate) is a water-soluble enantiomeric αalfa-aminoamide derivative with a combined dopaminergic and non-dopaminergic mode of action (Box 1, for the chemical structure). It has been developed as antiepileptic medication. Milacemide was first shown to exhibit weak anticonvulsant activity and inhibition of MAO-A and -B [43,44,45]. New αalfa-amino-amides have been developed, among which safinamide has been further investigated. Safinamide displays

MAO-B inhibitory activity and a voltage-sensitive channel-blocking activity; its neuroprotective and neurorescuing properties have also been investigated. It can be used as add-on treatment to LD~~levodopa~~ or a DAA and can improve motor symptoms [46,47] and some of the non-motor symptoms of PD [48]. Safinamide has completed the Phase III development program as add-on therapy to DAAs and to LD~~levodopa~~ in patients with early and mid-~~-~~to-~~-~~late-~~-~~stage PD, respectively, and its beneficial effect on the motor symptoms of PD has been confirmed [49]. Table 2 highlights the place of safinamide in the therapeutic spectrum of PD and Table 3 presents some of the clinical trials conducted with safinamide in PD patients.

5. Pharmacokinetics of safinamide

Orally administered safinamide displays favorable pharmacokinetic properties, which are linearly and proportionally related to the administered dose [50]. The absorption is complete and reliable and is not appreciably influenced by food. The absolute bioavailability is high, at 95%. The pharmacokinetics is dose-proportional across the therapeutic dose range, with low inter-subject variability. In a study of the pharma~~k~~cokinetics of safinamide, administered as a single dose of 400 mg [^{14}C] safinamide methanesulfonate to healthy volunteers, maximum concentration was achieved at 1 h for the parent drug, at 7 h for the plasma and at 1.5 h for the whole-blood [^{14}C] radioactivity [51]. Its extravascular distribution is extensive, corresponding to the high lipophilicity. The plasma protein binding (92%) is apparently lower than the extravascular tissue binding [50,52]. Safinamide reaches high concentrations in the CNS [47].

The biotransformation of safinamide is considerable. About 1.5~~%~~ and 7% is excreted in unchanged form in the feces and urine, respectively [52], which is indicative of the practically complete absorption of the drug and very little biliary excretion. The metabolism of

safinamide has two principal routes. One metabolic route leads to a carboxylic acid metabolite (NW-1689) and presumably involves several enzymes, such as CYP~~cytochrome P450~~ enzymes, MAO-A and the aldehyde dehydrogenases. A CYP3A4 inhibitor (troleandromycin) exerted only a minimal effect on the clearance of safinamide *in vitro*. An investigation of the effects of another CYP3A4 inhibitor, ketoconazole, on the metabolic clearance of safinamide in healthy individuals in a monocentric, open-label, randomized, two-period cross-over clinical trial showed that the CYP3A4-mediated metabolism did not ~~contribute~~ significantly contribute to the metabolic clearance of safinamide *in vivo* 53. The results also revealed that safinamide can be co-administered with potent CYP3A4 inhibitors without a requirement for dose adjustment. The other metabolic route is the direct amide hydrolysis of safinamide by amidases, leading to the metabolite safinamide acid (NW-1153). *In vivo* animal studies on rats, and *in vitro* studies on rat and human hepatocytes, suggested that NW-1153 is not a metabolic end- product, but an intermediate~~,~~ converted to NW-1689.

The main circulating plasma metabolite[AuQ3] of safinamide is NW-1689, which undergoes glucuronidation to become NW-1689 acyl glucuronide. The deaminated acid and the N-dealkylated acid have been identified as major metabolites in the plasma and urine. Other urinary metabolites identified in a more recent study are the ~~beta~~β-glucuronide of the N-dealkylated acid, monohydroxy safinamide and minor urinary metabolites such as the glycine conjugate of the N-dealkylated acid and 2-(4-hydroxybenzylamino)propanamide 51.

The systemic clearance of safinamide[AuQ4] is low and its~~. The~~ terminal half-life is about 26 h 54. In the case of the administration of radioactively labeled safinamide, the terminal half-life was 22 h for the unchanged drug and 80 h for the radioactivity. This permits a once-~~-~~daily administration. A steady-state concentration is achieved on day 5 of the once-~~-~~daily dosing treatment regimen 51.

