CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

SAFINAMIDE (ONSTRYV)

(Valeo Pharma Inc.)

Indication: For add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic Parkinson disease (PD) in patients experiencing "off" episodes while on a stable dose of levodopa. Safinamide has not been shown to be effective as monotherapy for the treatment of PD.

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Abbreviations

ADL	activities of daily living
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
CDR	CADTH Common Drug Review
CI	confidence interval
CrI	credible interval
COMT	catechol-O-methyltransferase
DA	dopamine agonist
DB	double-blind
DIC	deviance information criteria
DRS	Dyskinesia Rating Scale
EQ-5D	EuroQol 5-Dimensions
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels
GRID-HAMD	grid-based Hamilton Rating Scale for Depression
GRID-HAMD-17	grid-based 17-item Hamilton Rating Scale for Depression
HRQoL	health-related quality of life
ICC	intraclass correlation coefficient
ITC	indirect treatment comparison
ITT	intention-to-treat (population)
LOCF	last observation carried forward
MAO-B	monoamine oxidase B
MID	minimal important difference
MMSE	Mini-Mental State Examination
PD	Parkinson disease
PDQ-39	Parkinson's Disease Questionnaire 39
PDQSI	Parkinson's Disease Questionnaire 39 Summary Index
PGIC	Patient's Global Impression of Change
PP	per-protocol
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-36	Short Form (36) Health Survey
UPDRS	Unified Parkinson's Disease Rating Scale
WDAE	withdrawal due to adverse event

Drug	Safinamide (Onstryv)
Indication	For add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic Parkinson disease (PD) in patients experiencing "OFF" episodes while on a stable dose of levodopa. Safinamide has not been shown to be effective as monotherapy for the treatment of PD.
Reimbursement Request	As per indication
Dosage Form(s)	Tablets, 50 mg and 100 mg safinamide (as safinamide mesylate), oral
NOC Date	January 10, 2019
Sponsor	Valeo Pharma Inc.

Executive Summary

Introduction

Parkinson disease (PD) is the second most common neurodegenerative disease after Alzheimer disease.[1] PD is characterized by chronic neurodegeneration of the striatal region of the brain, resulting in the deficiency of the neurotransmitter dopamine.[2] The clinical manifestations of PD include tremor, rigidity of muscles, bradykinesia, and postural instability leading to a loss of control of voluntary movement.[3,4] The impairment in motor function worsens over time for the majority of patients, despite effective symptomatic treatment, due to the progressive degeneration of nigrostriatal dopamine terminals.[3,5] Motor fluctuations, also called "ON–OFF" fluctuations, are changes in a patient's ability to move. During the ON period, the patient experiences a positive response to the medication, while during the OFF period, the symptoms of PD re-emerge. Initially, the OFF episodes may manifest as predictable and occur near the end of each medication dose. As PD progresses, the treatment effect of the medication begins to wear off earlier and last for a shorter amount of time, and the OFF episodes may become more sudden and/or unpredictable.

In North America, PD affects between 100 and 200 individuals per 100,000 people over 40 years of age.[4] Canadian survey data from 2010 to 2012 yielded prevalence estimates for diagnosed PD of 0.2% in the household population and 4.9% in residents of long-term care facilities.[6] PD is more common in men than women and the incidence of the disease generally increases with age.[4,6]

Safinamide (Onstryv) is a highly selective and reversible inhibitor of monoamine oxidase B (MAO-B).[7] The mechanism of action is unknown, but it is thought that blocking the catabolism of dopamine via MAO-B inhibition increases extracellular levels of dopamine in the striatum and subsequently increases dopaminergic activity. Safinamide is indicated as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing OFF episodes while on a stable dose of levodopa.[7] Safinamide has not been shown to be effective as monotherapy for the treatment of PD.[7]

The objective of this report was to perform a systematic review of the beneficial and harmful effects of safinamide oral tablets, 50 mg or 100 mg, as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing OFF episodes while on a stable dose of levodopa.

Results and Interpretation

Included Studies

Two phase III randomized controlled trials (RCTs) met the inclusion criteria for the CADTH Common Drug Review (CDR) systematic review. SETTLE (N = 549) and Study 016 (N = 669) were 24-week, multi-centre, double-blind (DB), placebo-controlled RCTs conducted in adult patients with idiopathic PD. Patients were levodopa-responsive and receiving a stable dose of levodopa plus benserazide or carbidopa with or without the addition of a catechol-O-methyltransferase (COMT) inhibitor.

SETTLE included patients from Canada (4.2%), the US, Australia, Europe, and Asia. Study 016 included patients from India, Italy, and Romania.

The objective of SETTLE was to evaluate the safety and efficacy of a dose range of safinamide 50 mg/day to 100 mg/day compared with placebo as add-on therapy in patients with idiopathic PD with motor fluctuations who are receiving a stable dose of levodopa. In SETTLE, patients were randomized in a 1:1 ratio to treatment with safinamide 50 mg/day to 100 mg/day or placebo.

The objective of Study 016 was to evaluate the efficacy and safety of two oral doses of safinamide (50 mg/day and 100 mg/day) compared with placebo as add-on therapy in patients with idiopathic PD with motor fluctuations who were currently receiving a stable dose of levodopa. In Study 016, patients were randomized in a 1:1:1 ratio to treatment with safinamide 50 mg/day, safinamide 100 mg/day, or placebo. In both trials, the primary efficacy outcome was change in daily ON time from baseline to week 24.

In both trials, the primary efficacy outcome was change in daily ON time from baseline to week 24 assessed using diary cards. Secondary outcomes in both trials included: daily OFF time, Unified Parkinson's Disease Rating Scale (UPDRS) sections II and III. SETTLE included the Parkinson's Disease Questionnaire 39 (PDQ-39) as a secondary outcome, and Study 016 included the Dyskinesia Rating Scale (DRS) and cognition as secondary outcomes. While the outcomes assessed in the trials were relevant to the clinical population with PD, outcomes related to the frequency of patient-rated ON or OFF episodes, time to response, and use of health care services were not assessed in either trial. Important outcomes (EuroQol 5-Dimensions [EQ-5D] and Patient's Global Impression of Change [PGIC]) were only assessed in SETTLE and were not included in the statistical testing hierarchy. In both trials, symptom-related outcomes pertaining to depression and mental state (grid-based version of the Hamilton Rating Scale for Depression [GRID-HAMD] and the Mini-Mental State Examination [MMSE]) were not included in the statistical testing hierarchy in either trial. Study 016 did not include the PDQ-39, and SETTLE did not include the DRS in each of its statistical testing hierarchies. These outcomes were considered tertiary or exploratory; they were not adjusted for multiplicity and are at risk of an inflated type I error.

Key limitations of SETTLE and Study 016 related to the eligibility criteria, which reduced the generalizability of the trials to the Canadian clinical population, and the lack of evidence comparing safinamide with other active treatments. Both SETTLE and Study 016 had

inclusion and exclusion criteria for patient eligibility that excluded patients with late-stage PD or certain comorbidities (e.g., depression). The exclusion criteria created an enriched study population, one that may be more likely to respond to the treatment. A total of 80% of the patients in the Study 016 study population were Asian (recruited from India), which may have an impact on generalizability to the Canadian population. The doses of safinamide in Study 016 (50 mg/day, 100 mg/day) were associated with unique trials arms and were not representative of the dose administered in a clinic setting, where patients would start on the 50 mg/day dose and increase to 100 mg/day, depending on tolerability. The differential impact of dyskinesia (higher in safinamide arms) may have contributed to the unblinding of patients and investigators. The Health Canada indication for safinamide specifies that it is indicated as an add-on therapy to a regimen that includes levodopa. The majority of patients enrolled in each trial were being treated concomitantly with medications for PD, in addition to levodopa. While subgroup data are available for the patients who were taking only levodopa (in addition to their assigned treatment), the utility of the data is fairly limited, as the study was not powered to detect a difference in efficacy for the subgroup (N = 83). Due to this limitation, conclusions cannot be drawn regarding this subgroup; the efficacy of safinamide compared with placebo remains unclear in patients treated only with levodopa and no other concomitant medications for PD.

One long-term extension study (Study 018) presented efficacy and safety data for patients up to 78 weeks following their participation in Study 016 (Appendix 6).[8] Patients remained in their original treatment groups: safinamide 50 mg/day, safinamide 100 mg/day, or placebo. One sponsor-submitted indirect treatment comparison (ITC)[9] and one published ITC by Binde et al., 2018 met the inclusion criteria for this review. These ITCs assessed indirect evidence comparing safinamide 50 mg/day and safinamide 100 mg/day with placebo and other treatments for PD (Appendix 7).[10]

Efficacy

According to the clinical expert and the patient input collected for this review, improvement in ON and OFF time is useful for determining a clinically meaningful response. Based on the primary outcome (change from baseline to week 24 in daily ON time) in SETTLE, the difference between safinamide 50 mg/day to 100 mg/day and placebo was 0.96 hours (95% confidence interval [CI], 0.56 to 1.37; P < 0.001) in favour of safinamide. In Study 016, the difference in change from baseline with safinamide 50 mg/day compared with placebo was 0.51 hours (95% CI, 0.07 to 0.94; P = 0.0223). Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was 0.55 hours (95% CI, 0.12 to 0.99; P = 0.0130) in favour of safinamide. Minimal important difference (MID) values were not identified in the literature; however, the clinical expert consulted for this review stated that a clinically relevant difference would be between one to two hours. The assessment for daily ON time showed a statistically (but not clinically) significant improvement for safinamide (all doses) compared with placebo in both trials at week 24. For the assessment of daily OFF time at week 24 in SETTLE, the difference in change from baseline between safinamide 50 mg/day to 100 mg/day and placebo was −1.03 hours (95% CI, −1.40 to −0.67; P < 0.001) in favour of safinamide (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was −0.6 hours (95% CI, −0.9 to −0.2; P = 0.0043) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −0.6 hours (95% CI, −1.0 to −0.2; P = 0.0034) in favour of safinamide. While a statistically significant (P < 0.05) and clinically relevant improvement was observed for safinamide 50 mg/day to 100 mg/day in SETTLE, based on an MID of −1 hour to −1.3 hours, a clinically

relevant improvement for both safinamide doses in Study 016 was not observed. Overall, these findings confirm a statistically significant impact for safinamide on PD-related motor fluctuations. Although superior to placebo, the difference captured by the motor diaries has only a modest clinical impact.

According to the clinical expert consulted for this review, along with the improvement in motor fluctuations, a positive effect on mobility, as assessed by the motor examination score (UPDRS[11] Section III), and activities of daily living (ADL), as assessed by the ADL score (UPDRS Section II), is useful for determining a clinically meaningful response to treatment in patients with PD; this was echoed by the patient groups that provided input for this review. For the assessment of the motor examination score (UPDRS Section III) during the ON phase at week 24 in SETTLE, the difference in change from baseline for safinamide 50 mg/day to 100 mg/day compared with placebo was −1.82 units (95% CI, −3.01 to −0.62; P = 0.003), in favour of safinamide (Table 10). In Study 016, the difference in change from baseline for safinamide 50 mg/day compared with placebo was −1.8 units (95% CI, −3.3 to −0.4; P = 0.0138) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −2.6 units (95% CI, −4.1 to −1.1; P = 0.006) in favour of safinamide. In both trials, the change from baseline in motor examination score showed statistically significant improvements for treatment with safinamide (50 mg/day to 100 mg/day in SETTLE; 50 mg/day and 100 mg/day in Study 016) compared with placebo in both trials at week 24, but clinically relevant improvements were only found for safinamide 100 mg/day in Study 016 based on an MID of 2.0 units to 6.2 units. For the assessment of the ADL score (UPDRS Section II) during the ON phase at week 24 in SETTLE, the difference in change from baseline between safinamide 50 mg/day to 100 mg/day and placebo was −0.43 units (95% CI, −1.02 to 0.16; P = 0.149) in favour of safinamide (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was −0.5 units (95% CI, −1.2 to 0.2; P = 0.1253) in favour of safinamide. The difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −1.0 units (95% CI, −1.7 to −0.3; P = 0.0060) in favour of safinamide. For the ADL assessment, the safinamide 100 mg/day arm in Study 016 was the only treatment that showed both a statically significant and clinically relevant improvement compared with placebo, based on an MID of 0.5 units to 2.2 units.

The clinical expert consulted for this review stated that reduction of dyskinesia was among the outcomes that are considered in determining a clinically meaningful response to treatment; however, based on the DRS, treatment with safinamide was no different than placebo for any of the doses (50 mg/day to 100 mg/day, 50 mg/day, 100 mg/day) considered in the trials. Improvement with respect to the PDQ-39 showed statistically and clinically meaningful differences in SETTLE for safinamide 50 mg/day to 100 mg/day compared with placebo. Symptom-related outcomes pertaining to depression and mental state assessed using the GRID-HAMD and MMSE, respectively, showed no statistical difference compared with placebo for any of the doses considered in the trials. Health-related quality-of-life (HRQoL) outcomes using the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) and patient satisfaction using the PGIC were assessed in SETTLE only and favoured safinamide 50 mg/day to 100 mg/day compared with placebo, although neither outcome was adjusted for multiplicity.

The long-term extension study (Study 018) presented data for patients following their participation in Study 016 up to week 78. Generally, the efficacy results reflected the results from Study 016 for outcomes related to ON time and UPDRS sections II and III, although some numerical reductions in efficacy were observed for treatment with safinamide

50 mg/day for motor examination (UPDRS Section III) and ADL (UPDRS Section II) compared with the 24-week results from Study 016. Efficacy outcomes should be considered exploratory, as Study 018 was not powered to detect statistical differences for any of the outcomes assessed.

Two ITCs met the inclusion criteria for this review. [redacted] Evidence from the published Binde et al., 2018 ITC suggests improved efficacy in UPDRS compared with placebo. The utility and quality of the Binde et al., 2018 ITC is limited due to poor reporting of methods. Limitations pertaining to inadequate reporting of study and patient characteristics prevent the ability to assess generalizability to the Canadian clinical population. Definitive conclusions regarding the efficacy of safinamide compared with placebo cannot be made based on the Binde et al., 2018 ITC.

Harms

In SETTLE, 67.9% of patients in the safinamide 50 mg/day to 100 mg/day arm and 69.1% of patients in the placebo arm experienced an adverse event (AE). In Study 016, 65.9% of patients in the safinamide 50 mg/day arm, 65.6% of patients in the safinamide 100 mg/day arm, and 68.5% of patients in the placebo arm experienced an AE. The most common AE was dyskinesia. Dyskinesia occurred in 14.6% of patients in the safinamide 50 mg/day to 100 mg/day arm compared with 5.5% of patients in the placebo arm in SETTLE. In Study 016, 21.1% of patients in the safinamide 50 mg/day arm and 18.3% of patients in the safinamide 100 mg/day arm compared with 12.6% of patients in the placebo arm experienced dyskinesia. In both studies, dyskinesia, insomnia (identified only in Study 016 for the 100 mg/day dose), and nausea occurred more frequently in the safinamide arm(s) compared with placebo. Serotonin syndrome (a theoretical risk of MAO inhibition) was not specifically evaluated in either trial.

In SETTLE, more patients in the placebo arm (9.5%) experienced serious adverse events (SAEs), compared with the safinamide 50 mg/day to 100 mg/day arm (6.6%). In Study 016, 3.6% of patients in the safinamide 50 mg/day arm and 9.8% of patients in the safinamide 100 mg/day arm compared with 8.1% of patients in the placebo arm experienced SAEs. SAEs did not occur in more than three patients in any of the harms categories for any of the treatment arms. In SETTLE, 5.5% of patients in the safinamide 50 mg/day to 100 mg/day arm and 4.0% of patients in the placebo arm experienced a withdrawal due to adverse event (WDAE). In Study 016, 4.9% of patients in the safinamide 50 mg/day arm, 7.6% of patients in the safinamide 100 mg/day arm, and 5.0% of patients in the placebo arm experienced a WDAE. The most common WDAEs were attributed to dyskinesia.

In SETTLE, one patient in the safinamide 50 mg/day to 100 mg/day arm and two patients in the placebo arm died. In Study 016, five patients in the safinamide 100 mg/day and two patients in the placebo arm died. None of the deaths that occurred in either study were reported by the sponsor as related to the study drug.

The exclusion criteria in SETTLE and Study 016 created an enriched study population and may represent a population that was not at an increased risk of potential treatment-related AEs, including comorbidities, which may have rendered a benefit–harm profile that is more optimal than what could be seen in real-world clinical practice.

The long-term extension study (Study 018) assessed the safety of safinamide up to 78 weeks. No new safety signals arose over the course of Study 018. Safety results should also be interpreted with caution, given the enriched study population and limited generalizability to the Canadian population.

[redacted] Evidence from the published Binde et al., 2018 ITC suggests no difference in the occurrence of SAEs compared with placebo based on 95% credible intervals (CrIs). Definitive conclusions regarding the safety of safinamide compared with placebo and other treatments cannot be made based on either ITC, due to several limitations.

Clinician Input[1]

All CADTH review teams include at least one clinical specialist with expertise in the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by one clinical specialist with expertise in the diagnosis and management of PD.

Description of the Current Treatment Paradigm for the Disease

The current treatment paradigm for PD involves treatment with the following: levodopa/carbidopa, levodopa/benserazide, MAO-B inhibitors (selegiline and rasagiline), COMT inhibitors (entacapone, also combined with levodopa/carbidopa), anticholinergics (mainly biperiden and trihexyphenidyl), dopamine agonists (DAs) (mainly pramipexole, ropinirole, and rotigotine), DA apomorphine subcutaneous injection, and amantadine. Amantadine is off-label for PD-related dyskinesias; its use has been extensively evaluated and recommended by international and national guidelines.[3,12,13] Other interventions include deep brain stimulation, intestinal infusion of levodopa/carbidopa, and rehabilitation. These interventions treat only the symptoms and have no effect on the natural history of the disease.

Treatment Goals and Unmet Needs

The most important goal for any PD therapy is improving (possibly restoring) quality of life, which is impaired by motor and non-motor signs to a different and variable individual extent. The interventions described previously treat only the motor symptoms of the disease, thus improving functionality and quality of life. Rigidity and, to some extent, bradykinesia, respond well to the treatment; however, some signs of PD are more resistant, or response is individual and/or depends on the disease progression. These signs include gait, balance,

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

and bulbar disorders (e.g., swallowing and speech). Other non-motor symptoms (e.g., sleep problems, pain, mood issues, constipation) can respond to these treatments if they are caused by dopaminergic dysfunctions. There are currently no treatments available to reverse the course of PD and some treatments are associated with bothersome side effects, such as levodopa-induced dyskinesias or behavioural changes induced by DAs.

Place in Therapy

Safinamide has an MAO-B inhibition property similar to other currently available MAO-B inhibitors (rasagiline and selegiline); it also has a mechanism of action similar to amantadine but its effect on dyskinesias is less, although no head-to-head trials are available. Safinamide also has a unique mechanism of action similar to zonisamide, an antiepileptic drug used in some countries (e.g., Japan) for the treatment of PD, as well. Safinamide is the only MAO-B inhibitor of novelty in the PD landscape, but its real clinical impact is poorly studied in clinical trials and probably marginal. Like many other therapeutics, safinamide will not address the underlying disease process; however, it will be used in combination with levodopa to reduce the motor fluctuations and possibly improve dyskinesias (probably by reducing the levodopa dose). In the opinion of the clinical expert consulted by CDR, the use of safinamide is not expected to cause a shift in the current treatment paradigm for PD.

Due to the its reversible mechanism of action, it is possible that safinamide may be better tolerated than current MAO-B inhibitors, which are irreversible inhibitors. Thus, the clinical expert believes that safinamide can be used as the first drug when motor fluctuations (e.g., wearing-off phenomena) are the main PD-related complications to treat. Safinamide's effect on dyskinesias is less effective than amantadine; for this reason, amantadine should be tried first, before prescribing safinamide for the management of dyskinesias..

Patient Population

Patients best suited for treatment with safinamide include those with mild to moderate motor fluctuations without dyskinesias. Patients most in need of interventions are the ones with severe motor fluctuations and/or troublesome dyskinesias (e.g., patients undergoing deep brain stimulation or levodopa/carbidopa intestinal infusion). Patients with troublesome dyskinesias will likely not benefit from safinamide.

Patients best suited for treatment with safinamide should be easily identified, as PD is not a challenging condition to diagnose in routine clinical practice. Challenges in identifying appropriate patients may occur for patients with recently manifesting neurological symptoms and those with more progressive forms of parkinsonism (e.g., multiple system atrophy or progressive supranuclear palsy); however, the diagnosis of PD is rather accurate after four years from disease onset. Patients who are pre-symptomatic, levodopa-naive, or who have no motor fluctuations should not be treated with safinamide considering its current indications, but its mechanism of action (particularly the MAO-B inhibition) might suggest some disease-modifying effect, in keeping with the existing literature on selegiline and rasagiline. However, further studies are needed before substantiating this hypothesis. In conclusion, patients with mild to moderate motor fluctuations without dyskinesias are most likely to exhibit a response to treatment with safinamide, whereas patients with troublesome dyskinesias would not be considered suitable for treatment with safinamide.

Assessing Response to Treatment

Clinically meaningful responses to treatment include reduction of motor signs (e.g., UPDRS Section III) and fluctuations/dyskinesias (e.g., UPDRS Section IV), improvement of functioning (e.g., UPDRS Section II), and quality of life (e.g., PDQ-39). Treatment response should be assessed every three to six months.

Discontinuing Treatment

Treatment with safinamide should be discontinued if any of the following factors are present: inefficacy, treatment intolerance, indication no longer present (e.g., fluctuating PD patient who undergoes deep brain stimulation or levodopa/carbidopa intestinal infusion).

Prescribing Conditions

Neurologists with experience in PD should be used for the diagnosis, treatment, and monitoring of patients eligible for treatment with safinamide. Treatment with safinamide can be conducted at outpatient neurology clinics.

Conclusions

Safinamide is a selective and reversible inhibitor of MAO-B indicated as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing OFF episodes while on a stable dose of levodopa. Two DB RCTs provided efficacy and safety evidence for safinamide 50 mg/day to 100 mg/day, safinamide 50 mg/day, and safinamide 100 mg/day compared with placebo up to 24 weeks. Key limitations of the trials were related to patient eligibility criteria that created an enriched population, reduced external validity that limits generalizability to the Canadian population, and a lack of evidence comparing safinamide with other active treatments.

Based on the trial results, improvement in ON time (primary end point) and OFF time were statistically superior to placebo; however, the differences have only a modest clinical impact. Improvement in mobility and ADL were statistically superior to placebo; however, only the high dose of safinamide (100 mg/day) showed a clinically relevant difference. Statistical differences were not observed for improvement in dyskinesia. AEs for dyskinesia and nausea occurred more frequently in the safinamide arms compared with placebo.