Safinamide has proved to be safe and well tolerated. The vital signs and the biochemical analysis of the blood and urine showed no differences as compared with placebo. No difference in the pressor response to intravenous administration of safinamide was encountered in healthy volunteers relative to placebo administration [55,56].

6. Pharmacodynamics of safinamide

The precise mechanism through which safinamide improves the symptoms of PD is uncertain (Figure 1, for the effect of safinamide in PD). As mentioned earlier, safinamide has a combined dopaminergic and non-dopaminergic mechanism of action, including the selective and reversible inhibition of MAO-B, activity-dependent sodium channel antagonism and inhibition of glutamate release *in vitro*. The dopaminergic mode of action is through potent and highly selective reversible MAO-B inhibition, thereby enhancing the brain dopamine concentration [47,57].

The selectivity of safinamide for MAO-B has been shown to be 1000 times higher as compared with placebo. The selectivity ~~for~~ of MAO-B over MAO-A is greater than in the cases of selegiline and rasagiline [47,50,52,58,59,60]. In the event of unspecific MAO inhibition, dietary amines enter the circulation, induce noradrenaline release from peripheral adrenergic neurons and cause a hypertensive response, the *cheese effect*. The high selectivity of safinamide for MAO-B makes no dietary restrictions necessary. Reversibility explained by non-covalent binding to the core of the enzyme has been demonstrated in *in vitro* experiments [61]. The reversibility of safinamide avoids potential drug interactions [56].

Studies of the pharmacokinetics and pharmacodynamics of safinamide in healthy volunteers showed that a relevant inhibition of MAO-B starts at a dose of 25 µg/kg and is dose-dependent and progressive, with full inhibition observed at a single dose ~~higher than~~ ≥ 600

µg/kg. No inhibition of MAO-A was observed. The inhibition of MAO-B was effective in a dose-related manner in the microgram per kilogram~~µg/kg~~ range and complete in the milligram/kilogram range. Safinamide inhibits the inactivation of both exogenous dopamine formed from LD~~levodopa~~ and endogenous dopamine [50].

In clinical studies, elevation of the dose of safinamide administered above the dose providing complete MAO-B inhibition provides a further clinical improvement, suggesting that, besides MAO-B inhibition, safinamide also exhibits other modes of action. The non-dopaminergic mode of action occurs through the inhibition of glutamate release by blocking the activity of the voltage-dependent sodium channels [47,62,63]. Safinamide displays high affinity for sodium channel binding site II. Inhibition of the fast sodium channel is concentration- and state-dependent. Safinamide is more potent at depolarized membrane potentials, when most of the channels are inactivated, as compared with the resting potential, suggesting that safinamide preferentially interacts with the inactivated sodium channel. Safinamide keeps the sodium channels in an inactivated state and prevents their activation. The blockade is enhanced during high-frequency stimulation, when the channels are in an inactivated state. This suggests that safinamide leaves the physiological activity unaffected and depresses abnormal activity [47].

In rat cortical neurons, safinamide modulates N-type calcium channels and might therefore inhibit presynaptic neurotransmitter release. Safinamide inhibits glutamate release in animal models [47]. At high doses, safinamide inhibits dopamine uptake [52,64] and might also inhibit dopamine reuptake and enhance dopamine release [65]. Diminution of glutamate release may have a neuroprotective property [62].

The neuroprotective effect has been studied both in cell cultures and in animal models [58]. Safinamide prevents *in vitro* veratridine-induced neuronal cell death and protects the

hippocampal neurons in rat from kainic acid-induced neuronal loss 47. In MPTP-lesioned mice, pretreatment with safinamide prevented the forebrain dopamine depletion and neuronal death in the SN~~substantia nigra~~, an effect also exhibited by selegiline and rasagiline 66. Treatment with safinamide after MPTP administration to black C57 mice led to a dose-dependent sparing of the dopaminergic neurons relative to the control 47. In another experiment, safinamide administered 30 min prior to and after bilateral carotid artery occlusion in Mongolian gerbils resulted in complete prevention of the hippocampal neuronal damage 58.