No new efficacy or safety signals arose over the course of a long-term extension study up to 78 weeks. Results from a sponsor-submitted ITC and a published ITC by Binde et al., provide some evidence that may suggest increased efficacy for safinamide compared with placebo for OFF time and UPDRS; however, limitations in both ITCs prevent any definitive conclusions from being made regarding the efficacy and safety of safinamide compared with placebo and other treatments for PD.

Table 1: Summary of Results

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Change from baseline in motor examination score during ON phase (UPDRS Section III)					
Baseline, n	274	275	223	224	222
Mean (SD)	22.26 (11.66)	23.05 (12.65)	27.3 (12.66)	28.3 (13.30)	28.7 (12.02)
Week 24, n	274	275	214	217	217
Mean (SD)	18.83 (10.87)	21.22 (11.78)	21.1 (12.04)	21.3 (12.53)	23.9 (12.60)
LS mean change from baseline (SD)	−3.52 (0.46)	−1.70 (0.46)	−6.1	−6.9	−4.3
LS difference (95% CI)	−1.82 (−3.01 to −0.62)		−1.8 (−3.3 to −0.4)	−2.6 (−4.1 to −1.1)	
P value	0.003[a]		0.0138[b]	0.0006[b]	
Change from baseline in daily ON time[c]					
Baseline, n	274	275	223	224	221
Mean, hours (SD)	9.30 (2.41)	9.06 (2.50)	9.37 (2.259)	9.52 (2.426)	9.30 (2.155)
Week 24, n	274	274	181	183	174
Mean, hours (SD)	10.73 (2.75)	9.63 (2.77)	10.88 (2.698)	11.01 (2.685)	10.32 (2.494)
LS mean change from baseline (SE)	1.52 (0.15)	0.56 (0.15)	1.23	1.28	0.72
LS difference (95% CI)	0.96 (0.56 to 1.37)		0.51 (0.07 to 0.94)	0.55 (0.12 to 0.99)	
P value	< 0.001[a]		0.0223[d]	0.0130[d]	
Change from baseline in daily OFF time					
Baseline, n	274	275	223	224	221
Mean, hours (SD)	5.34 (1.97)	5.38 (2.01)	5.2 (2.08)	5.2 (2.16)	5.3 (2.06)
Week 24, n	274	275	215	217	214
Mean, hours (SD)	3.77 (2.56)	4.84 (2.59)	3.9 (2.58)	3.9 (2.48)	4.5 (2.66)
LS mean change from baseline (SE)	−1.65 (0.14)	−0.62 (0.14)	−1.3	−1.3	−0.7
LS difference (95% CI)	−1.03 (−1.40 to −0.67)		−0.6 (−0.9 to −0.2)	−0.6 (−1.0 to −0.2)	
P value	< 0.001[a]		0.0043[b]	0.0034[b]	
Dyskinesia Rating Scale					
Baseline, n	274	275	223	224	222
Mean (SD)	2.79 (3.50)	2.57 (3.08)	3.9 (3.89)	3.7 (4.07)	3.4 (3.93)
Week 24, n	274	275	199	204	202
Mean (SD)	2.67 (2.99)	2.33 (2.69)	3.7 (3.80)	3.5 (3.90)	3.1 (3.57)
LS mean change from baseline (SE)	−0.06 (0.14)	−0.29 (0.14)	NR	NR	
LS difference (95% CI)	0.23 (−0.14 to 0.60)		NR	NR	
P value	0.223[a]		0.1812[c]	0.2431[c]	

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Change from baseline in ADL score during ON phase (UPDRS Section II)					
Baseline, n	274	275	223	224	222
Mean (SD)	9.97 (5.53)	10.43 (6.29)	11.8 (5.66)	12.1 (5.82)	12.3 (5.92)
Week 24, n	274	275	214	217	217
Mean (SD)	8.90 (5.44)	9.68 (5.94)	9.8 (6.01)	9.7 (6.42)	10.7 (6.24)
LS mean change from baseline (SE)	−1.22 (0.23)	−0.79 (0.23)	−1.7	−2.2	−1.2
LS difference (95% CI)	−0.43 (−1.02 to 0.16)		−0.5 (−1.2 to 0.2)	−1.0 (−1.7 to −0.3)	
P value	0.149[a]		0.1253[d]	0.0060[d]	
SAEs, N (%)	18 (6.6)	26 (9.5)	8 (3.6)	22 (9.8)	18 (8.1)
WDAEs, N (%)	15 (5.5)	11 (4.0)	11 (4.9)	17 (7.6)	11 (5.0)
Deaths, n	1	2	0	5	2
Notable harms					
Constipation	11 (4.0)	11 (4.0)	7 (3.1)	7 (3.1)	5 (2.3)
Dyskinesia	40 (14.6)	15 (5.5)	47 (21.1)	41 (18.3)	28 (12.6)
Hallucinations	6 (2.2)	6 (2.2)	4 (1.8)	3 (1.3)	4 (1.8)
Impulsive behaviour	1 (0.4)	1 (0.4)	NA	NA	NA
Insomnia	10 (3.6)	5 (1.8)	3 (1.3)	7 (3.1)	6 (2.7)
Melanoma	1 (0.4)	0	0	0	0
Nausea	16 (5.8)	15 (5.5)	7 (3.1)	8 (3.6)	6 (2.7)
Postural/orthostatic hypotension	4 (1.5)	1 (0.4)	5 (2.2)	6 (2.7)	6 (2.7)
Serotonin syndrome	NA	NA	NA	NA	NA
Vomiting	5 (1.8)	5 (1.8)	2 (0.9)	2 (0.9)	3 (1.4)

ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; NA = not applicable; PD = Parkinson disease; SAE = serious adverse event; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale; WDAE = withdrawal due to adverse event.

[a] Parametric ANCOVA model is based on the change from baseline to end point with fixed effects for treatment, region, and baseline value as a covariate. All P values, LS means, and CIs are calculated from the ANCOVA model.

[b] Treatments were compared using an ANCOVA with terms for treatment, centre, and baseline as a covariate.

[c] Treatments were compared with placebo using a Wilcoxon rank sum test.

[d] Treatments were compared using an ANCOVA with baseline as a covariate and treatment and site as main effects.

Source: Clinical Study Reports for SETTLE23 and Study 01624.

Introduction

Disease Prevalence and Incidence

PD is the second most common neurodegenerative disease after Alzheimer disease.[1] It is characterized by chronic neurodegeneration of the striatal region of the brain, resulting in the deficiency of the neurotransmitter dopamine.[2] One of the primary functions of the striatum is to facilitate voluntary movement. In North America, PD affects between 100 and 200 individuals per 100,000 people over 40 years of age.[4] Canadian survey data from 2010 to 2012 yielded prevalence estimates for diagnosed PD of 0.2% (55,000 patients) in the household population and 4.9% (12,500 patients) in residents of long-term care facilities.[6] PD is more common in men than women and the incidence of disease generally increases with age.[6]

The clinical manifestations of PD include tremor, rigidity of muscles, bradykinesia, and postural instability leading to loss of control of voluntary movement.[3,4] The impairment in motor functions worsens over time for the majority of the patients, despite effective symptomatic treatment, due to the progressive degeneration of nigrostriatal dopamine terminals.[3,5] Motor fluctuations, also called ON–OFF fluctuations, are changes in a patient's ability to move. During the ON period, the patient experiences a positive response to the medication, while during the OFF period, the symptoms of PD re-emerge. Initially, the OFF episodes may manifest as predictable and occur near the end of each medication dose. As PD progresses, the treatment effect of the medication begins to wear off earlier and last for a shorter amount of time, and the OFF episodes may become more sudden and/or unpredictable.

Patient's HRQoL is therefore severely affected when their daily life, work, hobbies, and social activities are difficult to maintain.[14] Besides being a motor system disorder, PD is also associated with non-motor symptoms, including cognitive dysfunction and dementia, mood disorders, gastrointestinal symptoms, sleep disturbances, fatigue, pain, and sensory disturbances.[4]

Patient input submitted for this review highlights the "loss of confidence" associated with PD and the impact on daily life. This reported loss of confidence is due in large part to medication "wearing off" or OFF times. Patients specifically mentioned that PD has negatively impacted their ability to socialize and maintain relationships because they have had to stop engaging in recreational activities (e.g., sports) or family life. An impact on the lives of caregivers was also reported. They commonly reported a lack of time due to the demands of caring for a person with PD, which creates a challenge in maintaining social and recreational activities.

Standards of Therapy

The therapies for idiopathic PD vary by severity of symptoms and disease, degree of functional disability, level of physical activity and productivity, patient characteristics, patient preference, and cost.[3,15] Treatments for motor symptoms can be broadly categorized as pharmacologic, non-pharmacologic (e.g., education, exercise, physiotherapy, and nutrition), and surgical therapy. As the disease progresses, patients rely on more medications to maintain their ability to function.[3,15]

A number of dopaminergic anti-PD medications are marketed worldwide, including in Canada. Four main drugs have anti-Parkinson activity and are considered symptomatic therapies: levodopa, DAs, MAO-B inhibitors, and amantadine.[15] Levodopa, a precursor of dopamine, remains the most effective oral drug for the management of motor symptoms in the early stages of PD. The *Canadian Guideline for Parkinson Disease* recommends that levodopa be given in combination with any of the following based on PD stage and tolerability: fixed combination with dopa-decarboxylase inhibitors (carbidopa or benserazide), MAO-B inhibitors (e.g., rasagiline), anticholinergics (trihexyphenidyl and procyclidine) or in fixed combination with carbidopa and entacapone (a COMT inhibitor).[3] The most common early side effects associated with levodopa include nausea, somnolence, dizziness, and headache. More serious adverse reactions to levodopa may include confusion, hallucinations, delusions, agitation, psychosis, and orthostatic hypotension, particularly in older patients.[15] Prolonged use of levodopa may be related to dyskinesia, wearing-off episodes (end-of-dose deterioration), and ON–OFF phenomenon (a switch between mobility and immobility).[2,3] Medications with different mechanisms of action can be administered as an adjunct to levodopa in an attempt to reduce OFF time.

DAs are thought to stimulate dopamine receptors directly and do not need to be converted in the brain to be active.[3] It is suggested that DAs have a role in patients with advanced PD as a treatment for motor complications of levodopa.[15] In Canada, commonly prescribed DAs include non–ergot derived DAs such as ropinirole, pramipexole, and rotigotine as well as ergot-derived DAs such as bromocriptine, either as monotherapy or combination therapy with levodopa. According to the *Canadian Guideline for Parkinson Disease*, a non–ergot derived DA should be preferred to an ergot-derived DA in most cases, due to the risk of pleuropulmonary and cardiac valve fibrosis related to the use of the latter. DAs are commonly used in early PD; however, they are restricted in patients over the age of 70.[3] Similar to levodopa, the common AEs associated with DAs include nausea, vomiting, sleepiness, orthostatic hypotension, confusion, and hallucinations. Long-term use of DAs is associated with the development of impulse control disorders such as pathologic gambling, compulsive sexual behaviour, and compulsive buying in up to 50% of the patients.[15] Apomorphine is another non-ergot DA. Its role as an add-on therapy when other anti-parkinsonism drugs have not controlled the existing motor fluctuations has been demonstrated.[16] Apomorphine can be administered through a variety of routes, including subcutaneous, transdermal, nasal or pulmonary, sublingual, and rectal.[16,17] Subcutaneous apomorphine (Movapo) was reviewed by CDR in 2017, and it was recommended to be reimbursed as adjunctive therapy in coping with OFF episodes for patients who are receiving optimized PD therapy.[18]

MAO-B inhibitors, such as rasagiline and selegiline, prevent the metabolism of dopamine in the brain. COMT inhibitors, such as entacapone, increase the bioavailability of levodopa in the periphery. Anticholinergics, such as trihexyphenidyl and benztropine, are used mostly in patients with tremor; lack of effectiveness and neuropsychiatric side effects limit their use in older patients.[3] Amantadine, as monotherapy or as combination therapy with anticholinergic drugs and with levodopa, is indicated for the treatment of PD. Common AEs related to amantadine include nausea, dizziness, and insomnia, while orthostatic hypotensive episodes, congestive heart failure, depression, psychosis, urinary retention, convulsions, reversible leukopenia and neutropenia, and abnormal liver function are important AEs.[19]

Continuous enteral infusion of levodopa/carbidopa in a gel formulation and deep brain stimulation are invasive treatment options for patients with inadequate management of motor complications using optimized standard therapies.[3] However, patient selection, side

effects associated with these invasive approaches, uncertain long-term motor benefits, and costs are barriers for their widespread use. Therefore, the optimization of oral anti-PD medications remains the most common treatment option, particularly among advanced PD patients where ensuring an adequate plasma dopamine level and managing symptoms during unpredictable or drug wearing-off episodes are constant challenges.

Drug

Safinamide (Onstryv) is a selective and reversible MAO-B inhibitor.[7] The mechanism of action is unknown, but it is thought that blocking the catabolism of dopamine via MAO-B inhibition increases extracellular levels of dopamine in the striatum and subsequently increases dopaminergic activity.

Safinamide is indicated as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing OFF episodes while on a stable dose of levodopa.[7] Safinamide has not been shown to be effective as monotherapy for the treatment of PD.[7] Safinamide is available as 50 mg and 100 mg tablets (as safinamide mesylate) for oral use.

The recommended starting dose for safinamide is 50 mg once per day, administered orally.[7] After two weeks, the dose may be increased to 100 mg once per day based on individual clinical need and tolerability.[7] When discontinuing treatment, safinamide 100 mg/day should be tapered by decreasing the dose to 50 mg/day for one week prior to stopping.

Table 2 provides details regarding the mechanism of action, indication, route and dose of administration, and side effects of safinamide and relevant comparators.

Table 2: Key Characteristics of Safinamide, Selegiline, Entacapone, Amantadine, Apomorphine, Rotigotine, Ropinirole, and Pramipexole

	Safinamide	Selegiline	Entacapone	Amantadine	Apomorphine	Rotigotine	Ropinirole	Pramipexole
Mechanism of Action	Reversible MAO-B inhibitor; blocks the catabolism of dopamine.	Irreversible MAO-B inhibitor.	Reversible COMT inhibitor.	Antiviral drug; the mechanism of action in PD is unclear.	Non-ergot DA; believed to stimulate D_2 receptors of the caudate-putamen.	Non-ergot DA; believed to increase the activities of the D_3, D_2, and D_1 receptors of the caudate-putamen.	Non-ergot DA; believed to stimulate D_2 receptors of the caudate-putamen.	Non-ergot DA; believed to stimulate D_2 receptors of the caudate-putamen.
Indication[a]	Add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing OFF episodes while on a stable dose of levodopa.	Adjunct to levodopa (with or without a decarboxylase inhibitor) in the management of the signs and symptoms of PD, including in newly diagnosed patients before symptoms begin to affect the patient's social or professional life, at which time more efficacious treatment becomes necessary.	Adjunct to levodopa/carbidopa or levodopa/benserazide preparations to treat patients with idiopathic PD who experience the signs and symptoms of end-of-dose wearing-off.	Not indicated in Canada for treatment of PD. Indicated for the prevention (prophylaxis) and treatment of respiratory infections caused by influenza A virus strains.	APO SC: acute, intermittent treatment of hypomobility and OFF episodes (end-of-dose wearing-off and unpredictable ON/OFF episodes) in patients with advanced PD.	Treatment of signs and symptoms of idiopathic PD; can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa.	Treatment of signs and symptoms of idiopathic PD; can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa.	Treatment of signs and symptoms of idiopathic PD; can be used both as early therapy without concomitant levodopa and as an adjunct to levodopa. Symptomatic treatment of moderate-to-severe idiopathic restless legs syndrome.
Route of Administration	Oral	Oral	Oral	Oral	Subcutaneous	Transdermal	Oral	Oral

	Safinamide	Selegiline	Entacapone	Amantadine	Apomorphine	Rotigotine	Ropinirole	Pramipexole
Recommended Dose	Safinamide should be started with a dose of 50 mg once per day, administered orally. After two weeks, the dose may be increased to 100 mg once per day based on individual clinical need and tolerability.	The recommended dose for monotherapy in newly diagnosed patients, or as an adjunct to levodopa (usually with a decarboxylase inhibitor), is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch.	The recommended dose is one 200 mg tablet administered concomitantly with each dose of levodopa/ carbidopa or levodopa/ benserazide up to 8 times daily (1,600 mg/day).	Adults: Daily dosage is 200 mg (two 100 mg capsules as a single daily dose or split into one capsule of 100 mg twice a day).	APO SC should be initiated with the use of a concomitant antiemetic. The antiemetic should be started ≥ 2 days prior to the initial dose of APO SC. Recommended starting dose of APO SC is 0.2 mL (2 mg). Titrate on the basis of effectiveness and tolerance, up to a maximum recommended dose of 0.6 mL (6 mg).	Early-stage PD: A single daily dose should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose of up to a maximal dose of 8 mg/24 h. Advanced-stage PD: A single daily dose should be initiated at 4 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose of up to a maximal dose of 16 mg/24 h.	The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose. After week 4, daily dosage may be increased by 0.5 mg to 1.0 mg per dose weekly until an optimal therapeutic response is established. The maximum daily dose for patients without dialysis is not specified in the product monograph; however, in clinical trials, a dose of 24 mg/day was the target maximum. The recommended maximum dose is 18 mg/day in patients receiving	Dosages should be increased gradually from a starting dose of 0.375 mg/day given in three divided doses and should not be increased more frequently than every 5 to 7 days. The maximal recommended dose is 4.5 mg per day. In patients with a creatinine clearance between 30 mL/min and 50 mL/min, the initial daily dose should be administered in two divided doses, starting at 0.125 mg twice a day (0.25 mg daily). A maximum daily dose of 2.25 mg should not be exceeded.

	Safinamide	Selegiline	Entacapone	Amantadine	Apomorphine	Rotigotine	Ropinirole	Pramipexole
							regular dialysis. Patients with severe renal impairment (creatinine clearance less than 30 mL/min without regular dialysis) have not been studied and administration of ropinirole to such patients is not recommended.	In patients with a creatinine clearance between 15 mL/min and 30 mL/min, the daily dose should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of 1.5 mg should not be exceeded.
Serious side effects/safety issues	Warnings/ precautions: Sudden onset of sleep.	Some of the most serious adverse reactions reported with the combination of selegiline hydrochloride and levodopa were hallucinations and confusion, particularly visual hallucinations.	Warnings/ precautions: Sudden onset of sleep.		Warnings/ precautions: Sudden onset of sleep and somnolence.	Warnings/ precautions: Sudden onset of sleep.	Warnings/precautions: Sudden onset of sleep.	Warnings/ precautions: Sudden onset of sleep and somnolence.

APO = apomorphine; COMT = catechol-O-methyltransferase; DA = dopamine agonist; MAO-B = monoamine oxidase B; PD = Parkinson disease; SC = subcutaneous.

[a] Health Canada indication.

Sources: Product monographs for safinamide (Onstryv),[7] selegiline,[20] entacapone,[21] amantadine,[22] apomorphine SC injection (Movapo),[23] rotigotine (Neupro),[24] ropinirole (Requip),[25] and pramipexole.[26]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of safinamide oral tablets, 50 mg or 100 mg, as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing OFF episodes while on a stable dose of levodopa.

Methods

All sponsor-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 3.

Table 3: Inclusion Criteria for the Systematic Review

Patient population	Adult patients with PD experiencing OFF episodes while on a stable dose of levodopa. Subgroups: • Baseline severity of PD (e.g., severity of episodes) • Baseline dose of levodopa • Background oral medications for PD • Type of OFF episode (e.g., wearing off, partial OFF/delayed OFF/no ON, or unpredictable OFF)
Intervention	Safinamide oral tablets, 50 mg or 100 mg, once per day (starting dose: 50 mg once per day; after two weeks, the dose may be increased to 100 mg once per day based on individual clinical need and tolerability)
Comparators	Levodopa used as monotherapy or in combination with: • dopamine agonists (e.g., bromocriptine, pramipexole, ropinirole, rotigotine transdermal patch) • MAO-B inhibitors (e.g., selegiline, rasagiline) • COMT inhibitors (e.g., entacapone) • amantadine[a] • apomorphine • placebo
Outcomes	**Efficacy outcomes:** • Mobility (or hypomobility) by validated measure[b] (e.g., change from pre-dose in MDS-UPDRS scores at study end point) • Duration of "OFF" episodes[b] (e.g., duration of each OFF episodes, sum of time OFF episodes per day) • Frequency of patient-rated ON or OFF episodes[b] • Symptom reduction (e.g., tremor, bradykinesia, rigidity and postural instability, sleep disturbance, cognition/memory, changes in mood/depression)[b] • HRQoL measured with a validated instrument[b] • Patient satisfaction (e.g., PGI-I) • Time to response (e.g., interval between drug administration and an observed effect) • Use of health care services (e.g., hospitalization) • Activities of daily living (e.g., MDS-UPDRS)[b] **Harms outcomes:** • AEs[b] • SAEs • WDAEs • Mortality

	• Notable harms: dyskinesia, nausea or vomiting, somnolence, postural hypotension, impulsive behaviour, sudden onset of sleep, insomnia, hallucinations, constipation, melanoma, serotonin syndrome
Study design	Published and unpublished phase III or IV RCTs

AE = adverse event; COMT = catechol-O-methyl transferase; HRQoL = health-related quality of life; MAO-B = monoamine oxidase B; MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating Scale; PD = Parkinson disease; PGI-I = Patient's Global Impression of Improvement; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse events.

[a] Used off-label for the treatment of PD in Canada.

[b] Identified as an important outcome in the patient input submission to the CADTH Common Drug Review.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[27]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Onstryv, Xadago, and safinamide. Two clinical trial registries were searched: the US National Institutes of Health's clinicaltrials.gov and the World Health Organization's International Clinical Trials Registry Search Portal (ICTRP).

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on July 2, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on October 16, 2019.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters):[28] Health Technology Assessment (HTA) Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. See Appendix 2 for more information on the grey literature search strategy

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of three studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

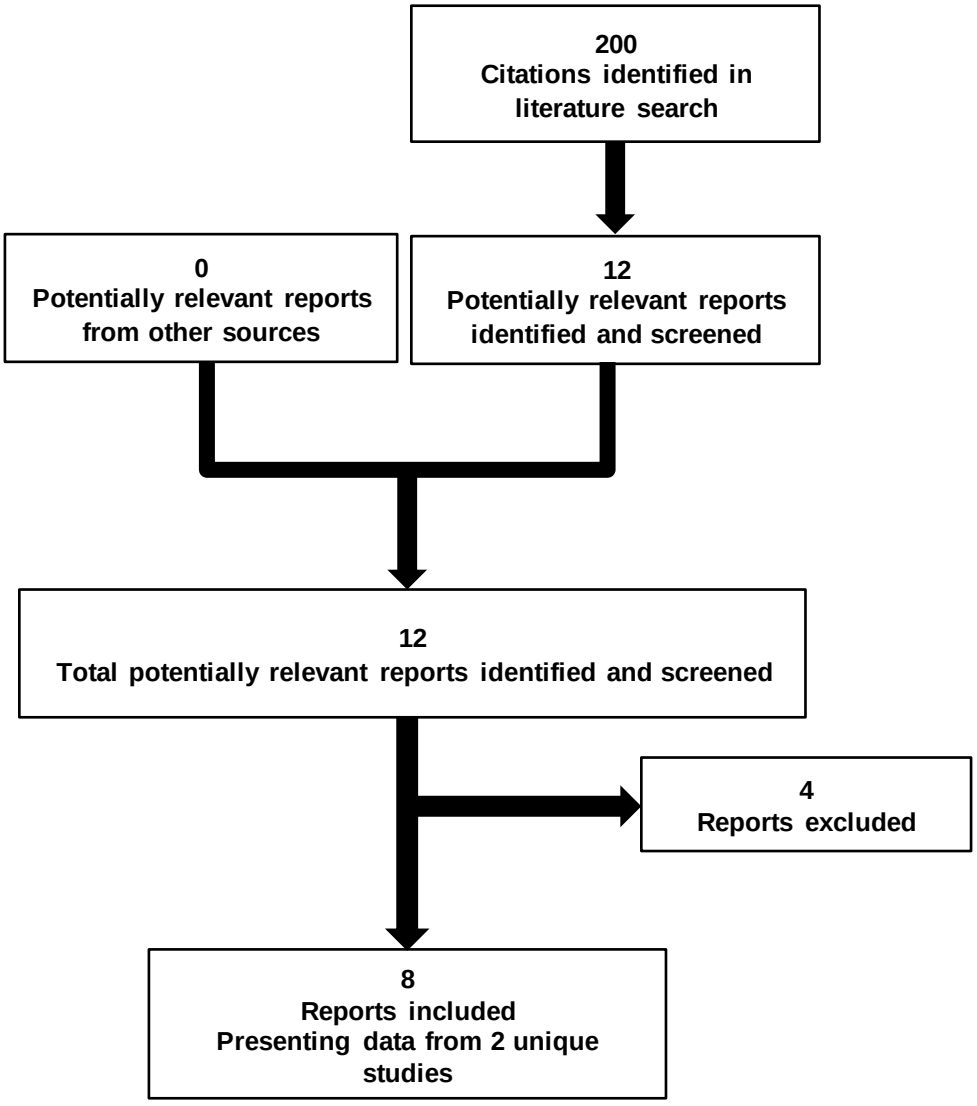

Table 4: Details of Included Studies

		SETTLE	Study 016
Designs & Populations	**Study design**	DB, placebo-controlled RCT	DB, placebo-controlled RCT
	Locations	Canada, the US, Australia, Europe, Asia	India, Italy, Romania
	Randomized (N)	549	669
	Inclusion criteria	• Age 30 to 80 years. • Diagnosis of idiopathic PD of more than 3 years' duration with a Hoehn and Yahr stage of 1 to 4 during an OFF phase; the diagnosis was based on medical history and neurological examination. • Levodopa-responsive and receiving treatment with a stable dose of levodopa plus benserazide or carbidopa. • Motor fluctuations, with > 1.5 hours OFF time during the day.	• Age 30 to 80 years. • Diagnosis of idiopathic PD of more than 5 years' duration (or 3 years with approval by the clinical research medical monitor). • Levodopa-responsive and receiving treatment with a stable dose of levodopa plus benserazide or carbidopa. • Motor fluctuations, with > 1.5 hours OFF time during the day.
	Exclusion criteria	• Any indication of forms of parkinsonism, other than idiopathic PD. • Late stage of PD and experiencing severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations in their symptoms. • Current clinically significant gastrointestinal, renal, hepatic, endocrine, pulmonary, or cardiovascular disease, including acute gastric ulcer, hypertension that is not well controlled, asthma, COPD, and type 1 diabetes. • Second- or third-degree atrioventricular block or sick sinus syndrome, uncontrolled atrial fibrillation, severe or unstable angina, congestive heart failure, myocardial infarction within 3 months of the screening visit, or a significant ECG abnormality. • Current diagnosis of substance abuse or history of alcohol or drug abuse in the past 3 months. • History of or current psychosis (e.g., schizophrenia or psychotic depression) or a score ≥ 3 on item 2 (thought disorder) or item 3 (depression) of the UPDRS Section I at screening. • Depression, as indicated by a GRID-HAMD score > 17. • Evidence of dementia or cognitive dysfunction, as indicated by a MMSE score < 22, or a score ≥ 3 on item 1 (mentation) of the UPDRS Section I at screening.	
Drugs	**Intervention**	Safinamide: one 50 mg tablet once daily; option to increase to one tablet (100 mg) once daily after 14 days if suitable tolerability. Taper phase: one 50 mg safinamide tablet or one small placebo tablet once daily.	1. Safinamide: one 50 mg tablet once daily and one placebo tablet once daily. Taper phase (optional): two placebo tablets once daily. 2. Safinamide: two 50 mg tablets once daily. Taper phase (optional): one 50 mg tablet once daily and one placebo tablet once daily.
	Comparator	Placebo: one tablet (small, 7 mm or large, 9 mm) once daily. Taper phase: one small (7 mm) placebo tablet once daily.	Placebo: two tablets once per day. Taper phase: two tablets once per day.
	Run-in	10 days + 4 weeks	10 days + 4 weeks
	Double-blind	24 weeks	24 weeks
	Follow-up	3 years	78 weeks[a]

		SETTLE	Study 016
Outcomes	**Primary end point**	Change from baseline to week 24 in daily ON time[b]	Change from baseline in daily ON time[b]
	Other end points	• Daily OFF time • UPDRS Section III and II score • PDQ-39	• Daily OFF time • UPDRS Section III and II score • DRS
Notes	**Publications**	Cattaneo, 2017 Schapira, 2017 Cattaneo, 2016	Cattaneo, 2016 Boroghain, 2014

COPD = chronic obstructive pulmonary disease; DA = dopamine agonist; DB = double-blind; DRS = Dyskinesia Rating Scale; ECG = electrocardiogram; GRID-HAMD = grid-based Hamilton Rating Scale for Depression; MMSE = Mini-Mental State Examination; PD = Parkinson disease; PDQ-39 = Parkinson's Disease Questionnaire 39; RCT = randomized controlled trial; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: Two additional reports were included: CADTH Common Drug Review submission[31] and Health Canada's reviewers report.[32]

[a] Study 018 includes data up to 78 weeks including the 24-week data from Study 016.

[b] ON time refers to on time without dyskinesia plus on time with minor dyskinesia.

Source: Clinical Study Reports for SETTLE[29] and Study 016.[30]

Included Studies

Description of Studies

Two phase III, 24-week RCTs were identified and included in this systematic review (SETTLE and Study 016). Study 016 included an 18-month extension study (Study 018) described in Appendix 6. SETTLE and Study 016 were multi-centre, DB, placebo-controlled RCTs in patients 30 to 80 years of age with idiopathic PD on a stable dose of levodopa. Table 5 shows a summary of the study design for both trials.

The objectives of SETTLE were to evaluate the safety and efficacy of a dose range of safinamide 50 mg to 100 mg compared with placebo as add-on therapy in patients with idiopathic PD with motor fluctuations who are receiving a stable dose of levodopa. SETTLE took place between March 5, 2009 and February 23, 2012. Patients were randomized in a 1:1 ratio to treatment with safinamide 50 mg/day to 100 mg/day or placebo using an interactive voice response system (IVRS) stratified by region.

The objective of Study 016 was to evaluate the efficacy and safety of two oral doses of safinamide (50 mg/day and 100 mg/day) compared with placebo as add-on therapy in patients with idiopathic PD with motor fluctuations who were currently receiving a stable dose of levodopa. Patients were randomized a 1:1:1 ratio to treatment with safinamide 50 mg/day, safinamide 100 mg/day, or placebo using permuted-block randomization (block size of six) using statistical analysis software (SAS) stratified by region.

In both trials, patients were evaluated for eligibility over a 10-day screening period. Over the course of the trials, all patients, regardless of assigned intervention, were permitted the concomitant use of DAs, anticholinergic, or amantadine if patients were on a stable dose. During the 10-day screening period, levodopa and other PD medications (if applicable) were optimized (via dose changes or timing of administration) to minimize motor symptoms. At the end of the screening period, patients entered a four-week stabilization phase for the assessment of levodopa and PD medication stabilization. Changes in PD medications were permitted at any time during the stabilization phase; however, any change made during this period required an additional four-week observation following the change. At the end of the stabilization phase, patients had to have achieved their optimum dose and regimen of

levodopa, continued to experience end-of-dose wearing-off, and demonstrated their ability to accurately maintain a diary, with the help of their caregiver. Following stabilization, patients were randomized and treated for 24 weeks with their respective treatments. After the 24-week period, patients in both studies could enter an extension study (three-year extension for SETTLE, or 78-week extension [Study 018] for Study 016). If patients did not enter the extension, those who discontinued the trial early entered a one-week taper phase that allowed for the gradual reduction of the study dose.

Table 5: Summary of Study Design

Study	Period	Screening and run-in period	Stabilization phase	Treatment period	Taper phase	Extension study
SETTLE	Duration	10 days	4 weeks	24 weeks	1 week	3 years
	Study days	−38 to −29	−28 to −1	1 to 168	169 to 175	–
	Treatment	10 days	4 weeks	Study drug (safinamide 50 mg/day to 100 mg/day) or placebo, and other PD medication plus levodopa	Patients who discontinued at week 24 had their dose of study drug tapered and then discontinued	Safinamide 50 mg/day to 100 mg/day, open-label
Study 016	Duration	10 days	4 weeks	24 weeks	1 week	78 weeks (Study 018)[a]
	Study days	−38 to −29	−28 to −1	0/1 to 168	169 to 175	169 to 715
	Treatment	Levodopa (stable dose) and other PD medications (if allowed by protocol)	Optimize levodopa dose; continue other PD medications	Stable levodopa dose and other PD medications; add-on study medication	Patients who discontinued at week 24 had their dose of study drug tapered and then discontinued	Continued on same dose of study drug; flexible dosing on levodopa and other PD medications

PD = Parkinson disease.

[a] Study 018 includes data up to 78 weeks, including the 24-week data from Study 016.

Populations

Inclusion and Exclusion Criteria

The study populations in SETTLE and Study 016 consisted of patients with idiopathic PD (more than three years' duration in SETTLE; more than five years' duration in Study 016), with a Hoehn and Yahr stage of 1 to 4 during an OFF phase. In both studies, the diagnosis was based on medical history and neurological examination. In Study 016, patients who have had idiopathic PD for at least three years could be included with the approval of the clinical research medical monitor. SETTLE included patients from Canada, the US, Australia, Europe, and Asia. The greatest proportion of patients were recruited from Western Europe (39.9%) and Asia (30.6%), while only 4.2% of patients were recruited from Canada. Study 016 included patients from India, Italy, and Romania. The majority of patients were enrolled from sites in India, which accounted for 80.6% of the study population. In both studies, patients were included if they were between 30 and 80 years of age. In both trials, patients had to be levodopa-responsive and receiving a stable dose of levodopa plus benserazide or carbidopa with or without the addition of a COMT inhibitor. In

both trials, patients could also be receiving concomitant treatment with stable doses of a DA and/or an anticholinergic. In SETTLE, patients could also be receiving concomitant treatment with stable doses of amantadine. Patients were included if they had motor fluctuations and more than 1.5 hours of OFF time during the day.

Exclusion criteria were similar between trials. Patients were excluded from the trials if they had any form of PD other than idiopathic or were in a late stage of PD and experiencing severe, disabling peak-dose or biphasic dyskinesia or unpredictable or widely swinging fluctuations in their symptoms, or both. In both trials, patients were excluded with the following conditions: current diagnosis of substance abuse or history of alcohol or drug abuse in the past three months; current clinically significant gastrointestinal, renal, hepatic, endocrine, pulmonary, or cardiovascular disease, including acute gastric ulcer, hypertension that is not well controlled, asthma, chronic obstructive pulmonary disease (COPD), and type 1 diabetes; history or current psychosis, or a score of 3 or more on item 2 of the UPDRS Section I or depression (score of 3 or more on item 3 of the UPDRS Section I); depression (score greater than 17 on GRID-HAMD).

Baseline Characteristics

The baseline characteristics were generally balanced between arms for each study. In SETTLE, patients were approximately 62 years of age; male patients accounted for 59.3% to 62.4% and 66.8% to 68.4% were white. In Study 016, patients were approximately 60 years of age; male patients accounted for approximately 72% and approximately 80% of the total study population were Asian (recruited from India). In Study 016, the average duration of PD was between 7.94 years and 9.29 years. All patients were concomitantly treated with dopaminergic drugs (Table 7). Concomitant medications (excluding PD medications) were similarly used between arms in each trial (Table 8).

Table 6: Summary of Baseline Characteristics

Characteristics	SETTLE		Study 016		
	Safinamide 50 mg/day or 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Age, mean years (SD)	61.7 (9.0)	62.1 (8.9)	60.1 (9.65)	60.1 (9.19)	59.4 (9.41)
Male, n (%)	171 (62.4)	163 (59.3)	157 (70.4)	163 (72.8)	160 (72.1)
Race, n (%)					
White	183 (66.8)	188 (68.4)	43 (19.3)	45 (20.1)	42 (18.9)
Black or African American	3 (1.1)	2 (0.7)	NA	NA	NA
Asian	88 (32.1)	85 (30.9)	180 (80.7)	179 (79.9)	180 (81.1)
Other	0	0	NA	NA	NA
Region, n (%)					
Asia	84 (30.7)	84 (30.5)	NA	NA	NA
East Europe	30 (10.9)	30 (10.9)	NA	NA	NA
West Europe	109 (39.8)	110 (40.0)	NA	NA	NA
North America	51 (18.6)	51 (18.5)	NA	NA	NA
Duration of PD (years)					
Mean (SD)	NA	NA	7.94 (3.910)	8.15 (3.788)	8.29 (3.759)

Characteristics	SETTLE		Study 016		
	Safinamide 50 mg/day or 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Levodopa daily dose					
Mean, mg (SD)	760.8 (445.9)	792.3 (400.7)	NA	NA	NA
UPDRS Section I					
Mean (SD)	1.26 (1.34)	1.28 (1.49)	12.3 (5.92)	11.8 (5.66)	12.1 (5.82)
UPDRS Section II					
Mean (SD)	9.97 (5.57)	10.43 (6.32)	11.8 (5.66)	12.1 (5.82)	12.3 (5.92)
UPDRS Section III					
Mean (SD)	22.35 (11.75)	23.25 (12.87)	27.3 (12.66)	28.3 (13.30)	28.7 (12.02)
UPDRS Section IV					
Mean (SD)	5.94 (2.94)	5.96 (2.88)	5.6 (2.79)	5.6 (2.41)	5.6 (2.68)
Hoehn and Yahr staging					
Mean (SD)	2.48 (0.59)	2.49 (0.61)	2.8 (0.62)	2.8 (0.64)	2.8 (0.67)
[redacted]					
MMSE					
Mean (SD)	28.65 (1.46)	28.64 (1.58)	28.1 (1.95)	27.9 (2.18)	27.9 (2.10)
GRID-HAMD-17					
Mean (SD)	4.74 (4.04)	4.99 (4.13)	6.0 (3.70)	6.0 (3.54)	5.9 (3.70)
CGI-S					
Normal/not at all ill	0	0	NA	NA	NA
Borderline ill	7 (2.6)	4 (1.5)	NA	NA	NA
Mildly ill	54 (19.7)	45 (16.5)	NA	NA	NA
Moderately ill	162 (59.1)	160 (58.8)	NA	NA	NA
Markedly ill	48 (17.5)	60 (22.1)	NA	NA	NA
Severely ill	3 (1.1)	3 (1.1)	NA	NA	NA
Prior					
Patients who received at least one prior medication for PD	17 (6.2)	18 (6.5)	22 (9.9)	26 (11.6)	21 (9.5)
[redacted]					

Characteristics	SETTLE		Study 016		
	Safinamide 50 mg/day or 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
[redacted]					

CGI-S = Clinical Global Impression – Severity of Illness; GRID-HAMD-17 = 17-item grid-based Hamilton Rating Scale for Depression; MMSE = Mini-Mental State Examination; NA = not applicable; PD = Parkinson disease; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Prior PD medication was defined as any medication, other than the study medication, that started and ended before the first administration of the study drug.

Source: Clinical Study Reports for SETTLE[29] and Study 016.[30]

Interventions

After screening and stabilization, patients in both trials were randomized to receive treatment for 24 weeks.

In SETTLE, eligible patients received treatment with safinamide (dosing range of 50 mg/day to 100 mg/day) or placebo. All patients randomized to the safinamide arm started treatment with 50 mg/day. If 50 mg/day was tolerated (assessed on day 14), the dose was increased to 100 mg/day; otherwise, patients remained on the 50 mg/day dose. In SETTLE, the safinamide 50 mg/day dose was provided as a small tablet, the safinamide 100 mg/day dose was provided as a large tablet, and placebo was administered as a small or large tablet.

In Study 016, eligible patients received treatment with safinamide 50 mg/day, safinamide 100 mg/day, or placebo. Patients randomized to the safinamide 50 mg/day arm started at the 50 mg/day dose and remained on that dose for the duration of the study. Patients randomized to the safinamide 100 mg/day arm started at the 100 mg/day dose; those who did not tolerate the 100 mg/day dose were permitted to drop to the 50 mg/day dose. The reduced dose was to be administered for a minimum of five days before attempting to increase the dose back to 100 mg/day.

To maintain blinding, the dose administered to all treatment groups in both trials could be reduced, although the drop-back doses for the safinamide 50 mg/day and placebo groups were the same as the starting doses. In Study 016, the safinamide 50 mg/day dose was provided as a small tablet and the safinamide 100 mg/day dose was provided as two small tablets. Placebo was matched using one or two small tablets, respectively.

In both trials, patients were required to be taking a stable dose of levodopa with or without the addition of a COMT inhibitor. In both trials, patients could also be receiving concomitant treatment with stable doses of a DA and/or an anticholinergic. In SETTLE, patients could also be receiving concomitant treatment with stable doses of amantadine. Concomitant medications for PD had to be stable; it was considered a major protocol violation if an anti-PD treatment was used other than a stable dose of DAs and levodopa or any of the following: oral neuroleptics, depot neuroleptics, and deep brain stimulation. Concomitant medications for PD are provided in Table 7; all patients were concomitantly treated with dopaminergic drugs. Concomitant medications, excluding those used for PD, are provided in Table 8; these concomitant medications were used similarly between arms in each trial.

Table 7: Summary of Concomitant Medications for PD

	SETTLE		Study 016		
	Safinamide 50 mg/day or 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Patients who received at least one concomitant medication for PD,[a] n (%)	274 (100)	275 (100)	223 (100)	224 (100)	222 (100)
Dopaminergic drugs	274 (100)	275 (100)	223 (100)	224 (100)	222 (100)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dopamine agonists	[redacted]	[redacted]	142 (63.7)	128 (57.1)	137 (61.7)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adamantane derivatives	[redacted]	[redacted]	29 (13.0)	30 (13.4)	34 (15.3)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Entacapone	[redacted]	[redacted]	52 (23.3)	55 (24.6)	56 (25.2)
Anticholinergic drugs	[redacted]	[redacted]	74 (33.2)	87 (38.8)	87 (39.2)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PD = Parkinson disease.

[a] Frequency > 5%.

Source: Clinical Study Reports for SETTLE[29] and Study 016.[30]

Table 8: Summary of Concomitant Medications (Excluding PD Medications)

	SETTLE		Study 016		
	Safinamide 50 mg/day or 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SETTLE		Study 016		
	Safinamide 50 mg/day or 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
[redacted]					

PD = Parkinson disease.

[a] Frequency > 5%.

Source: Clinical Study Reports for SETTLE[29] and Study 016.[30]

Outcomes

Assessment of ON/OFF Time

In both trials, the primary efficacy outcome was change from baseline to week 24 in daily ON time. This was assessed using diary cards, where the ON phase was defined as the patient functioning as well as can be expected for that patient, irrespective of whether or not they were having dyskinesias. This corresponded to the ON phase without dyskinesia and the ON phase with non-troublesome/minor dyskinesia. Patients and caregivers were fully trained on the use of diary cards at the screening visit. The diary was maintained by patients over a period of 18 hours (6 a.m. to midnight) each day for three consecutive days at 30-minute intervals. At each interval, the patient or caregiver recorded if the patient was: in an ON phase without dyskinesia; in an ON phase with non-troublesome/minor dyskinesia; in an ON phase with troublesome dyskinesia; in an OFF phase; or asleep. Diaries were recorded for three days preceding a scheduled visit; an average of the last two (valid) days was used for analysis. Diaries with more than two missing hours (out of 18 hours) were invalid.

The validity and reliability of the diary cards used to assess ON time have been assessed in the literature and are described in detail in Appendix 5.[33-36] MID values for ON time were not identified in the literature; however, input from the clinical expert consulted for this review stated that the minimal clinically relevant difference would be one to two hours.

The change from baseline to week 24 in OFF time was a secondary outcome in both trials. OFF time was defined as a lack of mobility, bradykinesia, or akinesia, and assessed using diary cards. Diary cards were used in both trials to assess OFF time and was assessed in a manner similar to ON time. The validity and reliability of the diary cards used to assess OFF time has been assessed in the literature and is described in detail in Appendix 5.[33-36] The MID for improvement in OFF time has been identified as −1 hour to −1.3 hours.[37]

Mobility

Change from baseline to week 24 in motor examination (UPDRS Section III) during the ON phase was a secondary efficacy outcome in both trials. The UPDRS is a longitudinal rating tool for PD composed of four sections that assess mentation, behaviour, and mood (Section I); ADL (Section II); motor examination (Section III); and complications of therapy (Section IV). Section III consists of 14 items, with 27 separate ratings on a scale from 0 (normal/absent/none) to 4 (severe impairment), with higher scores indicating worse symptoms. The total score for UPDRS Section III ranges from 0 to 108. The validity and reliability of the UPDRS Section III has been assessed in the literature and is described in detail in Appendix 5. The MID for the motor examination score (UPDRS Section III) has been identified in the literature at 2.0 units to 6.2 units in patients with early PD (Hoehn and Yahr stages 1 to 3), and 5.2 units for varying stages of PD, although these MID values are not specific to the ON phase. The clinical expert consulted for this review stated that a clinically relevant difference would be 4.0 units.

ADL

Change from baseline to week 24 in ADL score (UPDRS Section II) during ON was a secondary outcome in both trials. Section II consists of 13 ADL, with each item rated on a scale of 0 (normal) to 4 (severe impairment), with higher scores indicating greater impairment. The total score ranges from 0 to 52. Similar to UPDRS Section III, the validity and reliability of UPDRS Section II has been assessed in the literature and is described in detail in Appendix 5. The MID for the ADL score (UPDRS Section II) has been identified as 0.5 units to 2.2 units in patients with early PD (Hoehn and Yahr stages 1 to 3), although these MID values are not specific to the ON phase.