The antidyskinetic effect of safinamide has been tested in MPTP-lesioned dyskinetic macaque monkey, in comparison with and in combination with amantadine. LID and ~~p~~Parkinsonian symptoms were measured and plasma levels of safinamide were monitored during the experiments. Two acute and one semi-chronic experiment were conducted. Safinamide pretreatment dose-dependently reduced the duration and the intensity of dyskinesia measured by the LID scores. An inverse correlation was found between the LID and the safinamide blood levels. Safinamide also prolonged the duration of the effect of LD~~levodopa~~ as compared with amantadine, which, although reducing LID, also reduced the duration of the antiparkinsonian response to LD~~levodopa~~. When amantadine was added to safinamide, only a modest additional antidyskinetic effect was achieved and no reduction in the duration of the antiparkinsonian effect of LD~~levodopa~~ was seen 67.

The tremorolytic action of safinamide has been investigated in animal models. Safinamide significantly reduced the tremulous jaw movements induced in rats by pilocarpine, pimozide and galantamine, supporting the efficacy of safinamide in ~~p~~Parkinsonian tremor 68.

7. Clinical trials with safinamide in PD

7.1 Clinical efficacy of safinamide as compared with placebo

The safety and efficacy of different doses of safinamide (0.5 or 1 mg/kg) on motor function were investigated in a 3-month placebo-controlled study (Study 009) on 172 early stage PD patients [69]. Those patients with a ≥~~more than~~ 30% improvement in the UPDRS motor subscore relative to the baseline were defined as responders. The responder rate in the group on high-dose safinamide (median 70 mg/day) was 37.5%, which was significantly higher than that in the placebo group (21.4%). The decrease in UPDRS motor score was 3.3. The study also proved the safety of safinamide [70].

7.2 Safinamide as adjunct therapy to a DAA

Safinamide was the first medication tested in clinical trials as an adjunct to DAAs. In the subgroup of the patients enrolled in the above study who were on a stable dose of a single DAA, the patients receiving safinamide as an adjunct to a DAA exhibited a significantly better response as compared with placebo. A small open-label study led to the same result [65, 70].

The efficacy and safety of a high (150 –~~to~~ 200 mg) and a low (50 –~~to~~ 100 mg) dose range of safinamide as add-on therapy to a single stable dose of DAA were evaluated in comparison with placebo in a study enrolling 269 patients (Study 015, NCT00643045). The primary end-point was the change in the UPDRS motor scores relative to the baseline. The extension study (Study 017, NCT00642889) was a 12-month, randomized, double-blind, placebo-controlled pre-planned study to evaluate the long-term efficacy and safety of safinamide as add-on therapy ~~in~~ for early stage PD. A total of 227 patients were randomized to 100 ~~mg~~ or 200 mg/day safinamide ~~once daily,~~ or to placebo added to a DAA. The primary efficacy end-point was the time from baseline to an increase in the DAA dose, addition of another DAA, addition of LD~~levodopa~~ or other PD treatment (defined as intervention) or discontinuation

due to the lack of efficacy. The treatment was well tolerated, with no difference in the occurrence of adverse events between the safinamide and the placebo groups. The median time to intervention for the pooled safinamide groups was 559 days, whereas in the placebo group it was 466 days, although the difference between the two groups did not reach statistical significance. Patients receiving 100 mg safinamide exhibited an intervention rate that was significantly lower than that ~~for~~ of the placebo group~~,~~ and a delay of 9 days in the median time to intervention, as revealed by the *post-hoc* analysis [71]. The lower dose of safinamide added to the DAA resulted in a statistically significant improvement in UPDRS motor scores over the placebo group. A statistically significant improvement was also measured in the quality of life scores in the pooled dose group and in the individual dose groups [70].

MOTION (NCT00605683) was a 24-week, randomized, double-blind, placebo-controlled international Phase III clinical trial that investigated safinamide in early idiopathic PD as add-on therapy to a DAA. A total of 679 patients with a disease duration of ≤~~less than~~ 5 years who had been on a stable dose of a single DAA for at least 4 weeks prior to enrolment were randomized to receive either 50 mg of safinamide, 100 mg of safinamide or placebo as add-on therapy. The primary end-point was the change in the mean UPDRS-section III value relative to the baseline. The secondary outcome measures were the change from baseline to week 24 in the ADL, cognition, the health-related quality of life, the change in global clinical status and the responder rates in the motor function evaluation [72]. Safinamide was well tolerated, with adverse events such as nausea, dizziness, somnolence, headache and back pain reported. The drop-out rate was about 11%, with 607 patients completing the trial. Safinamide 100 mg/day as add-on to DAA therapy significantly improved the UPDRS motor score and certain quality of life measures as compared with the placebo. The extension study (NCT01028586) enrolled 507 patients receiving 50 or 100 mg of safinamide or placebo for 78 weeks. The

primary end- point was the time to intervention, whereasile the secondary end- points were the proportion of patients requiring intervention, the change in UPDRS motor scores, the ADL scores, a change in the CGIclinical global impression, and quality of life and cognitive measures 73.