Assessment of Dyskinesia

The DRS was assessed as an exploratory outcome in SETTLE and as a secondary outcome in Study 016. The DRS includes a set of three tasks to measure the severity of dyskinesia in PD, with each item scored on a five-point ordinal scale from 0 to 4. Higher scores correspond with more severe dyskinesia. No evidence of validity and limited evidence of reliability were identified in the literature. An MID has not been identified in the literature.

Impact of PD on Quality of Life

The PDQ-39 was assessed as a secondary outcome in SETTLE and a tertiary outcome in Study 016. The PDQ-39 is a disease-specific HRQoL measure consisting of eight domains (mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort) graded on a five-point scale (0 = never, 4 = always). Each domain is coded on a scale of 0 (no problem at all) to 100 (maximum level of a problem). Further, an overall single summary index (Parkinson's Disease Questionnaire Summary Index [PDQSI]) representing the global HRQoL can be created by averaging the eight subscale scores. The PDQSI is also coded on a scale ranging from 0 to 100, with higher scores indicating worse quality of life.[38,39] The validity and reliability of the PDQ-39 has been assessed in the literature and is described in detail in Appendix 5. The MID for the overall PDQ-39 score has been identified as −1.6 units.[40]

The grid-based 17-item Hamilton Rating Scale for Depression (GRID-HAMD-17) was assessed in both trials as a tertiary outcome. The GRID-HAMD-17 is based on the 17-item Hamilton Rating Scale for Depression, which is a widely used measure in clinical trials for

major depressive disorder. The GRID-HAMD-17 assesses depression and was developed to standardize the administration and scoring of the scale without significantly altering the original intent of the items or the scoring profile. Each of the 17 items, which assess symptoms, is rated both in frequency and severity. Item scores range from 0 to 4 or 0 to 2, with higher scores corresponding to greater frequency and/or intensity. The possible score range is 0 to 52. Limited validity and acceptable reliability of the GRID-HAMD-17 has been identified in the literature and is described in detail in Appendix 5. An MID for patients with PD has not been identified in the literature.

The MMSE was assessed in both trials as a tertiary outcome. The MMSE is a brief, commonly used test to assess cognitive function. It consists of 11 items that evaluate attention and orientation, memory, registration, recall, calculation, language, and ability to draw a complex polygon. The score ranges from 0 to 30, with lower scores corresponding with increasing cognitive impairment. The validity and reliability of the MMSE has been assessed in the literature and is described in detail in Appendix 5. An MID for patients with PD has not been identified in the literature.

The EQ-5D-3L was assessed in the SETTLE trial as a secondary outcome. The EQ-5D-3L is a generic, preference-based, HRQoL measure consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels representing no problems (1), some problems (2), and extreme problems (3). The validity of the EQ-5D-3L has been assessed in the literature and is described in detail in Appendix 5. An MID for the index score in patients with PD has been identified as 0.10 to 0.11 units.

The PGIC was assessed in the SETTLE trial as an exploratory outcome. The PGIC assess the change in the patient's overall clinical status from baseline to various time points during the study. It uses a seven-point scale ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change.

The harms outcomes assessed included AEs, SAEs, WDAEs, and death.

Statistical Analysis

The statistical analysis was performed similarly in SETTLE and Study 016; in both trials, the sample size was calculated based on the primary end point (change from baseline to week 24 in daily ON time measured by diary cards).

In SETTLE, an estimated 484 patients were required to achieve at least 90% power and detect a difference of 0.75 hours in the primary end point. The power calculation was performed using a two-sided, two-sample t-test assuming the following: a common standard deviation (SD) of 2.35 hours, a type I error rate of 5%, and a 14% dropout rate. Assumptions for treatment difference and SD were based on the PRESTO study. The sample size calculation was based on the 1:1 randomization ratio for the safinamide 50 mg/day and placebo arms. No relevant subgroup analyses were performed in SETTLE. Sensitivity analyses were performed based on the completer population (described subsequently). Other sensitivity analyses of the primary end point were performed based on a combination of the analysis population (intention-to-treat [ITT], modified ITT [mITT], completer, or per-protocol), the analysis approach (on-treatment or observed case), and the statistical modelling approach (analysis of covariance [ANCOVA] or mixed-model repeated measure). Additionally, if statistically significant (P value ≤ 0.05) and clinically meaningful differences between the treatment groups existed in any of the demographic parameters,

then an additional analysis of the efficacy end point was conducted by adjusting the demographic parameter. The corresponding subgroup analyses were explored if the interaction between the treatment factor and the demographic factor was significant.

In Study 016, an estimated 660 patients were required to achieve 87% power and detect a difference of 0.78 hours in the primary end point. The power calculation assumed the following: a two-tailed probability of type I error equal to 0.05, a common SD of 2.32 hours, and a 14% dropout rate. Assumptions for treatment difference and SD were based on the PRESTO study. The sample size calculation was based on the 1:1:1 randomization ratio for the safinamide 50 mg/day, safinamide 100 mg/day, and placebo arms. Study 016 was powered to detect a difference between each safinamide arm and placebo; each test (safinamide 100 mg/day versus placebo, safinamide 50 mg/day versus placebo) was performed using a two-sided 5% test. In both studies, randomization was stratified by region and an IVRS was used for randomization and treatment allocation. Ad-hoc subgroup analyses were performed for ON time and OFF time by PD medication at baseline and by country. Relevant subgroup analysis pertaining to patients who were taking only levodopa (i.e., not taking Comtan, Stalevo, amantadine, DAs, or anticholinergics), was described in this report.

Statistical analysis in both trials was performed using SAS version 8.2 or higher. In both trials, the primary end point was analyzed using an ANCOVA model based on the change from baseline to end point, with fixed effects for treatment, region, and baseline value as a covariate. An interaction with region (in SETTLE only) and centre (in Study 016 only) was assessed at a P value of less than 0.10. The primary end point was assessed using a two-sided t-test at the 0.05 level of significance.

In SETTLE, missing data for the primary end point at week 24 were imputed by a last observation carried forward (LOCF) approach using the last post-baseline on-treatment value. All ANCOVA-based assessments used an LOCF for missing data. In Study 016, missing data for all end points was imputed using an LOCF approach for missing data.

In both trials, all continuous variables were summarized using descriptive statistics. Categorical data were presented by number of subjects and relative frequencies.

To preserve type I error, the identified secondary end points were analyzed according to a study-specific hierarchy as long as a significant difference between the safinamide arm and placebo arm was determined. Other end points in SETTLE and Study 016 were assessed on an exploratory basis (e.g., PGIC, EQ-5D). Study 016 accounted for multiplicity associated with the testing of both the safinamide 100 mg/day and safinamide 50 mg/day arms by using a sequence of comparisons approach where, for each outcome, the safinamide 100 mg/day compared with placebo test was performed first (based on a two-sided 5% test); if a significant difference was detected, the safinamide 50 mg/day compared with placebo test was performed (based on a two-sided 5% test).

In SETTLE, key secondary end points were evaluated based on the following hierarchy:

- daily OFF time as measured by diary cards, change from baseline to week 24
- UPDRS Section III score during the ON phase, change from baseline to week 24
- UPDRS Section II (ADL) score during the ON phase, change from baseline to week 24
- PDQSI score, change from baseline to week 24.
- In Study 016, secondary end points were evaluated based on the following hierarchy:

- decrease in total daily OFF time, as measured by diary cards, change from baseline to end point
- UPDRS Section III during ON phase (based on diary), mean change from baseline to end point
- change in cognition (cognitive test battery), mean change from baseline to end point
- improvement in the DRS during ON phase, change from baseline to end point
- UPDRS Section II during ON phase (based on diary), mean change from baseline to end point.

Analysis Populations

SETTLE and Study 016 both had ITT and safety populations.

- The ITT population included all randomized patients. In Study 016, it was specified that the ITT population included randomized patients whether or not they received a dose of their assigned study drug or the correct treatment as designated in the protocol.
- The safety population included all patients who received at least one dose of the study drug and had a subsequent safety assessment.

SETTLE included the following populations: mITT, completer, per-protocol (PP), and screening.

- The mITT population included randomized and treated patients with both baseline and at least one set of post-baseline primary efficacy end point data.
- The completer population included all ITT population patients who had a baseline assessment and completed the regularly scheduled week 24 visit regardless of treatment status.
- The PP population included all ITT population patients who had a baseline assessment and completed the regularly scheduled 24-week treatment period without any major protocol deviations.

Study 016 included the following populations: retrieved drop out population (RDO).

- The RDO population included all randomized patients who discontinued prematurely but returned for their efficacy assessment at week 12 and week 24.

Patient Disposition

A total of 851 and 900 patients were screened in SETTLE and Study 016, respectively. In SETTLE, 302 (35.5%) failed screening; almost all patients who failed screening did so because they did not meet eligibility criteria (n = 249, 29.3%); no further explanation was provided. In Study 016, 231 (25.7%) failed screening with the most common reasons attributed to "other" (n = 132, 14.7%) and withdrawal of consent (n = 49, 5.4%), where "other" refers to reasons other than death, SAE, AE, non-compliance, withdrawal of consent, lost to follow-up.

In SETTLE, 274 patients were randomized to the safinamide 50 mg/day to 100 mg/day arm while 275 were randomized to the placebo arm. In Study 016, 223 and 224 patients were randomized to the safinamide 50 mg/day and 100 mg/day treatment arms, respectively, while 222 patients were randomized to the placebo arm. In SETTLE and Study 016 the proportion of patients that discontinued the trial was similar between trial arms. In SETTLE, 10.6% of patients in the safinamide 50 mg/day to 100 mg/day arm discontinued compared

with 12.4% in the placebo arm. In Study 016, 9.4% of patients in the safinamide 50 mg/day arm, 12.9% in the safinamide 100 mg/day, and 11.3% in the placebo arm discontinued the trial. In SETTLE, "other" was the most common reason for discontinuations; no explanation for what "other" consisted of was provided. The most common reason for discontinuation in Study 016 was attributed to AEs.

Table 9: Patient Disposition

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day	Placebo	Safinamide 50 mg/day	Safinamide 100 mg/day	Placebo
Screened, N	851		900		
Randomized, N	274	275	223	224	222
Completed study, N (%)	245 (89.4%)	241 (87.6%)	202 (90.6%)	195 (87.1%)	197 (88.7%)
Discontinued, N (%)	29 (10.6%)	34 (12.4%)	21 (9.4%)	29 (12.9%)	25 (11.3%)
Adverse events	12 (4.4%)	10 (3.6%)	11 (4.9%)	13 (5.8%)	11 (5.0%)
Withdrawal of consent	NA	NA	5 (2.2%)	6 (2.7%)	7 (3.2%)
Lost to follow-up	3 (1.1%)	2 (0.7%)	4 (1.8%)	4 (1.8%)	3 (1.4%)
Non-compliance	NA	NA	1 (0.5%)	2 (0.9%)	2 (0.9%)
Death	1 (0.4%)	2 (0.7%)	0	4 (1.8%)	1 (0.5%)
Other	13 (4.6%)	20 (7.3%)	NA	NA	2 (0.9%)
ITT, N	274	275	223	224	222
PP, N	230	216	NA	NA	NA
Safety, N	274	275	223	224	222
mITT, N	270	273	NA	NA	NA

ITT = intention-to-treat; mITT = modified intention-to-treat; NA = not applicable; PP = per-protocol.

Source: Clinical Study Reports for SETTLE[29] and Study 016.[30]

Exposure to Study Treatments

In the SETTLE safinamide treatment arm, safinamide was administered at a dose of 50 mg/day for 14 days. If the dose was well tolerated, patients were increased to the target dose of 100 mg/day through week 24. Patients in both the safinamide (N = 274) and placebo (N = 275) arms were treated for a median of 170 days. In the safinamide arm, the average daily dose of safinamide was 90.09 mg (SD = 12.13 mg). The majority of patients in the safinamide group were switched to the 100 mg dose after two weeks of treatment with the 50 mg dose. At day 14, a total of 219 of 241 patients (90.9%) in the safinamide group and 225 of 239 patients (94.1%) in the placebo group were prescribed the 100 mg target dose. This corresponds to a mean total exposure of 14,836.1 mg (SD = 3,952.3 mg). In SETTLE, 15 (5.5%) of patients treated with safinamide discontinued treatment due to treatment-emergent adverse events (TEAEs), while 11 (4.0%) patients in the placebo group discontinued treatment due to TEAEs.

In Study 016, patients in the safinamide treatment arms were started at the 50 mg/day (N = 223) or 100 mg/day (N = 224) dose, according to their allocation. For the patients randomized to the safinamide 100 mg/day arm, those who did not tolerate the 100 mg/day dose were permitted to drop to the 50 mg/day dose. The reduced dose was to be administered for a minimum of five days before attempting to increase the dose back to

100 mg/day. The number of patients randomized to 100 mg/day who dropped to 50 mg/day was not available. Patients in all treatment arms were treated for approximately 170 days (median). In the safinamide 50 mg/day arm, the mean total exposure was 8,174.1 mg (SD = 1,716.89 mg). The mean total exposure for the safinamide 100 mg/day arm was 15,764.3 mg (SD = 4,213.35 mg). In Study 016, 11 (4.9%) patients in the safinamide 50 mg/day arm, 17 (7.6%) patients in the safinamide 100 mg/day arm, and 11 (5.0%) patients in the placebo arm discontinued the trial due to TEAEs.

Critical Appraisal

Internal Validity

Baseline and demographic characteristics were sufficiently reported and were generally well balanced across the treatment arms in both trials.

Both trials were conducted using DB methodology where the raters, caregivers, and patients were blinded. IVRS was used for randomization and treatment allocation. Patients received a blinded treatment kit corresponding to their randomization group. To maintain blinding in SETTLE, treatment could be tapered for patients in any treatment group. In Study 016, it was specified that the safinamide and placebo tablets were identical in appearance; it is unclear if the same was true for SETTLE. Unblinding of patients could occur if it was related to a safety concern.

Both trials included design elements that were employed to ensure groups were treated similarly. Patients were required to be on a stable dose of levodopa and were not restricted from using other medications for PD (stabilized during a four-week period before the 24-week intervention), regardless of treatment group. During the 10-day screening period, the investigator optimized the PD medications (changed the dose or timing of dose administration) for all patients and observed them for four weeks (stabilization period). Additionally, all patients who discontinued the study at week 24 (instead of continuing in an extension study) had their dose tapered and discontinued over one week. In the safinamide arm in SETTLE, the dose was increased from 50 mg/day to 100 mg/day after 14 days, if tolerated. Each dose was associated with a different-sized pill. The placebo arm was similarly treated with two corresponding sizes of placebo pill.

The dose amounts in both trials (safinamide 50 mg/day, 100 mg/day) were appropriate. The selection of these doses was based on previous trials (Study 009 and Study 015) and is consistent with the product monograph.

In SETTLE and Study 016, the proportion of patients who discontinued the trial was similar between trial arms with the most common reason for discontinuation attributed to AEs. Dyskinesia occurred more frequently in the safinamide arms in both trials compared with placebo; this difference creates the potential for unblinding for patients and investigators.

In SETTLE, the impact of missing data on the primary efficacy end point was assessed using sensitivity analysis (of the analysis population, the analysis approach, and the statistical modelling with explicit or implicit missing data imputation). The amount of missing data for primary and secondary end points was minimal and not of concern.

External Validity

In SETTLE, 4.2% of patients were recruited from Canada. Patients in SETTLE were approximately 62 years of age; most patients in the study were white, and male patients

accounted for 59.3% to 62.4% of the study population. The mean Hoehn and Yahr stage in SETTLE was 2.48 for the safinamide arm and 2.49 for the placebo arm. The distribution of patients by Hoehn and Yahr stage was not available. The demographic characteristics of patients included in Study 016 were less reflective of the Canadian clinical populations, as approximately 80% of the patients were Asian (recruited from India) and none of the patients were recruited from Canada. In Study 016, patients were approximately 60 years of age; male patients accounted for approximately 72% of the study population and the average duration of PD was between 7.94 years and 9.29 years. The mean Hoehn and Yahr stage in Study 016 was 2.8 in each arm; most patients were categorized as stage 2.5 or 3, with similar distributions between treatment arms.

Both SETTLE and Study 016 had several inclusion and exclusion criteria for patient eligibility that contributed to an enriched population. The eligibility restrictions compromised the generalizability of findings, as those included in the trials were not representative of the Canadian clinical population. For example, patients with late-stage PD were excluded from the trials; patients were included in the trials if they had a Hoehn and Yahr stage of 1 to 4. Patients experiencing severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations in their symptoms were excluded from participating in the trials although this would be representative of some of the patients seen in the clinical population. Additionally, in both trials, patients were excluded if they had any of the following conditions: substance abuse or history of alcohol or drug abuse in the past three months; current clinically significant gastrointestinal, renal, hepatic, endocrine, pulmonary, or cardiovascular disease, including acute gastric ulcer, hypertension (that is not well controlled), asthma, COPD, and type I diabetes; history or current psychosis; or depression. The study population included in both trials was enriched and may represent a population of patients who are more likely to respond to the treatment and less likely to experience potential treatment-related AEs compared with patients with both PD and comorbidities; this rendered a benefit–harm profile that is more optimal than what would likely be seen in real-world clinical practice.

In both trials, patients were required to be on a stable dose of levodopa. Patients were also permitted the concomitant use of other medications for PD. Several patients used DAs (ropinirole and pramipexole). The use of these concomitant medications for PD is consistent with typical treatment in Canada. While use of stabilized DAs and other medications for PD was balanced between treatment arms, it is possible that the use of these medications could alter the efficacy evaluations by biasing the difference in treatment arms toward the null, thereby making it more difficult to observe a treatment effect. The Health Canada indication for safinamide specifies that it is indicated as an add-on therapy to a regimen that includes levodopa. In addition to levodopa, the majority of patients enrolled in each trial were being concomitantly treated with other PD medications. For Study 016, subgroup data were available for patients who were taking levodopa in addition to their assigned treatment. Although these subgroup data were available for only 83 patients (approximately 12% of the total ITT population), it may provide some insight into how safinamide may work in patients who are treated solely with levodopa.

Both SETTLE and Study 016 used placebo as a comparator, even though alternative adjunct therapy to levodopa is available (e.g., MAO-B), thereby preventing direct comparison with other relevant PD therapeutics.

The dose of safinamide in SETTLE is consistent with the dose specified in the product monograph. Treatment with safinamide should be started with a dose of 50 mg once per

day, administered orally; after two weeks, the dose may be increased to 100 mg once per day based on individual clinical need and tolerability. The dose administration in SETTLE is consistent with what is anticipated for clinical practice. Study 016 randomized patients according to treatment with either the 50 mg/day or 100 mg/day dose in a 1:1 ratio. Patients started on their assigned dose and continued the dose until the end of the trial, unless it had to be stepped down (e.g., if a patient did not tolerate the dose). This method of dose administration is inconsistent with the method of administration outlined in the product monograph and with anticipated clinical administration, as patients randomized to the 50 mg/day arm were not permitted to move up to the 100 mg/day dose.

SETTLE and Study 016 used several end points that were consistent with outcomes that were identified as important to patients. According to the clinical expert consulted for this review, the 24 weeks of follow-up in both trials was of sufficient duration to observe relevant clinical effects. Study 018, a 78-week extension of Study 016, provides additional long-term efficacy and safety data (see Appendix 6).

Efficacy

Only those efficacy outcomes identified in the review protocol are reported subsequently. See Appendix 4 for detailed efficacy data.

Motor Examination Score (UPDRS Section III)

For the assessment of the motor examination score (UPDRS Section III) during the ON phase at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was −1.82 units (95% CI, −3.01 to −0.62; P = 0.003) in favour of safinamide (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was −1.8 units (95% CI, −3.3 to −0.4; P = 0.0138) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −2.6 units (95% CI, −4.1 to −1.1; P = 0.006) in favour of safinamide. The MID for the motor examination score (UPDRS Section III) has been identified as 2.0 units to 6.2 units in patients with early PD, and 5.2 units for varying stages of PD, although these MID values are not specific to the ON phase. The clinical expert consulted for this review stated that a clinically relevant difference would be 4.0 units. Based on the range of MID values (2.0 units to 6.2 units), the between-arm least squares difference in motor examination score (UPDRS Section III) is not clinically relevant for the safinamide 50 mg/day to 100 mg/day arm in SETTLE, or the safinamide 50 mg/day arm in Study 016. Clinical relevance was determined only for the safinamide 100 mg/day arm in Study 016. Efficacy results in SETTLE for the mITT and PP populations were consistent with the main ITT population results.

Daily ON Time

For the assessment of daily ON time at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was 0.96 hours (95% CI, 0.56 to 1.37; P < 0.001) in favour of safinamide (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was 0.51 hours (95% CI, 0.07 to 0.94; P = 0.0223) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was 0.55 hours (95% CI, 0.12 to 0.99; P = 0.0130) in favour of safinamide. MID values were not identified in the literature; however, input from the clinical expert consulted for this review stated that a clinically relevant difference would be one to two hours. Based on the one- to two-hour

criteria, the between-arm least squares difference in daily ON time is not clinically relevant for any of the safinamide doses in either study. Efficacy results in SETTLE for the mITT and PP populations were consistent with main ITT population results. Subgroup data for patients who were taking only levodopa (in addition to their assigned treatment) was available for Study 016 (Table 13); this assessment was outside the pre-specified statistical hierarchy. For this subgroup, the difference in change from baseline between safinamide 50 mg/day and placebo was 1.5 hours (95% CI, 0.2 to 2.8; P = 0.0285) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo was 1.8 hours (95% CI, 0.4 to 3.3; P = 0.0137) in favour of safinamide.

Daily OFF Time

For the assessment of daily OFF time at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was −1.03 hours (95% CI, −1.40 to −0.67; P < 0.001) in favour of safinamide (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was −0.6 hours (95% CI, −0.9 to −0.2; P = 0.0043) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −0.6 hours (95% CI, −1.0 to −0.2; P = 0.0034) in favour of safinamide. The MID for improvement in OFF time has been identified as −1 hour to −1.3 hours. Based on the range of MID values (−1 hour to −1.3 hours), the between-arm least squares difference in daily OFF time is clinically relevant for the safinamide 50 mg/day to 100 mg/day arm in SETTLE, but not relevant for either safinamide arm in Study 016. Efficacy results in SETTLE for the mITT and PP populations were consistent with main ITT population results. Subgroup data for patients who were treated only with levodopa (in addition to their assigned treatment) were available for Study 016 (Table 13); this assessment was outside the pre-specified statistical hierarchy. For this subgroup, the difference in change from baseline between safinamide 50 mg/day and placebo was −1.2 hours (95% CI, −2.3 to −0.1; P = 0.0315) in favour of safinamide. The difference in change from baseline between safinamide 100 mg/day and placebo was −0.7 hours (95% CI, −1.8 to 0.5; P = 0.2670) in favour of safinamide.