Rasagiline was also investigated as add-on therapy to DAAsdopamine agonists in early- stage PD patients. ANDANTE was a Phase IV, 18-week, placebo-controlled, randomized, double-blind study (NCT01049984) to assess the efficacy and safety of rasagiline as add-on therapy to a single stable dose of a DAAdopamine agonist (6 mg/day of ropinirole or 1 mg/day of pramipexole daily) in early- stage PD patients, suboptimally controlled by the DAAdopamine agonist. The primary outcome measure was a change in the total UPDRS score value, whereas the secondary outcome measures were the UPDRS subscore values and the CGI-I values. Of the 328 patients randomized, 321 were included in the analysis of the clinical efficacy. The results were presented at the MDS Congress in 2013; significant improvements in the UPDRS total score and motor subscore values were reported as compared with the placebo arm. No significant differences in the occurrence of adverse events were seen in the two study arms and only a few patients needed LDlevodopa rescue therapy. The addition of rasagiline to a DAAdopamine agonist significantly improves the motor function with a favorable adverse event profile 74.

7.3 Safinamide as adjunct therapy to LDlevodopa

The potential antidyskinetic properties of safinamide were explored in clinical trials on PD patients suffering from LID. A total of 26 patients were enrolled in a Phase II, double-blind, placebo-controlled, parallel-group, dose--escalation trial (Safinamide-LID, NCT01113320). The primary outcome measure was the maximum reduction in Unified Dyskinesia Rating Score (UDysRS) compared to the baseline. Secondary end- points were the total *on* and *off*

times as evaluated by the patient diaries and the changes in the UPDRS scale and subscale scores and in the CGI~~clinical global impression~~ 75.

Study 016 (NCT01187966) and its extension study (Study 018, NCT01286935) evaluated the short- and the long-term safety and efficacy of safinamide as add-on therapy to LD~~levodopa~~ in patients with mid~~-~~to~~-~~late ~~-~~stage PD. The 24-month data were presented in 2011 at the poster session of the AAN meeting 76. In Study 016, 669 patients with idiopathic PD on a stable dose of LD~~levodopa~~ therapy were randomized to receive 50 mg/day of safinamide (223 patients), 100 mg/day of safinamide (224 patients) or placebo (222 patients) ~~daily~~ for 6 months. The 6-month treatment with safinamide (50 or 100 mg/day) significantly improved the motor function, increased the average duration of the *on* time with no dyskinesia or with minor dyskinesia~~,~~ and decreased the average duration of the *off* time relative to the placebo. Patients who completed the 24-week trial could continue the treatment in the extension study (544 patients). Changes in the LD~~levodopa~~ dose~~,~~ and treatment with other PD medication except a MAO-B inhibitor, were allowed. The primary end~~-~~ point was the degree of improvement in the Dyskinesia Rating Scale (DRS) scores during the *on* time as compared with the baseline value. At 2 years, the differences seen in the DRS scores for the 50 mg/day and the 100 mg/day safinamide groups were not significant, but the *post-hoc* analysis of the 100 mg/day safinamide subgroup with severe dyskinesia (DRS scores > 4 at baseline) demonstrated a significant improvement in the DRS scores ($p = 0.03$). Patient diary analysis showed that the improvement reported at 6 months was still present after 2 years of therapy ~~too~~. An increase in the daily *on* time with no/minor dyskinesia and a decrease in the daily *off* time were reported. Overall, the improvement was greater in the ~~daily~~ 100 mg/day safinamide group for the motor scores, ADL scores and clinical status. These patients were more likely to achieve a reduced LD~~levodopa~~ dose than ~~were~~ the patients from the other groups. There were few drop~~-~~outs~~,~~ and no safety concerns emerged 76,77,78,79.

The SETTLE trial (NCT00627640) evaluated the efficacy and safety of two different doses of safinamide (50 ~~and~~ 100 mg) as compared with placebo as add-on therapy to a stable dose of LD~~levodopa~~ and other anti-P~~p~~arkinson drugs (DAAs, anticholinergics, amantadine and/or COMT inhibitors) over 24 weeks in 549 subjects with advanced PD. The principal end~~-~~ point was the increase in mean *on* time without troublesome dyskinesia, as recorded in the patient diaries. A significant benefit of both doses of safinamide over placebo was revealed, with a significant improvement of ≥~~more than~~ 1 h in the *on* time as reported by the patient diaries and the caregiver and a 30% or more improvement in the motor symptoms (p = 0.018). Benefits were observed in the *off* time, in the quality of life measures (39-Item Parkinson's Disease Questionnaire [PDQ-39] and EQ[r5]-5D), ~~and~~ in the CGI~~clinical global impression~~ of severity and change~~,~~ and also in the *off* time after the morning dose of LD~~levodopa~~. The onset of the effect was rapid: improvements in both the *on* time and the *off* time were observed from week 2 onward. Tolerability was good and~~;~~ 484 patients completed the trial. No relevant changes were detected in vital signs, laboratory results, ECG or ophthalmological examinations. Adverse events such as nausea, urinary tract infections, falls, back pain and dyskinesia were reported. Transient mild dyskinesia occurred more frequently with safinamide~~,~~ but did not lead to discontinuation of the study. No increase in troublesome dyskinesia was observed [80, 81].

An open-label trial (NCT00865579) is currently evaluating the long-term safety and tolerability of safinamide in PD patients who have already completed a previous study with safinamide. The physical and neurological condition together with other safety parameters, such as vital signs, laboratory evaluations, ECG and quality of life measures were compared at different visits with the baseline [82].

7.4 Safinamide for PD-associated cognitive impairment

In order to explore the potential benefit of safinamide on cognitive impairment associated with PD 103, cognitively impaired, but non-demented PD patients were enrolled in a double-blind, randomized, placebo-controlled, parallel group Phase II clinical trial (NCT01211587). The primary outcome measures were the PD Cognitive Rating Scale and subscale scores, DRS-2 and subscale scores, the CGI~~clinical global impression~~ change in cognitive dysfunction, the Grid-Hamilton Depression Rating scale, the PD sleep scale and the apathy scale scores [83].

8. Safety and tolerability issues

In the clinical studies detailed above, the tolerability proved to be good. The clinical trials were accompanied by a drop-out rate of only about 11%. No relevant changes in vital signs, laboratory results, ECG or other examinations occurred. Adverse events such as nausea, dizziness, falls, somnolence, headache, back pain, urinary tract infections and transient mild dyskinesia were reported [73, 80, 81].

9. Regulatory affairs

The results of the SETTLE and MOTION trials were presented at the AAN, MDPD and MDS conferences. The Newron Company has started meetings with the European health authorities to discuss the results of the preclinical and clinical trials in order to achieve support for the registration of safinamide as an add-on therapy to DAAs in early stage PD and to LD~~levodopa~~ in advanced stage PD. Additional discussions with European health authorities, EMA and FDA for European and US approval and the regulatory submission were planned for QIV/2013 [84].

10. Conclusion~~s~~

The ~~alfa~~α-aminoamide derivative safinamide exhibits both a dopaminergic and a non-dopaminergic mode of action. It is a potent selective and reversible MAO-B inhibitor, a sodium-channel antagonist and an inhibitor of glutamate release. Safinamide has a dose-dependent, dose-proportional and linear favorable pharmacokinetic profile. Its biotransformation is extensive. It does not interact with CYP-~~450~~. Safinamide is well tolerated, with few side-effects.

Safinamide was investigated in Phase III clinical trials as adjunct therapy to DAAs for patients with early stage PD and to LD~~levodopa~~ therapy for patients in the mid-to-late-stages of PD. The results from the MOTION and SETTLE studies confirmed that safinamide comprises effective add-on therapy to DAAs in early-stage PD patients and to LD~~levodopa~~ in mid-to-late-stage PD. Safinamide significantly improved the motor function, as assessed by the UPDRS motor score in the MOTION study and improved the motor fluctuation assessed by the *on* time without troublesome dyskinesia in mid-to-late-stage PD patients in the SETTLE study. In the Phase III trials, significant improvements in the quality of life, assessed by the PDQ-39 test and/or by the EQ-5D scale were seen. ~~The Drug Summary~~ Box 1 presents the main characteristics of safinamide.