DRS

For the assessment using the DRS at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was 0.23 units (95% CI, −0.14 to 0.60; P = 0.223) (Table 10), although this outcome was not included in the pre-specified hierarchy for SETTLE. In Study 016, the difference in change from baseline between the safinamide arms and placebo was not reported. For safinamide 50 mg/day, the baseline value was 3.9 units (SD = 3.89) compared with 3.7 units (SD = 3.80) at week 24 (P = 0.1812 for comparison with placebo). For safinamide 100 mg/day, the baseline value was 3.7 units (SD = 4.07) compared with 3.5 units (SD = 3.90) at week 24 (P = 0.2431 for comparison with placebo). The MID for the DRS has not been identified in the literature.

Cogtest PD

The results of the Cogtest battery of tests for SETTLE and Study 016 are presented in Appendix 4. In SETTLE, the results for the Auditory Number Sequencing test (number of correct sequences) and Word List Memory test (delayed recognition discrimination, first trial, and non-listed words, second trial) were in favour of safinamide 50 mg/day to 100 mg/day. In Study 016, treatment with safinamide at doses of 50 mg/day and 100 mg/day was not associated with an increase or decrease in cognitive ability.

PDQ-39

In SETTLE, the PDQ-39 was assessed using the "summary score" (based on the average of the domain scores) at week 24, where the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was −2.33 units (95% CI, −3.98 units to −0.68; P = 0.006) in favour of safinamide (Table 10), although the testing of this outcome was outside of the pre-defined hierarchy for SETTLE. The MID for the overall PDQ-39 score has been identified as −1.6 units. Based on this MID, the between-arm least squares difference in PDQ-39 is clinically relevant for the safinamide 50 mg/day to 100 mg/day arm in SETTLE. Efficacy results in SETTLE for the mITT and PP populations were consistent with the main ITT population results.

In Study 016, the PDQ-39 was assessed using the "total score" (based on the sum of the domain scores) at week 24, where the difference in change from baseline between safinamide 50 mg/day and placebo was −4.6 units (95% CI, −20.0 to 10.9; P = 0.5603). The difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −16.5 units (95% CI, −31.9 to −1.1; P = 0.0360) in favour of safinamide, although this outcome was not included in the pre-specified hierarchy for Study 016.

GRID-HAMD

For the assessment using the GRID-HAMD at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was −0.31 units (95% CI, −0.93 to 0.30; P = 0.317) (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was −0.2 units (95% CI, −0.8 to 0.3; P = 0.3922). The difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −0.5 units (95% CI, −1.0 to 0; P = 0.0731) in favour of safinamide. This outcome was not included in the pre-specified hierarchy for either trial.

MMSE

For the assessment using the MMSE at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was −0.14 units (95% CI, −0.39 to 0.10; P = 0.255) (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was 0.1 units (95% CI, −0.4 to 0.2; P = 0.7047). The difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was 0 units (95% CI, −0.3 to 0.3; P = 0.9201). This outcome was not included in the pre-specified hierarchy for either trial.

EQ-5D (EQ-5D-3L)

For the assessment using the EQ-5D at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was 0.06 units (95% CI, 0.03 to 0.09; P < 0.001) in favour of safinamide (Table 10), although this outcome was not included in the pre-specified hierarchy. The EQ-5D was not assessed in Study 016.

PGIC

For the assessment using the PGIC at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was −0.40 units (95% CI, −0.57 to −0.22; P < 0.001) in favour of safinamide (Table 10), although this

outcome was not included in the pre-specified hierarchy. The PGIC was not assessed in Study 016.

ADL Score (UPDRS Section II)

For the assessment of the ADL score (UPDRS Section II) during the ON phase at week 24 in SETTLE, the difference in change from baseline between safinamide (50 mg/day to 100 mg/day) and placebo was −0.43 units (95% CI, −1.02 to 0.16; P = 0.149) in favour of safinamide (Table 10). In Study 016, the difference in change from baseline between safinamide 50 mg/day and placebo was −0.5 units (95% CI, −1.2 to 0.2; P = 0.1253) in favour of safinamide. The difference in change from baseline between safinamide 100 mg/day and placebo in Study 016 was −1.0 units (95% CI, −1.7 to −0.3; P = 0.0060) in favour of safinamide. The MID for the ADL score (UPDRS Section II) has been identified as 0.5 units to 2.2 units in patients with early PD, although these MID values are not specific to the ON phase. Based on the range of MID values (0.5 units to 2.2 units), the between-arm difference in ADL score (UPDRS Section II) was not clinically relevant for the safinamide 50 mg/day to 100 mg/day arm or the placebo arm in SETTLE, but was clinically relevant for both safinamide 50 mg/day and 100 mg/day in Study 016. Efficacy results in SETTLE for the mITT and PP populations were consistent with main ITT results.

Data for the following protocol-specified outcomes were not available: frequency of patient-rated ON or OFF episodes, time to response, and use of health care services.

Table 10: Efficacy Outcomes (ITT Population)

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Change from baseline in motor examination score during ON phase (UPDRS Section III)					
Baseline, n	274	275	223	224	222
Mean (SD)	22.26 (11.66)	23.05 (12.65)	27.3 (12.66)	28.3 (13.30)	28.7 (12.02)
Week 24, n	274	275	214	217	217
Mean (SD)	18.83 (10.87)	21.22 (11.78)	21.1 (12.04)	21.3 (12.53)	23.9 (12.60)
LS mean change from baseline (SD)	−3.52 (0.46)	−1.70 (0.46)	−6.1	−6.9	−4.3
LS difference (95% CI)	−1.82 (−3.01 to −0.62)		−1.8 (−3.3 to −0.4)	−2.6 (−4.1 to −1.1)	
P value	0.003[a]		0.0138[b]	0.0006[b]	
Change from baseline in daily ON time[c]					
Baseline, n	274	275	223	224	221
Mean, hours (SD)	9.30 (2.41)	9.06 (2.50)	9.37 (2.259)	9.52 (2.426)	9.30 (2.155)
Week 24, n	274	274	181	183	174
Mean, hours (SD)	10.73 (2.75)	9.63 (2.77)	10.88 (2.698)	11.01 (2.685)	10.32 (2.494)
LS mean change from baseline (SE)	1.52 (0.15)	0.56 (0.15)	1.23	1.28	0.72
LS difference (95% CI)	0.96 (0.56 to 1.37)		0.51 (0.07 to 0.94)	0.55 (0.12 to 0.99)	
P value	< 0.001[a]		0.0223[d]	0.0130[d]	

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Change from baseline in daily OFF time					
Baseline, n	274	275	223	224	221
Mean, hours (SD)	5.34 (1.97)	5.38 (2.01)	5.2 (2.08)	5.2 (2.16)	5.3 (2.06)
Week 24, n	274	275	215	217	214
Mean, hours (SD)	3.77 (2.56)	4.84 (2.59)	3.9 (2.58)	3.9 (2.48)	4.5 (2.66)
LS mean change from baseline (SE)	−1.65 (0.14)	−0.62 (0.14)	−1.3	−1.3	−0.7
LS difference (95% CI)	−1.03 (−1.40 to −0.67)		−0.6 (−0.9 to −0.2)	−0.6 (−1.0 to −0.2)	
P value	< 0.001[a]		0.0043[b]	0.0034[b]	
DRS					
Baseline, n	274	275	223	224	222
Mean (SD)	2.79 (3.50)	2.57 (3.08)	3.9 (3.89)	3.7 (4.07)	3.4 (3.93)
Week 24, n	274	275	199	204	202
Mean (SD)	2.67 (2.99)	2.33 (2.69)	3.7 (3.80)	3.5 (3.90)	3.1 (3.57)
LS mean change from baseline (SE)	−0.06 (0.14)	−0.29 (0.14)	NR	NR	
LS difference (95% CI)	0.23 (−0.14 to 0.60)		NR	NR	
P value	0.223[a]		0.1812[e]	0.2431[e]	
PDQ-39					
Baseline, n	274	275	223	224	222
Mean (SD)	27.47 (14.61)	26.94 (14.83)	225 (110.5)	229 (124.1)	230 (109.8)
Week 24, n	274	275	214	217	217
Mean (SD)	24.31 (13.73)	26.26 (14.92)	207 (126.8)	197 (122.9)	215 (116.2)
LS mean change from baseline (SE)	−2.95 (0.63)	−0.62 (0.63)	−16.4	−28.4	−11.9
LS difference (95% CI)	−2.33 (−3.98 to −0.68)		−4.6 (−20.0 to 10.9)	−16.5 (−31.9 to −1.1)	
P value	0.006[a]		0.5603[f]	0.0360[f]	
GRID-HAMD					
Baseline, n	274	275	223	224	222
Mean (SD)	4.74 (4.04)	4.95 (4.09)	6.0 (3.70)	6.0 (3.54)	5.9 (3.70)
Week 24, n	274	275	199	203	201
Mean (SD)	4.82 (4.33)	5.28 (4.91)	5.3 (3.74)	5.1 (3.52)	5.6 (4.08)
LS mean change from baseline (SE)	−0.07 (0.24)	0.24 (0.24)	−0.5	−0.8	−0.3
LS difference (95% CI)	−0.31 (−0.93 to 0.30)		−0.2 (−0.8 to 0.3)	−0.5 (−1.0 to 0)	
P value	0.317[a]		0.3922[f]	0.0731[f]	
MMSE					
Baseline, n	274	275	224	222	223
Mean (SD)	28.66 (1.46)	28.64 (1.58)	28.1 (1.95)	27.9 (2.18)	27.9 (2.10)
Week 24, n	274	275	181	186	184
Mean (SD)	28.46 (1.93)	28.59 (1.60)	27.9 (2.12)	27.9 (2.25)	27.8 (2.25)
LS mean change from baseline (SE)	−0.18 (0.09)	−0.04 (0.09)	−0.2	−0.2	−0.2

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
LS difference (95% CI)	−0.14 (-0.39 to 0.10)		−0.1 (−0.4 to 0.2)	0 (−0.3 to 0.3)	
P value	0.255[a]		0.7047[f]	0.9201[f]	
EQ-5D					
Baseline, n	274	275	NR	NR	NR
Mean (SD)	0.68 (0.18)	0.67 (0.20)	NR	NR	NR
Week 24, n	274	275	NR	NR	NR
Mean (SD)	0.71 (0.18)	0.65 (0.21)	NR	NR	NR
LS mean change from baseline (SE)	0.03 (0.01)	−0.03 (0.01)	NR	NR	NR
LS difference (95% CI)	0.06 (0.03 to 0.09)		NR	NR	NR
P value	< 0.001[a]		NR	NR	NR
PGIC					
Week 24, n	274	275	NR	NR	NR
Mean (SD)	3.28 (1.10)	3.67 (1.01)	NR	NR	NR
LS difference (95% CI)	−0.40 (−0.57 to −0.22)		NR	NR	NR
P value	< 0.001[g]		NR	NR	NR
Change from baseline in ADL score during ON phase (UPDRS Section II)					
Baseline, n	274	275	223	224	222
Mean (SD)	9.97 (5.53)	10.43 (6.29)	11.8 (5.66)	12.1 (5.82)	12.3 (5.92)
Week 24, n	274	275	214	217	217
Mean (SD)	8.90 (5.44)	9.68 (5.94)	9.8 (6.01)	9.7 (6.42)	10.7 (6.24)
LS mean change from baseline (SE)	−1.22 (0.23)	−0.79 (0.23)	−1.7	−2.2	−1.2
LS difference (95% CI)	−0.43 (−1.02 to 0.16)		−0.5 (−1.2 to 0.2)	−1.0 (−1.7 to −0.3)	
P value	0.149[a]		0.1253[f]	0.0060[f]	

ADL = activities of daily living; ANCOVA = analysis of covariance; CI = confidence interval; DRS = Dyskinesia Rating Scale; EQ-5D = EuroQol 5-Dimensions; GRID-HAMD = grid-based Hamilton Rating Scale for Depression; ITT= intention-to-treat; LS = least squares; MMSE = Mini-Mental State Examination; NR = not reported; PDQ-39 = Parkinson's Disease Questionnaire 39; PGIC = Patient's Global Impression of Change; SD = standard deviation; SE = standard error; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: PDQ-39 was assessed using the "summary score" for SETTLE and the "total score" for Study 016.

[a] Parametric ANCOVA model based on the change from baseline to end point with fixed effects for treatment, region, and baseline value as a covariate. All P values, LS, and CIs were calculated from the ANCOVA model.

[b] Treatments were compared using an ANCOVA with terms for treatment and centre and baseline as a covariate.

[c] ON time is defined as ON time without dyskinesia plus ON time with minor dyskinesia.

[d] Treatments were compared using a repeated measures model, based upon the change from baseline, with terms for baseline, treatment, centre, visit, treatment × centre, and treatment × visit. A Toeplitz covariance structure was used.

[e] Treatments were compared with placebo using a Wilcoxon rank sum test.

[f] Treatments were compared using an ANCOVA with baseline as a covariate and treatment and site as main effects.

[g] Parametric ANOVA model based on the change from baseline to end point with fixed effects for treatment and region. All P values, LS means, and CIs are calculated from the ANOVA model.

Source: Clinical Study Reports for SETTLE[29] and Study 016.[30]

Harms

Only those harms identified in the review protocol are reported subsequently. See Table 11 for detailed harms data.

AEs

AEs occurred similarly in patients in the safinamide arm(s) compared with placebo in both trials (Table 11). In SETTLE, 67.9% of patients in the safinamide 50 mg/day to 100 mg/day arm and 69.1% of patients in the placebo arm experienced an AE. In Study 016, 65.9% of patients in the safinamide 50 mg/day arm, 65.6% of patients in the safinamide 100 mg/day arm, and 68.5% of patients in the placebo arm experienced an AE.

The most common AE was dyskinesia, which effected more patients in the safinamide arm(s) compared with placebo in both trials. In SETTLE, 14.6% of patients in the safinamide 50 mg/day to 100 mg/day arm compared with 5.5% of patients in the placebo arm experienced dyskinesia. In Study 016, 21.1% of patients in the safinamide 50 mg/day arm and 18.3% of patients in the safinamide 100 mg/day arm, compared with 12.6% of patients in the placebo arm, experienced dyskinesia. Pain was assessed in Study 016 and occurred in more patients in the placebo arm (4.5%) compared with the safinamide 50 mg/day (0.9%) and safinamide 100 mg/day (1.8%) arms.

SAEs

In SETTLE, more patients in the placebo arm (9.5%) experienced SAEs, compared with the safinamide 50 mg/day to 100 mg/day arm (6.6%). In Study 016, 3.6% of patients in the safinamide 50 mg/day and 9.8% of patients in the safinamide 100 mg/day compared with 8.1% of patients in the placebo arm experienced SAEs. SAEs did not occur in more than three patients in any single category in any treatment arm.

WDAEs

In SETTLE, 5.5% of patients in the safinamide 50 mg/day to 100 mg/day arm and 4.0% of patients in the placebo arm experienced a WDAE. In Study 016, 4.9% of patients in the safinamide 50 mg/day arm, 7.6% of patients in the safinamide 100 mg/day arm, and 5.0% of patients in the placebo arm experienced a WDAE. The most common WDAEs were attributed to dyskinesia.

Mortality

In SETTLE, one patient in the safinamide 50 mg/day to 100 mg/day arm and two patients in the placebo arm died. One death each in the 50 mg/day to 100 mg/day and placebo arms were cited by the sponsor as not related to the study drug, while one death in the placebo arm was likely unrelated to the study drug, according to the sponsor.

In Study 016, five patients in the safinamide 100 mg/day arm and two patients in the placebo arm died. Five deaths were cited by the sponsor as not related to the study drug, while it is unknown whether two of the deaths in the safinamide 100 mg/day arm were related to the study drug.

Notable Harms

Notable harms identified in the protocol for this review included the following: constipation, dyskinesia, hallucinations, impulsive behaviour, insomnia, melanoma, nausea, postural/orthostatic hypotension, serotonin syndrome, and vomiting.

In both studies, dyskinesia, insomnia (identified only in Study 016 for the 100 mg/day dose), and nausea occurred more frequently in the safinamide arm(s) compared with placebo. Constipation, hallucinations, impulsive behaviour, melanoma, and vomiting occurred similarly between the treatment arms. Postural/orthostatic hypotension was reported more frequently in the safinamide arm compared with placebo in SETTLE only. Serotonin syndrome was not reported in either trial.

Constipation occurred in 4.0% of patients in both the safinamide 50 mg/day to 100 mg/day and placebo arms in SETTLE. In Study 016, 3.1% of patients in both the safinamide 50 mg/day arm and safinamide 100 mg/day arm experienced constipation compared with 2.3% of patients in the placebo arm.

Hallucinations occurred in 2.2% of patients in the safinamide 50 mg/day to 100 mg/day and placebo arms in SETTLE. In Study 016, 1.8% of patients in the safinamide 50 mg/day arm and 1.3% of patients in the safinamide 100 mg/day arm compared with 1.8% of patients in the placebo arm experienced hallucinations.

Dyskinesia occurred in 14.6% of patients in the safinamide 50 mg/day to 100 mg/day compared with 5.5% of patients in the placebo arm in SETTLE. In Study 016, 21.1% of patients in the safinamide 50 mg/day arm and 18.3% of patients in the safinamide 100 mg/day arm compared with 12.6% of patients in the placebo arm experienced dyskinesia.

Impulsive behaviour occurred in 0.4% of patients in both the safinamide 50 mg/day to 100 mg/day and placebo arms in SETTLE.

Insomnia occurred in 3.6% of patients in the safinamide 50 mg/day to 100 mg/day arm compared with 1.8% of patients in the placebo arm in SETTLE. In Study 016, 1.3% of patients in the safinamide 50 mg/day arm and 3.1% of patients in the safinamide 100 mg/day arm compared with 2.7% of patients in the placebo arm experienced insomnia.

Melanoma occurred in 0.4% of patients in the safinamide 50 mg/day to 100 mg/day compared with zero patients in the placebo arm in SETTLE. In Study 016, no patient experienced melanoma.

Nausea occurred in 5.8% of patients in the safinamide 50 mg/day to 100 mg/day arm compared with 5.5% of patients in the placebo arm in SETTLE. In Study 016, 3.1% of patients in the safinamide 50 mg/day arm and 3.6% of patients in the safinamide 100 mg/day arm compared with 2.7% of patients in the placebo arm experienced nausea.

Postural/orthostatic hypotension occurred in 1.5% of patients in the safinamide 50 mg/day to 100 mg/day arm compared with 0.4% of patients in the placebo arm in SETTLE. In Study 016, 2.2% of patients in the safinamide 50 mg/day arm and 2.7% of patients in the safinamide 100 mg/day arm compared with 2.7% of patients in the placebo arm experienced postural/orthostatic hypotension.

Vomiting occurred in 1.8% of patients in both the safinamide 50 mg/day to 100 mg/day and placebo arms in SETTLE. In Study 016, 0.9% of patients in both the safinamide 50 mg/day and safinamide 100 mg/day arms compared with 1.4% of patients in the placebo arm experienced vomiting.

Table 11: Harms

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
AEs					
Patients with > 0 AEs, N (%)	186 (67.9)	190 (69.1)	147 (65.9)	147 (65.6)	152 (68.5)
Most common AEs[a]					
Abdominal pain	0	6 (2.2)	NA	NA	NA
Anxiety	6 (2.2)	4 (1.5)	NA	NA	NA
Arthralgia	7 (2.6)	13 (4.7)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	9 (3.3)	14 (5.1)	10 (4.5)	12 (5.4)	13 (5.9)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	NA	NA	11 (4.9)	14 (6.3)	13 (5.9)
Constipation	11 (4.0)	11 (4.0)	[redacted]	[redacted]	[redacted]
Cough	6 (2.2)	3 (1.1)	NA	NA	NA
Depression	NA	NA	2 (0.9)	4 (1.8)	12 (5.4)
Diarrhea	7 (2.6)	7 (2.5)	NA	NA	NA
Dizziness	7 (2.6)	8 (2.9)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyskinesia	40 (14.6)	15 (5.5)	47 (21.1)	41 (18.3)	28 (12.6)
Dyspepsia	7 (2.6)	3 (1.1)	NA	NA	NA
Fall	18 (6.6)	10 (3.6)	[redacted]	[redacted]	[redacted]
Fatigue	3 (1.1)	8 (2.9)	NA	NA	NA
Hallucination	6 (2.2)	6 (2.2)	NA	NA	NA
Headache	12 (4.4)	17 (6.2)	13 (5.8)	11 (4.9)	10 (4.5)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	4 (1.5)	6 (2.2)	13 (5.8)	10 (4.5)	8 (3.6)
Hypoesthesia	8 (2.9)	2 (0.7)	NA	NA	NA
Insomnia	10 (3.6)	5 (1.8)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	3 (1.1)	6 (2.2)	NA	NA	NA
Nasopharyngitis	9 (3.3)	11 (4.0)	NA	NA	NA
Nausea	16 (5.8)	15 (5.5)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Parkinson disease	7 (2.6)	5 (1.8)	12 (5.4)	9 (4.0)	18 (8.1)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	10 (3.6)	8 (2.9)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	17 (6.2)	12 (4.4)	[redacted]	[redacted]	[redacted]

	SETTLE		Study 016		
	Safinamide 50 mg/day to 100 mg/day (N = 274)	Placebo (N = 275)	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
SAEs					
Patients with > 0 SAEs, N (%)	18 (6.6)	26 (9.5)	8 (3.6)	22 (9.8)	18 (8.1)
Most common SAEs[b]					
[redacted]					
WDAEs, N (%)	15 (5.5)	11 (4.0)	11 (4.9)	17 (7.6)	11 (5.0)
Most common reasons[b]					
[redacted]					
Deaths, n	1	2	0	5	2
Notable harms					
Constipation	11 (4.0)	11 (4.0)	7 (3.1)	7 (3.1)	5 (2.3)
Dyskinesia	40 (14.6)	15 (5.5)	47 (21.1)	41 (18.3)	28 (12.6)
Hallucinations	6 (2.2)	6 (2.2)	4 (1.8)	3 (1.3)	4 (1.8)
Impulsive behaviour	1 (0.4)	1 (0.4)	NA	NA	NA
Insomnia	10 (3.6)	5 (1.8)	3 (1.3)	7 (3.1)	6 (2.7)
Melanoma	1 (0.4)	0	0	0	0
Nausea	16 (5.8)	15 (5.5)	7 (3.1)	8 (3.6)	6 (2.7)
Postural/orthostatic hypotension	4 (1.5)	1 (0.4)	5 (2.2)	6 (2.7)	6 (2.7)
Serotonin syndrome	NA	NA	NA	NA	NA
Vomiting	5 (1.8)	5 (1.8)	2 (0.9)	2 (0.9)	3 (1.4)

AE = adverse event; NA = not applicable; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 2%.

[b] Frequency > 1.

Source: Clinical Study Reports for SETTLE[29] and Study 016.[30]

Discussion

Summary of Available Evidence

Two phase III RCTs were included in this CDR report. SETTLE (N = 549) and Study 016 (N = 669) were 24-week, multi-centre, DB, placebo-controlled RCTs conducted in adult patients with idiopathic PD on a stable dose of levodopa. In SETTLE, patients were randomized in a 1:1 ratio to treatment with safinamide 50 mg/day to 100 mg/day or placebo. In Study 016, patients were randomized in a 1:1:1 ratio to treatment with safinamide 50 mg/day, safinamide 100 mg/day, or placebo. In both trials, randomization was stratified by region. The primary efficacy end point in both trials was the change from baseline to week 24 in daily ON time. The objective of SETTLE was to evaluate the safety and efficacy of a dose range of safinamide 50 mg/day to 100 mg/day compared with placebo as add-on therapy in patients with idiopathic PD with motor fluctuations, who are receiving a stable dose of levodopa. No relevant subgroup analyses were performed in SETTLE. The objective of Study 016 was to evaluate the efficacy and safety of two oral doses of safinamide (50 mg/day and 100 mg/day) compared with placebo, as add-on therapy in patients with idiopathic PD with motor fluctuations, who were currently receiving a stable dose of levodopa. In Study 016, ad-hoc subgroup analyses for ON time and OFF time were performed by PD medication at baseline.

Key limitations of SETTLE and Study 016 related to the eligibility criteria that reduced the generalizability of the trials to the Canadian clinical population and the lack of evidence comparing safinamide with other active treatments. A total of 80% of the patients in the Study 016 study population were Asian (recruited from India), which also may reduce the generalizability. The doses of safinamide in Study 016 (50 mg/day, 100 mg/day) were associated with distinct trials arms and was not representative of dose administration in a clinic setting, where patients would start on the 50 mg/day dose and increase the dose to 100 mg/day, depending on tolerability.

The long-term extension study (Study 018) presented data for patients up to 78 weeks following their participation in Study 016 (Appendix 6). Patients remained in their original treatment groups: safinamide 50 mg/day, safinamide 100 mg/day, or placebo. ON time, ADL score (UPDRS Section II), motor symptoms (UPDRS Section III) and harms outcomes were assessed.

The sponsor-submitted ITC in this report (Appendix 7) summarized the indirect evidence comparing safinamide 50 mg/day and 100 mg/day with other treatments for PD (pramipexole, bromocriptine, rotigotine, ropinirole, entacapone, rotigotine, rasagiline and selegiline) on a background of levodopa. The outcomes evaluated in this analysis included OFF time, discontinuations due to AEs, and AEs. The published ITC by Binde et al., 2018 summarized the indirect evidence comparing placebo plus levodopa with MAO-B inhibitors, including safinamide, plus levodopa. The outcomes evaluated in this analysis include the UPDRS and SAEs.

Interpretation of Results

Efficacy

Based on the primary outcome (change from baseline to week 24 in daily ON time assessed via diary), treatment with safinamide (50 mg/day to 100 mg/day in SETTLE;

50 mg/day and 100 mg/day in Study 016) showed statistically (but not clinically) significant improvement compared with placebo in both trials at week 24 based on an MID of one to two hours. Similar findings were reported in Study 016 for the assessment of OFF time, yet a statistically significant and clinically relevant improvement was observed for safinamide 50 mg/day to 100 mg/day in SETTLE when compared with placebo, based on an MID of −1 hour to −1.3 hours. Subgroup analysis for patients treated only with levodopa and their assigned treatment generally reflected the results of the main analysis, although greater numerical differences were observed between treatment arms. Overall, these findings confirm that safinamide had a statistically significant impact on PD-related motor fluctuations. Although superior to placebo, the differences captured by the diaries indicate only a modest clinical impact. These outcomes were indicated to be important based on input from the patient groups.

According to the clinical expert consulted in this review, along with the improvement in motor fluctuations, a positive effect on mobility (as assessed by the motor examination score [UPDRS Section III]) and ADL (assessed by the ADL score [UPDRS Section II]) is useful for determining a clinically meaningful response to treatment in patients with PD; this was echoed by the patient groups that provided input for this review. In both trials, the change from baseline in motor examination score showed statistically significant improvements for treatment with safinamide (50 mg/day to 100 mg/day in SETTLE; 50 mg/day, and 100 mg/day in Study 016) compared with placebo in both trials at week 24; clinically relevant improvements were found only for safinamide 100 mg/day in Study 016 based on an MID of 2.0 units to 6.2 units. The motor examination score assessment was adjusted for multiplicity in both trials. For the change from baseline in ADL score, the safinamide 100 mg/day arm in Study 016 was the only treatment that showed both a statically significant and clinically relevant improvement compared with placebo based on an MID of 0.5 units to 2.2 units. ADL assessment was adjusted for multiplicity in both trials.

The clinical expert consulted for this review stated that reduction of dyskinesia was among the outcomes that are considered in determining a clinically meaningfully response to treatment; however, based on the DRS, treatment with safinamide was no different than placebo for any of the doses considered in the trials. The DRS assessment was adjusted for multiplicity in Study 016 but not in SETTLE.

Improvement with respect to the PDQ-39 showed statistically and clinically meaningful differences in SETTLE for safinamide 50 mg/day to 100 mg/day. The PDQ-39 assessment was adjusted for multiplicity in SETTLE but not in Study 016. Symptom-related outcomes pertaining to depression and mental state assessed using the GRID-HAMD and MMSE, respectively, showed no difference compared with placebo for any of the doses considered in the trials. Neither outcome was adjusted for multiplicity in the trials. HRQoL outcomes using the EQ-5D-3L and patient satisfaction using the PGIC were assessed in SETTLE only and showed statistically significant differences for safinamide 50 mg/day to 100 mg/day compared with placebo, although neither outcome was adjusted for multiplicity.

While the outcomes assessed in the trials were relevant to the clinical population with PD, outcomes related to the frequency of patient-rated ON or OFF episodes, time to response, and use of health care services were not assessed in either trial. Important outcomes (EQ-5D and PGIC) were assessed in SETTLE only and were not included in the statistical testing hierarchy. In both trials, symptom-related outcomes pertaining to depression and mental state (GRID-HAMD and MMSE) were not included in the statistical testing hierarchies. Study 016 did not include the PDQ-39, and SETTLE did not include the DRS in

each of their statistical testing hierarchies. These outcomes were considered tertiary or exploratory; they were not adjusted for multiplicity and are at risk of an inflated type I error.

The trials were designed to include patients who were taking a stable dose of levodopa plus benserazide or carbidopa with or without the addition of a COMT inhibitor. Patients in the trials were also permitted concomitant treatment with a DA and/or an anticholinergic. (In SETTLE, patients could also receive concomitant treatment with amantadine.) All PD concomitant medications were optimized and stabilized in the four weeks preceding the trial and could not be adjusted at any time during the trial. The Health Canada indication for safinamide specifies that it is indicated as an add-on therapy to a regimen that includes levodopa. In Study 016, the majority (approximately 88%) of patients were on levodopa and their assigned treatment plus an additional concomitant medication for PD. While subgroup data are available for the patients who were taking levodopa only (in addition to their assigned treatment), the utility of the data is fairly limited, as it is based on 83 patients and the study was not powered to detect a difference in efficacy for the subgroup. Due to this limitation, definitive conclusions cannot be drawn regarding this subgroup; the efficacy of safinamide compared with placebo remains unclear in patients treated only with levodopa.

The generalizability of the efficacy findings from both trials to the Canadian clinical population is questionable. A total of 80% of the patients in the Study 016 study population were Asian (recruited from India), which may have an impact on generalizability to the Canadian population. Both SETTLE and Study 016 had inclusion and exclusion criteria for patient eligibility that excluded patients with late-stage PD and certain comorbidities (e.g., depression). The exclusion criteria created an enriched study population and may represent a population that was more likely to respond to treatment.

The long-term extension study (Study 018) presented data for patients following their participation in Study 016 up to week 78 (Appendix 6). Generally, the efficacy results reflected the results from Study 016 for outcomes related to ON time and UPDRS Section III and II; although some numerical reductions in efficacy were observed for treatment with safinamide 50 mg/day for motor examination (UPDRS Section III) and ADL (UPDRS Section II) compared with the results from Study 016. Efficacy outcomes should be considered exploratory, as Study 018 was not powered to detect statistical differences for any of the outcomes assessed.

Two ITCs met the inclusion criteria for this review. [redacted]

Evidence from the published Binde et al., 2018 ITC suggests improved efficacy in UPDRS compared with placebo. The utility and quality of the Binde et al., 2018 ITC is limited due to poor reporting of methods. Limitations pertaining to inadequate reporting of study and patient characteristics prevent the ability to assess generalizability to the Canadian clinical population. Definitive conclusions regarding the efficacy of safinamide compared with placebo cannot be made based on the Binde et al., 2018 ITC.

Harms

AEs were reported by most patients. In SETTLE, 67.9% of patients in the safinamide 50 mg/day to 100 mg/day arm and 69.1% of patients in the placebo arm experienced an AE. In Study 016, 65.9% of patients in the safinamide 50 mg/day arm, 65.6% of patients in the safinamide 100 mg/day arm, and 68.5% of patients in the placebo arm experienced an AE. The most common AE was dyskinesia. In both studies, dyskinesia, insomnia (identified only in Study 016 for the 100 mg/day dose), and nausea occurred more frequently in the safinamide arm(s) compared with placebo. Serotonin syndrome was not specifically evaluated in either trial.

In SETTLE, more patients in the placebo arm (9.5%) experienced SAEs compared with the safinamide 50 mg/day to 100 mg/day arm (6.6%). In Study 016, 3.6% of patients in the safinamide 50 mg/day arm and 9.8% of patients in the safinamide 100 mg/day arm compared with 8.1%% of patients in the placebo arm experienced SAEs. SAEs did not occur in more than three patients in any single harm category in any of the treatment arms. In SETTLE, 5.5% of patients in the safinamide 50 mg/day to 100 mg/day arm and 4.0% of patients in the placebo arm experienced a WDAE. In Study 016, 4.9% of patients in the safinamide 50 mg/day arm, 7.6% of patients in the safinamide 100 mg/day arm, and 5.0% of patients in the placebo arm experienced a WDAE. The most common WDAEs were attributed to dyskinesia.

In SETTLE, one patient in the safinamide 50 mg/day to 100 mg/day arm and two patients in the placebo arm died. One death each in the 50 mg/day to 100 mg/day and placebo arms were cited by the sponsor as not related to the study drug, while one death in the placebo was likely unrelated to the study drug, according to the sponsor. In Study 016, five patients in the safinamide 100 mg/day arm and two patients in the placebo arm died. Five deaths were cited by the sponsor as not related to the study drug, while it is unknown whether two of the deaths in the safinamide 100 mg/day arm were related to the study drug.

The exclusion criteria in SETTLE and Study 016 created an enriched study population and may represent a population that was not at an increased risk of potential treatment-related AEs, including comorbidities, which may have rendered a benefit–harm profile that is more optimal than what could be seen in the real-world clinical practice.

The long-term extension study (Study 018) was designed to assess the efficacy and safety of safinamide up to 78 weeks. No new safety signals arose over the course of Study 018. Safety results should also be interpreted with caution, given the enriched study population and limited generalizability to the Canadian population.

[redacted] Evidence from the Binde et al., 2018 ITC suggests no difference compared with placebo in the occurrence of SAEs was determined based on 95% CrIs. Definitive conclusions regarding the safety of safinamide compared to placebo and other treatments can not be made based on either ITC due to several limitations.

Conclusions

Safinamide is a selective and reversible MAO-B inhibitor indicated as an add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms of idiopathic PD in patients experiencing OFF episodes while on a stable dose of levodopa. Two DB RCTs provided efficacy and safety evidence for safinamide 50 mg/day to 100 mg/day, safinamide 50 mg/day, and safinamide 100 mg/day compared with placebo up to 24 weeks. Key limitations of the trials were related to patient eligibility criteria that created an enriched population, reduced external validity that limits generalizability to the Canadian population, and a lack of evidence comparing safinamide with other active treatments.

Based on the trial results, improvement in ON time (primary end point) and OFF time were statistically superior to placebo; however, the differences had only a modest clinical impact. Improvement in mobility and ADL were statistically superior to placebo; however, only the high dose of safinamide (100 mg/day) showed a clinically relevant difference. Statistical differences were not observed for improvement in dyskinesia. AEs for dyskinesia and nausea occurred more frequently in the safinamide arms compared with placebo.

No new efficacy or safety signals arose over the course of a long-term extension study up to 78 weeks. Results from a sponsor-submitted ITC and a published ITC by Binde et al. provide some evidence that may suggest increased efficacy for safinamide compared with placebo for OFF time and UPDRS; however, limitations in both ITCs prevent any definitive conclusions from being made regarding the efficacy and safety of safinamide compared with placebo and other treatments for PD.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient input submissions were provided for this review. One submission was from Parkinson Canada and the other was from Parkinson Society British Columbia (PSBC).

Parkinson Canada is a national registered charity operating since 1965. The organization advocates on issues that concern the Parkinson disease community in Canada. The Parkinson Canada Research Program funds innovative research for better treatments and a cure (http://www.parkinson.ca/).

PSBC is a non-profit organization governed by a volunteer board of directors that was established in 1969. PSBC does not receive government funding and is supported entirely by donations from individuals, members, corporations, and foundations and the dedicated efforts of volunteers. PSBC stands for the person with Parkinson and their care partners, family, and friends. It is committed to offering support, sharing reliable information, and raising funds for programs and research (https://www.parkinson.bc.ca/).

Both of the patient groups that submitted input declared they did not receive any financial payment over the past two years from any company or organization that may have a direct or indirect interest in the drug under review.

2. Condition Related Information

The information for the Parkinson Canada submission was gathered from two 2017 surveys as well as an interview conducted by Parkinson Canada with a movement disorder specialist who has previous experience prescribing safinamide in Italy.

The PSBC submission was gathered in May 2019 through an online survey asking patients for their experience if they had used either rasagiline or selegiline.

Within each survey, 45% to 91% of the survey respondents identified as being a person with PD followed by respondents who identified themselves as caregivers for a person with a PD (9% to 39%).

Parkinson Canada's first survey showed that people with PD describe the "loss of confidence" they have experienced since developing PD and the impact this has had on their daily life. This reported loss of confidence is due in large part to medication wearing off or OFF times.

Nearly 40% of respondents specifically mentioned that PD has negatively impacted their ability to socialize and maintain relationships because they have had to stop engaging in recreational activities (e.g., sports) or family life. People with PD who report being able to maintain relationships and engage in daily activities often reported slowness of movement and balance issues as being a challenge to their participation. It is important to understand that PD is a progressive disease, causing abilities to change and making participation in daily activities increasingly more difficult over time.

In both submissions, respondents with PD indicated anxiety, stress, a loss of confidence, and sadness as the most common emotional impacts of the disease. Physical changes included impaired balance, muscle rigidity, and slowness of movement.

Caregivers most often reported a lack of time due to the demands of caring for a person with PD. This lack of time makes it challenging to maintain social and/or recreational activities. Caregivers also described the loss of confidence experienced by the person they care for (due to OFF times) as being a barrier to engaging in social or daily activities with the person they care for.

3. Current Therapy Related Information

People who responded to the survey indicated experience with a range of different symptomatic treatments, including medications (e.g., MAO-B inhibitors and levodopa/carbidopa), surgical procedures (e.g., deep brain stimulation), other forms of therapy (e.g., physiotherapy, occupational therapy, speech therapy, exercise) and psychological follow-up.

According to the Parkinson Canada survey, 67% of respondents with PD have experienced side effects when taking medications, including disturbed sleep, nausea, constipation, dyskinesia, fatigue, and hallucinations. Furthermore, 14% of respondents reported difficulties in receiving treatment, including difficulties in swallowing, remembering to take medication, and timing their medication with meals.

Patients who used levodopa reported dyskinesia or involuntary writhing movements, and people in an advanced state of PD frequently experience these to a severe extent, even when they are ON. However, without levodopa, they are then reduced to an OFF state, an even more disabling, frightening stage where breathing and swallowing are at risk.

4. Expectations About the Drug Being Reviewed

The importance of access to new medication was highlighted in both submissions. Patients reported the need for a medication that would cure the disease, stop disease progression, and effectively control symptoms. There is also an expressed need for longer-lasting medications that limit or eliminate OFF times with fewer side effects, such as hallucinations.

The following are examples from the patients' responses regarding their experiences and expectations for new treatments:

- "Parkinson disease, even on the best of days, severely limits one's daily activity. Off-periods bring everything to a halt and are disorienting and uncomfortable. Adding extra

functionality to a day makes a significant difference when one has only a few hours to begin with."

- "Every morning it takes an hour for my multiple medications to take effect, so that I can perform activities at a comfortable pace such as dressing and meal preparation. The effect of my medications wears off within 2 1/2 hours, causing very painful foot dystonia two to three times a day."
- "Cost, constantly travelling to drug store to pick up something as the insurance company only releases the coverage dependent of the individual cost. Very frustrating to have to drive back and forth 4 x to get the pills I need for my husband every month."
- "I am tired of the unpredictability of my current meds regime and having several times per day when I am not feeling well."
- "Medication that takes more rapid effect, does not lose its effectiveness before the next dose is due (effectiveness wears off), and is more effective in treating inertia (freezing) and inability to walk; also medication to permit intelligible and normal speech. These improvements would enable more normal mobility and communication with family and others."
- "Frequency and timing in conjunction with meals. Nobody with Parkinson's moves quickly and many have difficulty swallowing. A half-hour window in which to eat, so that protein does not interfere with the Levodopa is impossible to realize and causes stress for the person with Parkinson's and for the caregiver."

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 02, 2018
Alerts:	Biweekly search updates until project completion
Study Types:	No publication type filters were applied.
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.ot	Original title (Medline)
.rn	Registry number
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
/	At the end of a phrase, searches the phrase as a subject heading

MULTI-DATABASE STRATEGY

Line #	Search Strategy
1	(Onstryv* or Xadago* or safinamide* or fbap methanesulfonate* or NW 1015 or NW1015 or FCE 28073 or FCE28073 or PNU 151774* or PNU151774* or FCE 26743 or FCE26743 or EMD 1195686 or EMD1195686 or EC 603 772 2 or EC 6037722 or EC6037722 or 90ENL74SIG or YS90V3DTX0).ti,ab,kf,ot,hw,rn,nm.
2	1 use medall
3	*safinamide/
4	(Onstryv* or Xadago* or safinamide* or fbap methanesulfonate* or NW 1015 or NW1015 or FCE 28073 or FCE28073 or PNU 151774* or PNU151774* or FCE 26743 or FCE26743 or EMD 1195686 or EMD1195686 or EC 603 772 2 or EC 6037722 or EC6037722).ti,ab,kw,dq.

MULTI-DATABASE STRATEGY	
Line #	**Search Strategy**
5	or/3-4
6	5 use oemezd
7	6 not conference abstract.pt.
8	2 or 7
9	remove duplicates from 8

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Onstryv OR Xadago OR safinamide OR NW 1015 OR FCE 28073 OR PNU 151774E OR FCE 26743 OR EMD 1195686 OR EC 603 772 2]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms -- Onstryv OR Xadago OR safinamide OR NW 1015 OR FCE 28073 OR PNU 151774E OR FCE 26743 OR EMD 1195686 OR EC 603 772 2]

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	June 20, 2019 – July 02, 2019
Keywords:	[Onstryv OR Xadago OR safinamide OR Parkinson's]
Limits:	Publication years: none

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trial Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals
- Up-To-Date

Appendix 3: Excluded Studies

Table 12: Excluded Studies

Reference	Reason for Exclusion
Ameri AA. Idiopathic Parkinson's disease: Safinamide as add-on therapy to levodopa extends the on-time. Psychopharmakotherapie. 2017;24(2):91-92.[41]	Not published in English
Ameri AA. Idiopathic Parkinson's syndrome: Safinamide as add-on therapy to levodopa prolongs the on-time. Med Monatsschr Pharm. 2017;40(7):316-317.[42]	Not published in English, duplicate publication
Stocchi F, Borgohain R, Onofrj M, et al. A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson's disease patients. Mov Disord. 2012;27(1):106-112.[43]	Population does not meet inclusion criteria
Stocchi F, Radicati FG, Torti M. Drug safety evaluation of ropinirole prolonged release. Expert Opin Drug Saf. 2014;13(3):383-389.[44]	Population does not meet inclusion criteria

Appendix 4: Detailed Outcome Data

Table 13: Efficacy Outcomes for Patients on Levodopa Alone at Baseline (ITT Population)

	Study 016		
	Safinamide 50 mg/day (N = 36)	Safinamide 100 mg/day (N = 23)	Placebo (N = 24)
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

ITT = intention-to-treat.

[redacted]

Source: Clinical Study Report for Study 016.[30]

Table 14: Cogtest PD Battery Test Scores for SETTLE (ITT Population)

	Safinamide 50 mg/day or 100 mg/day (N = 274), placebo (N = 275)			
	LS mean difference	Lower 95% CI	Upper 95% CI	P value
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

	Safinamide 50 mg/day or 100 mg/day (N = 274), placebo (N = 275)			
	LS mean difference	Lower 95% CI	Upper 95% CI	P value
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intention-to-treat; LS = least squares; PD = Parkinson disease.

Source: Clinical Study Report for SETTLE.[29]

Table 15: Cogtest PD Battery Test Score for Study 016 (ITT Population)

		Mean	SD	Lower 95% CI	Upper 95% CI
Cogtest PD battery test score change in z score from baseline to week 24					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Mean	SD	Lower 95% CI	Upper 95% CI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; ITT = intention-to-treat; PD = Parkinson disease; SD = standard deviation.

Source: Clinical Study Report for Study 016.[30]

Appendix 5: Description and Appraisal of Outcome Measures

Aim

To describe the outcome measures listed in Table 16 and review their measurement properties (validity, reliability, responsiveness to change, and MID).

Table 16: Outcome Measures Included in Each Study

Outcome Measure	SETTLE	Study 016
Diary-recorded ON time	Primary	Primary
Diary-recorded OFF time	Key secondary	Secondary
UPDRS Section III (motor symptoms) during ON phase	Key secondary	Secondary
UPDRS Section II (activities of daily living) during ON phase	Key secondary	Secondary
Parkinson's Disease Questionnaire 39 (PDQ-39)	Key secondary	Exploratory
Cogtest Parkinson's disease battery	Exploratory	Secondary
Dyskinesia Rating Scale	Exploratory	Secondary
EuroQol 5-Dimensions 3-Levels (EQ-5D-3L)	Exploratory	NA
Grid-based 17-item Hamilton Rating Scale for Depression (GRID-HAMD-17)	Exploratory	Exploratory
Mini-Mental State Examination (MMSE)	Exploratory	Exploratory

NA = not applicable; UPDRS = Unified Parkinson's Disease Rating Scale.