11. Expert opinion

The cause of PD is multifactorial and the pathomechanism of the disease is not completely understood. There are many unmet needs of PD patients, such as the suitable treatment of many of the non-motor symptoms and a neuroprotective therapy capable of protecting the dopaminergic neurons from premature death. LD~~evodopa~~ ~~still~~ is still the best symptomatic treatment available, capable of alleviating the motor symptoms of the disease. The MAO-B inhibitors provide a lower symptomatic effect on motor symptoms as compared with LD~~levodopa~~. Besides an effect on motor symptoms, the delayed-start studies suggest disease-

modifying properties of the MAO-B inhibitors. As compared with the other compounds in this class of medication, safinamide bears a more favorable pharmacokinetic profile and complex pharmacodynamic properties.

Safinamide is a unique compound ~~in~~ exhibiting a combined non-dopaminergic and dopaminergic mode of action. It is a reversible MAO-B inhibitor, with a higher selectivity for MAO-B than for MAO-A, this selectivity being greater than in the cases of the other compounds available in this class of medications. It also inhibits the voltage-sensitive sodium channels and modulates the N-type calcium channels.

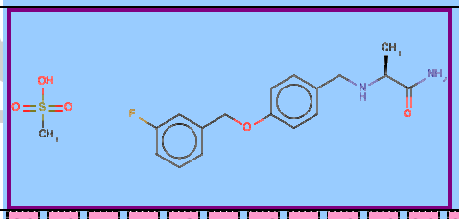
The symptomatic effect of safinamide has not yet been compared with those of other MAO-B inhibitors. The MOTION study that investigated safinamide as an add-on therapy to DAAs in early stage PD patients revealed positive outcomes in the *post-hoc* analysis for those patients taking 100 mg of safinamide. Rasagiline as add-on therapy to DAAs (ropinirole or pramipexole) showed more pronounced outcomes in the ANDANTE study. However, the results can~~-~~not be compared, due to the different inclusion criteria. The results suggest that the combination of a DAA with a MAO-B inhibitor delays the need for LD~~levodopa~~. Besides the symptomatic effect on the motor function, already confirmed in clinical trials, a tremorolytic, an antidyskinetic and presumably a neuroprotective effect could be further explored. Further trials are needed to assess the effects of safinamide on LD~~levodopa~~-induced fluctuations and dyskinesias as compared with placebo, amantadine and COMT inhibitors. In view of the various mechanisms involved in PD pathology, a compound combining favorable effects on dopaminergic and non-dopaminergic, glutamatergic neurotransmission might well have manifold effects in the treatment of PD.

The important roles played by glutamate in neurotoxicity and by glutamate antagonists in neuroprotection have been demonstrated in several animal models of PD and of other

neurodegenerative disorders. Neuroactive kynurenines with an antiglutamatergic effect are also investigated in this respect [85,86,87,88,89,90]. Safinamide-induced neuroprotection has been investigated in animal models (MPTP-treated mice, a rat kainic acid model and a gerbil ischemia model) and neuroprotective and neurorescuing effects have been revealed. Further research is necessary to investigate the potential neuroprotective effect of safinamide in PD patients.

The place of safinamide in the therapy of PD is yet to be determined. The favorable pharmacokinetic and side-effect profile and the possibility that the LD~~levodopa~~ dose can be reduced when safinamide is added together with the presumed neuroprotective properties outlined above~~,~~ suggest that safinamide is a valuable compound in the treatment of PD. It may serve as the first line of add-on therapy to DAA and LD~~levodopa~~ in the early- and the mid--to-late -stage disease, respectively.

Box 1. Drug summary.

Drug name	Safinamide
Phase	Pre-registration
Indication	Parkinson's disease
Pharmacology description	Monoamine oxidase B inhibitor
Route of administration	Oral
Chemical structure	
Pivotal trial(s)	69,70,71,72,73,75,76,77,78,79,80,81,82,83

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Declaration of interest

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Table 1. Symptoms of Parkinson's disease.