Findings

Table 17: Summary of Outcome Measures and Their Measurement Properties

Outcome Measure	Type	Conclusions about measurement properties	MID
Diary-recorded ON and OFF time	The PD home diary is used in patients experiencing motor fluctuations and dyskinesia to record ON and OFF times. For each half-hour period in the day, patients or caregivers characterize the period as one of the following: asleep, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, and ON with troublesome dyskinesia.	**Validity** There is some evidence for the content validity of OFF time, ON time without dyskinesia, and ON time with non-troublesome dyskinesia. There is some evidence for the construct validity of combined ON time without dyskinesia or with non-troublesome dyskinesia as well as for OFF time. **Reliability** Combined ON time without dyskinesia or with non-troublesome dyskinesia was found to have acceptable test–retest reliability. **Responsiveness** An MID for OFF time has been evaluated in one trial.	Improvement in OFF time: −1 hour to −1.3 hours in patients with advanced PD.

Outcome Measure	Type	Conclusions about measurement properties	MID
UPDRS-III (motor symptoms) and UPDRS-II (ADL) during ON phase	The UPDRS is a measure of disability and impairment in PD. It consists of four sections: Section I (mentation, behaviour, and mood), Section II (ADL), Section III (motor examination), and Section IV (complications of therapy in past week). The UPDRS-III (motor examination) uses a set of 14 tasks to assess motor function in patients with PD. There are 27 ratings, each scored on a 5-point Likert-type scale from 0 to 4, with higher scores indicating worse symptoms. The total score ranges from 0 to 108. The UPDRS-II (ADL) assesses impacts on ADL using 13 items administered by interview and scored on a 5-point Likert-type scale from 0 to 4, with higher scores indicating greater impairment. The total score ranges from 0 to 52.	**Validity** There is evidence of content validity for the UPDRS-III. There is evidence of convergent validity for both the UPDRS-II and UPDRS-III in the form of strong correlations with the Hoehn and Yahr scale and known measures of disability and functional impairment. **Reliability** There is evidence for acceptable internal consistency reliability, inter-rater reliability, and test–retest reliability for the UPDRS-II and UPDRS-III. **Responsiveness** Responsiveness of one or both subscales was assessed in five different studies using a mixture of anchor- and distribution-based methods.	Unless indicated, the studies reporting MIDs did not state whether the UPDRS-II or UPDRS-III were administered in the ON or OFF state. **UPDRS-II** Early PD: −0.5 to −2.2. Advanced PD: −1.8 to −2.3 (based on one study in which UPDRS-II score in the ON and OFF states was averaged). **UPDRS-III** Early PD: −2.0 to −6.2. Advanced PD: −5.2 to −6.5 (including one study that found an MID of ± 5 in the ON state). Varying stages: A moderate effect size corresponded to 5.2.
PDQ-39	The PDQ-39 is a disease-specific HRQoL measure consisting of eight domains (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort); graded on a five-point scale (0 = never, 4 = always).	**Validity** The PDQ-39 has been extensively validated in multiple settings (clinic-based, community-based, and longitudinal sample) and cultures. Convergent validity of its domains has been demonstrated through moderate to strong correlations with disease stages, measures of symptom severity, physical aspects of health status, and related scales of the SF-36. Weak correlations were found with psychosocial aspects. **Reliability** Multiple studies have found acceptable internal consistency reliability (except for the social support domain in one study) and test–retest reliability for all domains. **Responsiveness** Several studies have found varying levels of responsiveness for the domains, ranging from low to significant responsiveness. Individual domains may be more responsiveness to either improvement or worsening. Overall,	In patients with PD (information on PD severity not reported): • Overall score: −1.6 • Mobility: −3.2 • ADL: −4.4 • Emotional well-being: −4.2 • Stigma: −5.6 • Social support: −11.4 • Cognition: −1.8 • Communications: −4.2 • Pain: −2.1

Outcome Measure	Type	Conclusions about measurement properties	MID
		responsiveness was relatively higher for domains measuring physical and functional aspects of PD compared with psychosocial symptoms.	
Cogtest PD battery	The Cogtest uses a console with a touch-screen interface to capture responses to a battery of cognitive tests selected for patients with PD. The tests involve an auditory number sequencing test, spatial working memory test, a strategic target detection test, a word list learning test, a symbol digit substitution test, and a spatial planning test.	No evidence was found for the validity, reliability, and responsiveness of the Cogtest PD battery.	Unknown
DRS	A set of 3 tasks to measure the severity of dyskinesia in PD with each item scored on a 5-point ordinal scale from 0 to 4. Higher scores correspond with more severe dyskinesia.	**Validity** No evidence for the validity of the DRS was found. **Reliability** There is some evidence for acceptable inter-rater and test–retest reliability of the DRS. **Responsiveness** No evidence for the responsiveness of the DRS was found.	Unknown
EQ-5D-3L	The EQ-5D-3L is a generic, preference-based, HRQoL measure consisting of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels representing no problems (1), some problems (2), and extreme problems (3).	**Validity** The EQ-5D-3L is a well-validated measure of generic HRQoL. In patients with PD, it has been shown to correlate strongly with physical attributes of standard measures of functional disabilities and relatively weakly with psychosocial attributes. **Reliability** There was no information found on the reliability of the EQ-5D-3L in patients with PD. **Responsiveness** Responsiveness in patients with PD has been reported in 12 studies. There was varying responsiveness to clinical changes and limited sensitivity to detect changes in milder PD cases.	Index score in patients with PD: 0.10 to 0.11

Outcome Measure	Type	Conclusions about measurement properties	MID
GRID-HAMD-17	The GRID-HAMD-17 is based on the 17-item Hamilton Rating Scale for Depression, which is a widely used measure in clinical trials for major depressive disorder. The GRID-HAMD-17 assesses depression and was developed to standardize the administration and scoring of the scale without significantly altering the original intent of the items or the scoring profile. Each of the 17 items, which assess symptoms, is rated both in frequency and severity. Item scores range from 0 to 4 or 0 to 2, with higher scores corresponding to greater frequency and/or intensity. The possible score range is 0 to 52.	**Validity** The content validity of the original HAMD scale may be poor, as it contains some symptoms not in the official DSM-IV criteria and some symptoms that may not be recognized as associated with depression. There is some evidence of construct validity of the GRID-HAMD-17 total score as demonstrated by a strong correlation with the Structured Interview Guide for the HAMD in patients with major depressive disorder. **Reliability** Inter-rater and internal consistency reliability for the total score were found to be acceptable by the scale developers in patients with major depressive disorder. Information on reliability was not found for patients with PD. **Responsiveness** There was no information found on the responsiveness of the GRID-HAMD-17 in patients with PD.	Unknown in patients with PD
MMSE	The MMSE is a brief, commonly used test to assess cognitive function. It consists of 11 items that evaluate attention and orientation, memory, registration, recall, calculation, language, and ability to draw a complex polygon. The score ranges from 0 to 30, with lower scores corresponding with increasing cognitive impairment.	**Validity** There is some evidence of construct validity of the MMSE total score in patients with PD demonstrated by strong correlations with the Mattis Dementia Rating Scale total score and subtest scores. **Reliability** Internal consistency reliability of the MMSE total score has been found to be inadequate and the standard error of measurement was found to be 2.00 in patients with PD at various disease stages. **Responsiveness** The responsiveness of the MMSE total score to decline in cognition was found to be poor in patients with PD who did not have dementia.	Unknown in patients with PD

ADL = activities of daily living; DRS = Dyskinesia Rating Scale; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; GRID-HAMD-17 = grid-based 17-item Hamilton Rating Scale for Depression; HRQoL = health-related quality of life; MID = minimal important difference; MMSE = Mini-Mental State Examination; PD = Parkinson disease; PDQ-39 = Parkinson's Disease Questionnaire 39. PGI-C = Patient's Global Impression of Change; SF-36 = Short Form (36) Health Survey; UPDRS = Unified Parkinson's Disease Rating Scale; UPDRS-II = UPDRS Section II; UPDRS-III = UPDRS Section III.

PD Home Diary

The amount of time spent by patients with PD in the OFF state per day can be measured from patient diaries. One type of diary structure for assessing OFF time in patients with PD that has been evaluated is a grid system where patients or caregivers place a checkmark for each half-hour period under the category that best characterizes that period. The categories are the following: asleep, OFF, ON without dyskinesia, ON with non-troublesome dyskinesia, and ON with troublesome dyskinesia. In the SETTLE study and Study 016, the primary end point was defined as daily ON time without dyskinesia plus daily ON time with non-troublesome dyskinesia.

One study compared this diary against a reference diary indicating "good" time and "bad" time during waking hours in patients with PD on levodopa/carbidopa with at least one-half hour of troublesome dyskinesia and one hour of good function every day.[33] In 17 diary sets representing 816 half-hour periods, 85.5% of ON time without dyskinesia and 93.8% of ON time with non-troublesome dyskinesia were categorized as "good" time, while 89.9% of ON time with troublesome dyskinesia and 84.9% of OFF time were categorized as "bad" time.[33]

The test–retest reliability of the second version of the grid system was assessed in a separate study of 302 patients with PD from 10 countries on levodopa with motor fluctuations and moderately disabling dyskinesias who filled out daily diaries over six days.[34] The diary was shown to be both feasible and simple in its use (with an 83% completion rate without duplication or error); however, errors and non-compliance were more prevalent after three days of use.[34] The adaptability of the PD home diary for non-English speakers was further demonstrated after the diary was translated from English to the study participants' native languages.[34] While OFF time was not assessed, ON time without dyskinesia or with non-troublesome dyskinesia was found to have acceptable test–retest reliability (intraclass correlation coefficient [ICC] > 0.7).[35] Evidence of construct validity was provided by a moderate strength of correlation[36] of ON time without dyskinesia and with non-troublesome dyskinesia as a percentage of the waking day with a visual analogue scale asking: "How much of the day today did you experience a good response?" (Pearson correlation coefficient [r] = 0.41).[34] A major limitation of the study was that good ON time was not compared with other external measures of function and disability.

In a placebo-controlled trial of rasagiline in 472 patients with levodopa-treated PD, diary-recorded mean daily OFF time was compared against the Patient's Global Impression of Improvement (PGI-I) at both baseline and week 26.[45] Patient diaries had categories for ON, OFF, and asleep time.[45] Patients on the trial drug who reported a minimal improvement had a change in mean daily OFF time of −1.9 hours ± 2.2 hours (n = 69).[45] A PGI-I rating of "no change" in patients on placebo corresponded to −0.9 hours ± 2.5 hours (n = 44).[45] Subtracting the "no change" values in patients on placebo from "minimally improved" values in patients on the trial drug yielded an MID of −1.0 hours using PGI-I as an anchor.[45] A similar study testing immediate-release and extended-release versions of pramipexole in a similar sample of PD patients found MIDs for mean daily OFF time using the same method.[37] The minimal clinically important differences found were −1.3 hours for the immediate-release version (n = 55 for the drug, n = 43 for placebo) and −1.0 hours for the extended-release version (n = 66).[37]

UPDRS

The UPDRS is a widely used method for evaluating disability and impairment in PD. The scale is composed of four sections: Section I (mentation, behaviour, and mood: four items,

score range of 0 to 16), Section II (ADL:13 items, score range of 0 to 52), Section III (motor examination: 14 items, score range of 0 to 108), and Section IV (complications of therapy and symptoms including dyskinesia and OFF state: 11 items, score range of 0 to 23).[11] Individual items in sections I to III are scored on a five-point scale (0 to 4), with higher scores indicating worse symptoms, while Section IV includes a number of items scored either numerically (like sections I to III) or using zero or one (no or yes, respectively). The full scale takes 10 to 20 minutes to administer with a range of 0 (no disability) to 199 (worst disability).[11] The overall and subscale scores have been thoroughly assessed in several different languages. While a revised version of the scale was commissioned by the Movement Disorder Society (MDS) in 2007 (the MDS-UPDRS),[46] the original UPDRS was used in the pivotal trials.

A panel of 13 international experts independently rated the relevance of the scales and items of the UPDRS to assess content validity, with endorsement by at least 75% of the experts needed to establish satisfactory content validity.[47] With the exception of the UPDRS Section III (83.3%), none of the subscales attained the adequate standard.[47]

Four studies assessed the measurement properties of the original UPDRS in patients with varying degrees of PD severity, including an early validation study by the Cooperative Multicentric Group,[48] one multi-centre RCT that included Canada and the US,[49] a systematic review of 11 measures of PD,[50] and a large, multi-centre, cross-sectional study.[47,51]

The Cooperative Multicentric Group reported that the administration time for the UPDRS was brief (10 to 20 minutes).[48] The multi-centre study showed a low percentage of missing data across the four subscales (< 10%), indicating a high completion rate.[47,51] Together, these results demonstrate that the scale can be easily administered within a short period in clinical trial and population settings. Across all studies, internal consistency reliability was found to be adequate[35] for the full scale as well as the subscales ($0.79 \leq$ Cronbach's alpha ≤ 0.96).[47,48,50,51] Studies assessing inter-rater reliability found moderate to substantial inter-rater agreement[52] for most items ($0.50 <$ kappa < 0.90) and moderate agreement for a few ($0.40 <$ kappa < 0.50), with total scores highly correlated among raters ($r = 0.98$).[48,50] One multi-centre trial (including Canada and the US) evaluated the test–retest reliability of the UPDRS as measured by neurologists among patients with early-stage PD.[49] It reported acceptable[35] test–retest reliability for the total score (ICC of 0.92) and the four subscales (ICC range of 0.74 to 0.90).[49] One study investigated the intra-rater reliability of UPDRS Section III by clinicians in patients with advanced PD.[53] In both ON and OFF states, clinicians had excellent agreement with total UPDRS Section III scores (ICC approximately 0.90).[53]

Convergent validity has also been demonstrated for the total scale and subscales. A strong correlation[36] was found between the UPDRS and the Hoehn and Yahr scale ($r = 0.71$).[48] The same study compared the UPDRS with other known measures of disability and functional impairment (convergent validity). Between-scale correlations were strong[36] for the Intermediate Scale for Assessment of PD ($r > 0.80$), the Schwab and England ADL scale *(*$r > 0.80$), the MMSE ($r = 0.53$), and the Hamilton Scale for Depression ($r = 0.64$).[48] The authors of the large multi-centre study also evaluated the construct validity of the UPDRS by examining its relationship with Hoehn and Yahr stage and the Schwab and England scale. All four subscales showed moderate to strong correlations with both measures ($0.4 < |r| < 0.75$).[47,51] Small ceiling effects were observed in the subscales,

though this may have been due to the predominant inclusion of patients with milder symptoms.[47,51]

Three studies estimated MIDs for the UPDRS subscales in early PD patients. Schrag et al.(2006) estimated MIDs for the UPDRS total score, UPDRS Section II, and UPDRS Section III scores retrospectively among patients with early PD using data from two independent, active-controlled RCTs (N = 603 total).[54] Using the Clinical Global Impression of Improvement (CGI-I) as an anchor, the minimal change representing the MID following six months of anti-PD treatment was determined.[54] In the two RCTs, patients with minimal improvement had mean changes in the Section III score of −2.2 (standard error [SE] of 0.4) and −1.8 (SE of 0.4) and mean changes in the UPDRS Section III score of −5.0 (SE of 0.8) and −5.3 (SE of 0.8).[54] Mean changes tended to increase in magnitude with increasing Hoehn and Yahr stage.[54] Hauser et al. (2011) analyzed data from a placebo-controlled RCT composed of early PD patients (N = 404); total duration was six months.[45] Using the CGI-I as an anchor and two methods (mean change and a receiver operating characteristic curve), MIDs of −0.5 points to −0.7 points for the UPDRS Section II score and −2.0 points to −2.4 points for the UPDRS Section III score were found.[45] Another study by Sánchez-Ferro et al. (2018) estimated an MID for the UPDRS Section III in the ON state in early PD patients (N = 29 plus N = 29 control patients) in an everyday clinical setting, using combined distribution- and anchor-based methods.[55] After a mean of six months of treatment, the MID for improvement was −4.83 points and the MID for worsening was 4.38 points.[55] These values were rounded up to ± 5 points and it was noted that none of the control patients had a change of 5 points or more.[55]

Two other studies provided estimates of MIDs for subscales and total score among patients with varying stages of PD. One cross-sectional study (N = 653, representing all PD stages) used both distribution- and anchor-based approaches (based on the Schwab and England scale, Hoehn and Yahr stage, and Short Form [12] Health Survey) and reported a moderate effect size of 5.2 points for UPDRS Section III score when all methods were taken into account.[56] Using data from two other double-dummy, placebo-controlled RCTs among early PD patients (N = 539, 33 weeks) and advanced PD patients (N = 517, 18 weeks), Hauser et al. (2014) estimated the MIDs for UPDRS sections II and III using the PGI-I as an anchor in two groups (receiving either extended-release or immediate-release pramipexole).[37] Among early PD patients, the ranges of MIDs for UPDRS sections II and III were −1.8 points to −2 points and −6.1 points to −6.2 points, respectively. Among advanced PD patients, the ranges of MIDs for UPDRS sections II and III were −1.8 to −2.3 points (using the mean of the UPDRS Section II during ON and OFF times) and −5.2 points to −6.5 points, respectively.[37] MIDs were calculated by subtracting the mean change in placebo-treated patients rated as “no change” from the mean change in pramipexole-treated patients rated as “a little better.”[37]

Other than where indicated, it was not specified whether the estimated MIDs for UPDRS sections II and III in the studies were assessed in the ON or OFF states.

DRS

The DRS is a scale for assessing dyskinesia based on interference with ADL that was developed by modifying the Obeso Dyskinesia Rating Scale.[57] The scale uses three tasks to rate the severity of dyskinesia among patients with PD: walking, putting on a coat and buttoning it, and lifting a cup to the lips for drinking.[57] The tasks were chosen because they involve the large and small muscles of all extremities as well as trunk and neck control. Severity of dyskinesia based on the patient’s worst function is rated on a five-point ordinal

scale as described subsequently.[57] The type of dyskinesia(s) observed (chorea, dystonia, or other) and the most disabling type of dyskinesia are also recorded.[57]

- 0: Absent
- 1: Minimal severity, no interference with voluntary motor acts
- 2: Dyskinesias may impair voluntary movements but patient is normally capable of undertaking most motor acts
- 3: Intense interference with movement control and daily life activities are greatly limited
- 4: Violent dyskinesias, incompatible with any normal motor task.

The scale developers tested the DRS in a sample of 40 patients with PD on chronic dopaminergic therapy with varying types and severities of dyskinesia.[57] Video recordings of the patients performing the tasks were evaluated by physicians and nurses and each possible rating on the severity scale was represented.[57] Raters evaluated the same set of recordings two weeks apart.[57] Severity of dyskinesia showed acceptable (> 0.7) inter-rater (Kendall's coefficient of concordance = 0.76 and 0.876 for two separate sets of recordings) and test–retest (Spearman rank correlation coefficient [rho] = 0.855) reliability.[57] Information on the validity or MID of the DRS severity of dyskinesia scale was not found.

PDQ-39

The PDQ-39 is one of the most commonly used PD-specific HRQoL measures. Its measurement properties have been studied extensively and it has been recommended for use by the MDS.[58] The PDQ-39 is a self-administered questionnaire consisting of 39 items that measure eight domains of health: mobility (10 items), ADL (six items), emotional well-being (six items), stigma (four items), social support (three items), cognition (four items), communication (three items), and bodily discomfort (three items).[39] Each item is graded on a five-point Likert scale (0 = never, 4 = always), which are then added to generate the respective domain scores. Each domain is coded on a scale from 0 (no problem at all) to 100 (maximum level of a problem). Further, an overall single summary index (PDQSI) representing the global HRQoL can be created by averaging the eight subscale scores. The PDQSI is also coded on a scale ranging from 0 to 100, with higher scores indicating worse quality of life.[38,39]

The psychometric properties of the domain and index score of the PDQ-39 have been extensively evaluated in many studies across different geographic locations and with different languages. Only evidence for the English version of the scale is summarized here.

One study by Damiano et al.[59] assessed the comprehensiveness of PDQ-39 in a clinical trial setting based on a literature review and consultation with clinicians and patients. The authors found the PDQ-39 measures 10 out of 12 areas of HRQoL identified as relevant to PD patients, other than self-image and sexual function.[59]

The Damiano et al. study reported that the PDQ-39 has a short administration time, estimated to be less than 30 minutes, and can be uniformly administered by patients, interviewers, and caregivers.[59] One study by Jenkinson et al. validated the PDQ-39 in a cross-culture study across five countries (including Canada and the US).[60] Similar to the previous study, a high completion rate (> 82%) and a low percentage of missing scores (< 5%) was reported for both domain and index scores.[60] Additionally, assessments of the validity of the PDQ-39 have been conducted in different settings, including clinic-based,

community-based, and longitudinal samples, making the interpretation more generalizable.[59]

The UK-based research group that developed the scale assessed the reliability of the PDQ-39 and PDQSI internally with other domain scores and an acceptable internal consistency (Cronbach's alpha > 0.7 and > 0.8, respectively) was found, indicating the items performed well enough together to be a composite score. The test–retest reliability (range 0.68 to 0.94) was high.[38,39] A US study adapted the British version into a US version and found corroborating psychometric properties, with Cronbach's alpha greater than 0.7 for all but one domain (social support, alpha = 0.51), and high test–retest reliability (range 0.86 to 0.95).[61] Similarly, Damiano et al.[62] reported adequate internal consistency (Cronbach's alpha ≥ 0.7 and 0.85 for PDQSI) across domains, with the exception of social support (Cronbach's alpha = 0.57). Findings from the cross-national validation study were similar, with generally adequate internal consistency for all domains (Cronbach's alpha ≥ 0.7), except for social support.