Motor symptoms
Bradykinesia/akinesia
Hypokinesia
Tremor
Postural instability
Gait disorder
Non-motor symptoms
Neuropsychiatric symptoms
Psychosis
Hallucinations
Delusions/illusions
Depression
Apathy
Fatigue
Anxiety
Cognitive impairment/dementia
Sleep disorders
REM sleep behavior disorder
RLS
Vivid dreaming
Insomnia
Excessive daytime somnolence
Autonomic symptoms
Drooling
Increased sweating
Gastrointestinal dysfunction
Delayed gastric emptying
Constipation
Bladder dysfunction
Urgency
Frequency
Orthostatic hypotension
Sexual dysfunction
Sensory symptoms
Anosmia
Pain
Paresthesia

REM: Rapid eye movement, RLS: Restless legs syndrome.

Table 2. The place of safinamide in the treatment approaches ~~in~~ of Parkinson's disease.

Dopaminergic therapy	Non-dopaminergic therapy
Levodopa LCIG therapy	Anticholinergics Benztropine

Dopamine agonists Pramipexole Ropinirole Apomorphine pump MAO-B inhibitors Rasagiline Selegiline Safinamide	Trihexyphenidyl Ethopromazine Antiglutamatergic agents Amantadine **Surgical approaches** DBS Ablative surgery Neural transplantation and gene therapy
Drugs tested for symptomatic, antidyskinetic and neuroprotective properties	
Adenosine A2A receptor antagonists	Istradefylline~~, istradefylline~~[AuQ7]
Glutamate antagonists	Amantadine, kynurenines, safinamide
Glutamate receptor-related compounds	MGluR5 antagonists, MGluR4 agonists
Antiepileptic drugs with complex mechanism of action	Safinamide, zonisamide, levetiracetam
Vitamins	Folic acid, vitamin D
Antioxidants, scavenger of free radicals, compounds acting on mitochondria	Coenzyme Q10, creatine, inosine, vitamin E
Catecholamine reuptake inhibitor α2-adrenergic receptor antagonists Nicotine receptor agonist Serotonin modulators L-type Ca^{++} channel blocker	

DBS: Deep brain stimulation~~,~~ LCIG: Levodopa-carbidopa intraintestinal gel ~~therapy~~; MAO: Monoamine oxidase.

Table 3. Clinical trials with safinamide.

Definition	Phase/~~T~~type	Duration (months)	N	S dose (mg/day)	Characteristics	Outcome measures	Results (where available)
Safety and efficacy on motor function (Study 009) 69	Phase III PC	3	172	70 (median)	Early PD: compared to placebo	Responder rate (responders: ≥~~more than~~ 30% improvement in the UPDRS motor subscore compared to baseline) Decrease in UPDRS motor score Safety	37.5~~%,~~ versus 21.4% in the ~~placebo~~ P group 3.3.
Efficacy and safety (Study 015, NCT00643045) 70,71	Phase III PC	24 weeks	269	150~~-~~ – 200 50~~-~~ – 100	Early PD: add-on therapy to DA	Change in the UPDRS motor scores as compared to baseline	Improvement
Long-term efficacy and safety (Study 017, NCT00642889) 70,71	Phase III R, DB, PC, pre-planned	12	227	100 200	Early PD: Add-on therapy to a single stable dose of DA Extension of Study 015	The time from baseline to intervention (intervention: an increase in the DA dose, addition of another DA, addition of LD or other PD treatment~~)~~ or the discontinuation due to lack of efficacy) Intervention rate UPDRS motor scores Quality of life scores Safety	With 100 mg S: a delay in median time to intervention of 9 days (*post-hoc* analysis). The difference between the two S groups was not significant~~.~~ Significantly lower compared to P improvement No difference in the occurrence of adverse events between the active and the ~~placebo~~ P groups.
MOTION	Phase III	24 weeks	679	50	Early PD:~~,~~ add-on	Change in mean UPDRS-	Significant

(NCT00605683) [72]	R, DB, PC			100	therapy to ~~a~~ DA	section III value compared to baseline~~.~~ Change from baseline in the ADL, cognition, global clinical status, responder rates in motor function, health-related quality of life Safety	improvement with 100 mg S Significant improvement S was well tolerated
Extension study (NCT01028586) [73]		78 weeks	507	50 100	Early PD: add-on therapy to DA	Time to intervention Intervention rate The change in UPDRS motor scores, ADL scores, the change in CGI~~clinical global impression~~, a change in quality of life and cognitive measures	Improvement
S~~afinamide~~-LID (NCT01113320) [75]	Phase II DB, PC, parallel-group, dose-escalation	10-weeks	26		Late PD:~~,~~ antidyskinetic effect	The maximum reduction in UDysRS compared to baseline~~.~~ The total *on* and *off* time as evaluated by the patient diaries The change in UPDRS scale and subscale values The change in the CGI~~clinical global impression~~	
Short-term safety and efficacy of S (Study 016,	Phase III	6	669	50 100	Mid-to-late stage PD: ~~A~~add-on therapy to	Motor function The average amount of the *on* time with no	Significant improvement Increased

NCT01187966) [76]					LD	dyskinesia or with minor dyskinesia The average duration of the *off* time compared to P	Decreased
Long-term safety and efficacy of S. Extension of Study 016 (Study 018, NCT01286935) [76,77,78,79].	Phase III	18	544	50 100	Mid-to-late stage PD: Aadd-on therapy to LD	The degree of improvement in the DRS scores during *on* time compared to the baseline values pPatient diary analysis dDuration of daily *on* time with no/minor dyskinesia Dduration of the daily *off* time Motor scores, ADL scores and clinical status Safety	Significant improvement in patients with severe dyskinesia with 100 mg S (*post-hoc* analysis) Long-term improvement Increased Decreased Greater improvement in the daily 100 mg/day S group. Reduction of LD dose possible Few drop-outs and no safety concerns
SETTLE efficacy and safety of S (NCT00627640) [80,81]	Phase III PC	24 weeks	549	50 100	Advanced PD: aAdd-on therapy to a stable dose of LD and other antiparkinsonian drugs	Increase in mean *on* time without troublesome dyskinesia (patient diaries) Motor symptoms Decrease in *off*- time, quality of life measures and CGI The *off*-time after the morning dose of LD Tolerability, safety	Significant improvement for both doses A significant improvement of ≥more than 30% or more Good

Long-term safety and tolerability of S (NCT00865579) [82]	Phase III, open-label	3 -years			PD patients that have already completed a study with S	The physical and neurological condition Other safety parameters Quality of life measures	
Cognitive impairment associated with PD (NCT01211587) [83]	Phase II DB, PC, R, parallel group	24 -weeks	103		Cognitively impaired, but non-demented PD patients	PD Cognitive Rating Scale and subscale scores Dementia Rating Scale-2 and subscale scores The CGIclinical global impression, the change in cognitive dysfunction Grid-Hamilton Depression Rating scale PD sleep scale apathy scale	

See also text for references.

ADL: Activities of daily living; CGI: Clinical global impression; DA: Dopamine[r8] agonist; DB: Double-blind; DRS: Dyskinesia Rating Scale; LD: Levodopa; LID: Levodopa-induced dyskinesia; N: Number of patients enrolled; P: Placebo; PC: Placebo-controlled; PD: Parkinson's disease; R: Randomized; S: Safinamide; UDysRS: Unified Dyskinesia Rating Score; UPDRS: Unified Parkinson's Disease Rating Scale.

Figure 1. The effect of safinamide in the pathomechanism of PD is shown. Protein aggregation, oxidative stress, mitochondrial dysfunction and presumably the glutamate-induced excitotoxicity are major factors contributing to the pathology of PD. These factors cause the loss of pigmented neurons of the substantia nigra pars compacta leading to a dopamine-deficient state. The dopamine-deficient state, combined with the involvement of other neurotransmitter systems, is responsible for the development of the motor and non-motor symptoms of the disease. Safinamide improves the dopamine-deficient state through MAO-B inhibition (1) and improves the motor symptoms. It also exhibits an antiglutamatergic effect (2), which may be beneficial in the treatment of dyskinesia. Safinamide might also have a neuroprotective role; it may possibly also lower oxidative stress through MAO-B inhibition (3) and exert an anti-excitotoxic effect through glutamate inhibition (4).

PD: Parkinson's disease; MAO: Monoamine oxidase.

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