The developers of the PDQ-39 documented the construct (specifically convergent) validity of the individual domain score of the scale in comparison with other patient-reported measures of ill health, namely the Columbia Rating Scale and Hoehn and Yahr staging. While moderate to strong correlations were found between the scales for dimensions measuring the physical aspects of health status (mobility and ADL, Spearman's correlation, r > 0.5), psychosocial aspects had weak correlations (emotions, stigma, and social, r < 0.3).[60] In contrast, correlations between related domain scores of PDQ-39 and the Short Form (36) Health Survey (SF-36) were strong ($-0.66 \leq r \leq -0.8$).[63] The US-based study reported similar findings, with strong correlations between related domain scores of PDQ-39 and SF-36 ($-0.59 \leq r \leq -0.88$) with the exception of the subscale measuring social support ($r = -0.22$).[61] In addition, the PDQ-39 generally had strong correlations with five measures of symptoms severity (tremor, stiffness, slowness, freezing, jerking) as measured by the related scales of the SF-36 ($0.21 \leq r \leq 0.74$).[61] Concurrent validity in the English version of the PDQ-39 was only assessed by Harrison et al. by comparing the performance of PDQ-39 with other established measures of disease severity, depression, and anxiety.[64] Domains of the PDQ-39 that were related to the Beck depression inventory scores, the Barthel index, and the Royal Postgraduate Medical School severity scale had moderate to strong correlations (r ranged from 0.3 to 0.73).[64]

The US-based study assessed the discriminative ability of the PDQ-39 by measuring the scale's ability to discriminate between the stages of PD. Respondents consistently indicated a significantly higher score for each domain of the PDQ-39, with progressive worsening of five measures of symptoms severity (tremor, stiffness, slowness, freezing, jerking).[61] The discriminative ability was further demonstrated by Damiano et al. where higher (poorer) PDQ-39 domain and index scores were associated with more severe Hoehn and Yahr stages and dyskinesia as well as presence of comorbidities.[62]

The developers of the PDQ-39 reported moderate responsiveness for two of its domains (standardized mean change over time was 0.55 and 0.43 for mobility and ADL, respectively); responsiveness for the other six domains was low.[59] Harrison et al. assessed the comparative responsiveness of the PDQ-39 and other established measures of mood and motor function (the 28-item General Health Questionnaire and the Office of Population and Census Surveys disability instrument) in a UK population.[64] Results from their study showed the PDQ-39 and its subscales had superior responsiveness to change over time (except domains involving emotion and bodily discomfort). In a naturalistic study (e.g., no

intervention, examining patients over time) by Schrag et al., the PDQ-39 showed moderate to significant internal responsiveness in the population-based sample after one year in at least one measure of the social support, communication, and ADL subscales while, after four years, internal responsiveness was observed in the communication, ADL, stigma, mobility, and cognition subscales.[65] Additionally, in their clinic-based sample, Schrag et al. found some change in internal responsiveness at one year; however, this was observed only in the summary index and bodily pain and communication subscales.[65] While the authors did observe internal responsiveness in the PDQ-39 HRQoL scale, they also noted that it was much less than that observed using tools that measured impairment changes such as the Hoehn and Yahr and the UPDRS.[65] In a different study by Tu et al., both the internal and external responsiveness of the PDQ-39 and the SF-36 were examined in clinic-based patients with confirmed PD.[66] After a one-year follow-up, the authors ascertained (using the MDS-UPDRS Section III motor domain) that 16 of 74 patients had improved and 34 had worsened. Significant differences were observed between baseline and follow-up scores in the PDQ-39 mobility domains in patients who had improved, while significant differences were observed in the summary index score, body discomfort, communication, social support, and emotional well-being scores in patients who worsened.[66] Effect sizes and standardized response means (SRMs) of greater than 0.5 supported moderate to large responsiveness for the PDQ-39 mobility domain (SRM = 0.72) in improved patients, and the PDQ-39 social support, summary index, and communication (SRM = −0.51, −0.55, and −0.55, respectively) scores in patients who worsened.[66] The authors determined that the PDQ-39 was responsive to changes in motor difficulties over the year and their findings supported the longitudinal validity of this instrument in patients with PD.[66]

Floor and ceiling effects were evaluated by Damiano et al. on patients with varying degrees of PD severity using the self-completed and telephone interview versions of the PDQ-39. Both modes of administration generally showed low floor and ceiling effects across different domains (range of 0.0% to 6.1% for floor effects and 1.5 to 31.3% for ceiling effects), which was essentially eliminated by the index score. However, the stigma and social support subscale had noticeably high ceiling effects, indicating a high proportion of study participants had maximum scores for these two domains.[62] These findings were consistent with the cross-national validation study,[60] where a generally low floor and ceiling effects were seen across different domains (< 15% and 5%, respectively). However, the stigma and social support domain had a large floor effect (> 20% and > 50%, respectively), indicating a substantial proportion of the study participants scored at the floor (i.e., zero); but the floor effect was virtually eliminated by the index score.

The only study examining the scaling assumption in the English version of PDQ-39 was the cross-national study by Jenkinson et al.[60] The authors reported a higher-order factor analysis to create a single index score, PDQSI. The index score had eight values greater than 1 and explained > 50% of the variance, supporting the scaling assumptions.

One study by the original research group that developed the PDQ-39 scale investigated the MID for the index score as well as across different domains. A postal survey was conducted of randomly selected patients from 13 local branches of the Parkinson's Disease Society of the United Kingdom; the response rate was 53% (N = 728) and no information on PD severity or anchoring was provided. Findings from the study showed a varying mean MID for different domains: mobility (−3.2), ADL (−4.4), emotional well-being (−4.2), stigma (−5.6), social support (−11.4), cognitions (−1.8), communications (−4.2), and pain (−2.1), and −1.6 for the overall score.[40]

Cogtest PD Battery

The Cogtest uses a console with a touch-screen interface to capture responses to a battery of cognitive tests. The Cogtest PD battery consists of tests specifically selected for patients with PD. The tests involve an auditory number sequencing test, a spatial working memory test, a strategic target detection test, a word list learning test, a symbol digit substitution test, and a spatial planning test.

Although the protocol for Study 016 contains an appendix stating that the Cogtest PD battery has been validated in patients with PD and its test–retest reliability is robust in the PD population, it did not provide information to support these claims. No evidence in the published literature was found for its validity, reliability, or responsiveness in patients with PD.

EQ-5D-3L

The EQ-5D-3L is a generic, preference-based HRQoL instrument that has been applied to a wide range of health conditions and treatments, including PD.[67,68] The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, and 3) representing "no problems," "some problems," and "extreme problems," respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[67,68] The second part is a 20 cm visual analogue scale (EuroQol Visual Analogue Scale [EQ VAS]) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ VAS that best represents their own health on that day. The EQ-5D-3L produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ VAS.

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., the US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies, depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

The EQ-5D-3L has been extensively validated across countries around the world and in various conditions; however, evidence of its validity in patients with PD is relatively sparse. A systematic review by Xin et al. assessed the construct validity (convergent validity and discriminative ability) and responsiveness of the instrument in patients with PD.[69] Results from six studies showed that the correlations between the EQ-5D-3L index score and the eight-item Parkinson's Disease Questionnaire (PDQ-8) summary score, Hoehn and Yahr

staging, and UPDRS total score were strong (r = −0.75), moderate (−0.32 < r < −0.53), and moderate to strong (0.39 < |r| < 0.72), respectively. Five studies provided adequate information for the assessment of the discriminative ability of the EQ-5D-3L; four showed the index score had a satisfactory discriminative ability to accurately distinguish patients based on the presence of apathy, dyskinesia, wearing-off period, and sweating disturbances.[69] The remaining study found the EQ-5D-3L was adequate in differentiating clinically different groups based on PD severity as well as various motor and non-motor symptoms; however, the discrimination was more evident for mild and severe cases of PD and less evident for adjacent stages.[69]

The responsiveness of the EQ-5D-3L was reported in 12 studies in the aforementioned systematic review.[69] Six studies showed a statistically significant change in the EQ-5D index score over time, which was consistent with other established scales used as reference measures, including the UPDRS Section II, PDQ-39, PDQ-8, Hoehn and Yahr staging, and Hospital Anxiety and Depression Scale. In the remaining six studies, the aforementioned measures did not show a consistent pattern of increase or decrease with the progression of disease.[69]

Information regarding an MID for the EQ-5D among PD patients is scarce. The aforementioned systematic review reported an estimated MID of 0.10 (range of 0.04 to 0.17) and 0.11 (range of 0.08 to 0.14) based on the UPDRS and PDQ-39 score, respectively; however, this was obtained from a conference abstract.[69] Other reported MIDs for the EQ- 5D-3L range from 0.03 to 0.07.[70]

GRID-HAMD-17

The pivotal trials used the GRID-HAMD-17, which is based on the original 17-item Hamilton Rating Scale for Depression (HAM-D17). The HAM-D17 is the most frequently utilized outcome measure in clinical trials of major depressive disorder (MDD) and is considered by many to be the standard for assessment of depression. While numerous versions of this scale exist, the 17-item scale is the version most frequently used in efficacy trials.[71] The scale is clinician-rated; ratings are made on the basis of a clinical interview and additional available information, such as a family report.[72] As a measure of the severity of depression symptoms, the HAM-D17 addresses both somatic and psychological symptoms of depression.[73] Items are rated on either a five-point (0 to 4) or three-point (0 to 2) scale on which increasing scores represent increasing severity of symptoms.[74] Scores for the 17 items are summed to obtain a total score of 52, or 53 in some versions.[75]

The content validity of the HAM-D17 is poor, as there is only partial overlap between the content of this scale and the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) symptom inclusion diagnostic criteria for MDD.[71] Some symptoms on the HAM-D17 are not official DSM-IV criteria and, while some such symptoms are recognized as associated with depression (e.g., psychotic anxiety), the link to depression is more tenuous for other symptoms (e.g., loss of insight, hypochondriasis).[74] Conversely, important features of the DSM-IV criteria for depression, such as concentration difficulties, feelings of worthlessness, and reverse vegetative symptoms, are either buried within complex items or not captured at all.[74]

The GRID-HAMD-17 was developed with the goal of standardizing the administration and scoring of the HAMD without significantly altering the original intent of the items or the scoring profile.[76] For each item, the dimensions of intensity (absent, mild, moderate, severe, or very severe, or absent, mild, or marked) and frequency (absent, occasional, much of the

time, or almost all of the time) of a symptom are rated independently and each combination of intensity and frequency corresponds to a pre-specified score from 0 to 4 or 0 to 2 (with higher scores indicating more severity and/or more frequent symptoms), yielding a possible range of scores of 0 to 52.[77] For the GRID-HAMD-17, item content was clarified, clinical examples at each severity level were added to anchor descriptions, and references to inpatient-specific functioning were removed.[76] A semi-structured interview guide and a set of rating conventions were also included.[76] The GRID-HAMD-17 developers found that nine of 12 North American raters found the scale "very easy" or "easy" to use and that, in a trial of patients with MDD (N = 34) with a pool of 20 raters, inter-rater reliability for the change in total score over four weeks was acceptable (random-effects ICC of 0.91).[76] A separate study in patients with MDD (N = 150) in the US, both the GRID-HAMD-17 and the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) were administered and raters were not given any training for the scales.[76] In this study, internal consistency reliability was acceptable (alpha = 78), as was inter-rater reliability (ICC = 0.95).[76] The total scores for the GRID-HAMD-17 and SIGH-D were highly correlated (ICC = 0.81), providing some evidence for convergent validity of the GRID-HAMD-17 in patients with MDD.[76]

No evidence was found for the validity, reliability, responsiveness, or MID of the GRID-HAMD-17 in patients with PD.

MMSE

The MMSE is a brief, commonly used test that assesses cognitive function. It consists of 11 items that evaluate attention and orientation, memory, registration, recall, calculation, language, and ability to draw a complex polygon. The score ranges from 0 to 30, with lower scores corresponding with increasing cognitive impairment. It was originally developed for psychiatric patients but has since become commonly used in screening for dementia in clinical, research, and community settings.[78]

In a study by Isella et al. in a sample of 121 Italian patients with idiopathic PD across all Hoehn and Yahr stages (predominantly stages 1 to 3), the psychometric properties of the MMSE were evaluated in the ON state.[79] Internal consistency of the MMSE, as assessed by Cronbach's alpha, was not acceptable[35] (alpha = 0.563).[79] The reliability of the MMSE was evaluated using the SE of measurement, which was found to be 2.00.[79] It was noted that 12.4% of patients scored the highest possible score, indicating a ceiling effect.[79] Convergent validity was assessed against the Mattis Dementia Rating Scale, with a Spearman rho statistic (ρ) of 0.60 and above considered to be a strong correlation (and 0.30 to 0.59 a moderate correlation).[79] The total scores for the MMSE and DRS were strongly correlated (ρ = 0.60) and there were moderate correlations between the MMSE total score and each DRS subtest score (ρ ranging from 0.40 to 0.53).[79]

Responsiveness of the MMSE was assessed in 117 North American patients with PD (and without dementia) who had annual clinical evaluations (including the MMSE) and formal neuropsychological testing.[80] For each year-long interval, change in cognition was determined using the reliable change index for the neuropsychological battery for global cognition and each cognitive domain (executive, attention/working memory, language, visuospatial, and learning/memory).[80] The area under the curve (AUC) for the receiver operator characteristic curve for global scores was 0.56 (95% CI, 0.55 to 0.70) for decline in the MMSE, and AUC values ranged from 0.52 to 0.59 for the individual domains.[80] Using a one-point decline, the sensitivity of the MMSE was 41% (95% CI, 28% to 55%) and specificity was 66%. Standardized effect size (mean change divided by the SD in baseline

score) was −0.386 (less than what would be considered a moderate effect size) and the standardized response mean (mean change divided by the SD of change in score) was −0.602 for a change in cognition.[80] The authors concluded the responsiveness of the MMSE to a decline in cognition over time was poor.[80]

No information was found on an MID for the MMSE in patients with PD.

Appendix 6: Summary of Other Studies

Long-Term Safety Study (Study 018)

Study 018 was a long-term (78 weeks) safety study that was an extension of the pivotal trial Study 016 (24 weeks). Efficacy and harms outcomes should be considered exploratory in this study, as Study 018 was not powered to detect statistical differences for any of the outcomes assessed.

Methods

Study 018 was a DB, placebo-controlled, randomized extension study of Study 016 that allowed patients to continue treatment for up to 78 weeks. The primary objective of Study 018 was to determine the long-term efficacy and safety of two oral doses of safinamide (50 mg/day and 100 mg/day) compared with placebo as add-on therapy in patients with early idiopathic PD with motor fluctuations who were currently receiving a stable dose of levodopa.

Study 018 took place between January 12 and August 24, 2007. Patients were not directly enrolled into Study 018; they were recruited from Study 016. Patients who entered Study 018 were not re-randomized. Patients continued to take the same assigned treatment and dose that they received in Study 016 (safinamide 50 mg/day, safinamide 100 mg/day, or placebo) along with the same dose of levodopa.

While no formal sample size calculations were performed for Study 018, it was estimated that 550 patients would be entered into the trial.

Population

Study 018 included patients from 35 sites in India, 7 sites in Italy, and 10 sites in Romania.

The study population consisted of patients from Study 016 who wanted to continue their current medication and were not having any dose-limiting side effects, or those who discontinued treatment but returned for their scheduled efficacy evaluations at weeks 12 and 24. Patients were excluded if they experienced clinically significant AEs or showed clinically significant deterioration during participation in Study 016.

Table 18 presents a summary of baseline characteristics. The approximate mean age of patients in Study 018 was 60 years. Patients were more likely to be male (71.9% to 73.4%), and the majority of patients were Asian (78.4% to 81%). The duration of PD ranged from 8.46 years to 8.96 years. Baseline disease characteristics were similar between arms. Concomitant medications are presented in Table 19.

Table 18: Summary of Baseline Characteristics (mITT Population)

Characteristics	Study 018		
	Safinamide 50 mg/day (N = 179)	Safinamide 100 mg/day (N = 177)	Placebo (N = 171)
Age, mean years (SD)	59.9 (9.80)	60.0 (9.18)	60.2 (9.18)
Male, n (%)	131 (73.2%)	130 (73.4%)	123 (71.9%)
Race, n (%)			
White	34 (19.0)	34 (19.2)	37 (21.6)
Asian	145 (81.0)	143 (80.8)	134 (78.4)
Duration of PD (years)			
Mean (SD)	8.46 (3.847)	8.83 (3.885)	8.96 (3.853)
UPDRS total score[a] at Study 016 baseline, mean (SD)			
Section I	1.8 (1.37)	2.0 (1.54)	1.9 (1.44)
Section II	11.1 (5.46)	11.8 (5.55)	11.9 (5.64)
Section III	26.6 (12.28)	28.2 (12.39)	28.6 (12.19)
Section IV	5.3 (2.26)	5.5 (2.62)	5.6 (2.70)
Hoehn and Yahr staging[a] at Study 016 baseline			
Mean (SD)	2.74 (0.586)	2.77 (0.622)	2.77 (0.678)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
MMSE[a] at Study 016 baseline			
Mean (SD)	28.1 (1.90)	28.0 (2.06)	27.9 (2.01)
GRID-HAMD-17[a] at Study 016 baseline			
Mean (SD)	5.7 (3.56)	5.9 (3.55)	5.8 (3.62)
CGI-S[a] at Study 016 baseline			
Normal/not at all ill	0	0	0
Borderline ill	2 (1.1)	4 (2.3)	2 (1.2)
Mildly ill	39 (21.8)	35 (19.8)	35 (20.5)
Moderately ill	106 (59.2)	110 (62.1)	108 (63.2)
Markedly ill	31 (17.3)	26 (14.7)	25 (14.6)
Severely ill	1 (0.6)	2 (1.1)	1 (0.6)

CGI-S = Clinical Global Impression – Severity of Illness; GRID-HAMD-17 = grid-based 17-item Hamilton Rating Scale for Depression; mITT = modified intention-to-treat; MMSE = Mini-Mental State Examination; PD = Parkinson disease; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Last observation carried forward method of imputation.

Source: Clinical Study Report for Study 018.[8]

Table 19: Concomitant Medications for PD (Safety Population)

Characteristics	Study 018		
	Safinamide 50 mg/day (N = 189)	Safinamide 100 mg/day (N = 180)	Placebo (N = 175)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Note: Frequency > 5%

Source: Clinical Study Report for Study 018.[8]

Interventions

Patients entered in Study 018 continued to take the same treatment and dose they received in Study 016 (safinamide 50 mg/day, safinamide 100 mg/day, or placebo) along with the same dose of levodopa. Safinamide was provided as a 50 mg oral tablet. Each patient received a combination of two safinamide or matching placebo tablets daily, adding up to the amount of investigational product they were to receive based on the treatment group they were randomized to. This continued for the duration of the 78-week treatment phase followed by an optional one-week taper phase where patients continued treatment.

Outcomes

The primary efficacy outcome was mean change in DRS during ON time. The DRS includes a set of three tasks to measure the severity of dyskinesia in PD, with each item scored on a five-point ordinal scale from 0 to 4. Higher scores correspond with more severe dyskinesia.

Secondary outcomes included:

- change in ON time compared with Study 016 baseline
- change in ADL during ON time (UPDRS Section II) compared with Study 016 baseline
- change in motor symptoms (UPDRS Section III) during ON time compared with Study 016 baseline.

Statistical Analysis

No formal sample size calculations were performed for Study 018. it was estimated that 550 patients would be entered into the trial. Statistical analyses were performed using SAS version 9.1.3.

The primary efficacy outcome (mean change in total DRS severity score from baseline) was analyzed using a mixed linear model restricted maximum likelihood repeated measures model with treatment, centre, visit, and the treatment-by-visit interaction as fixed effects and the baseline value (from Study 016) as a covariate. The mean difference was presented with two-sided 95% CIs and P values. Secondary end points were assessed according to a pre-specified hierarchy in the order listed previously. The analyses were performed using the LOCF approach for imputation of missing data. This method of imputation aims to reduce bias due to attrition and preserve the sample size and power of the study. This methodology assumes that data are missing at random and that the observations from earlier time points represent the results at week 78. These assumptions are not verified, which can lead to uncertainty when interpreting results.

Study 018 included three populations: safety, ITT, and mITT.

The safety population included all patients who received at least one dose of the study drug in Study 018 and had at least one post-dose safety assessment.

The ITT population included all randomized patients from Study 016, whether or not they received a dose of their assigned study drug or the correct treatment, as designated in the protocol.

The mITT population included all patients who entered Study 018 with baseline/pre-treatment data from Study 016 and at least one set of post-dose efficacy data in Study 018.

Patient Disposition

In Study 018, 21.7% of patients in the safinamide 50 mg/day arm, 16.7% in the safinamide 100 mg/day arm, and 18.9% in the placebo arm discontinued the trial (Table 20). The most common reason for discontinuation across both trials was attributed to withdrawal of consent.

Table 20: Patient Disposition

	Study 018		
	Safinamide 50 mg/day	Safinamide 100 mg/day	Placebo
Randomized in Study 016, N	669		
Completed Study 016, N (%)	594 (88.8)		
Enrolled in Study 018, N (%)	544 (81.3)		
Randomized, N	189	180	175
Completed study, N (%)	148 (78.3)	150 (83.3)	142 (81.1)
Discontinued, N (%)	41 (21.7)	30 (16.7)	33 (18.9)
Non-serious adverse event	4 (2.1)	3 (1.7)	1 (0.6)
Serious adverse event	3 (1.6)	5 (2.8)	6 (3.4)
Withdrawal of consent	22 (11.6)	9 (5.0)	13 (7.4)

	Study 018		
	Safinamide 50 mg/day	Safinamide 100 mg/day	Placebo
Lost to follow-up	7 (3.7)	7 (3.9)	4 (2.3)
Non-compliance	1 (0.5)	0	2 (1.1)
Death	3 (1.6)	5 (2.8)	6 (3.4)
Other	2 (1.1)	1 (0.6)	4 (2.3)
ITT, N	223	224	222
Safety, N	189	180	175
mITT, N	179	177	171

ITT = intention-to-treat; mITT = modified intention-to-treat.

Source: Clinical Study Report for Study 018.[8]

Efficacy

Motor Examination Score (UPDRS Section III)

For the assessment of the motor examination score (UPDRS Section III) during the ON phase at week 78 in Study 018, the difference in change from baseline between safinamide 50 mg/day and placebo was −1.05 units (95% CI, −2.58 to 0.48; P = 0.1791) in favour of safinamide. The difference in change from baseline between safinamide 100 mg/day and placebo was −2.13 units (95% CI, −3.65 to −0.6; P = 0.0063) in favour of safinamide.

ON Time

For the assessment of mean ON time at week 78 in Study 018, the difference in change from baseline between safinamide 50 mg/day and placebo was 0.67 hours (95% CI, 0.23 to 1.11; P = 0.0031) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo was 0.83 hours (95% CI, 0.39 to 1.27; P = 0.0002) in favour of safinamide.

DRS

The assessment of the DRS was the primary efficacy end point for Study 018. For the assessment using the DRS at week 78, the difference in change from baseline between safinamide 50 mg/day and placebo was −0.51 units (95% CI, −1.32 to 0.29; P = 0.2125) in favour of safinamide. Similarly, the difference in change from baseline between safinamide 100 mg/day and placebo was −0.59 units (95% CI, −1.40 to 0.21; P = 0.1469) in favour of safinamide.

ADL Scale (UPDRS Section II)

For the assessment of the ADL score (UPDRS Section II) during the ON phase at week 78, the difference in change from baseline between safinamide 50 mg/day and placebo was −0.52 units (95% CI, −1.29 to 0.25; P = 0.1857) in favour of safinamide. The difference in change from baseline between safinamide 100 mg/day and placebo was −1.06 units (95% CI, −1.83 to −0.29; P = 0.0068) in favour of safinamide.

Table 21: Efficacy Results (ITT Population)

	Study 016		
	Safinamide 50 mg/day (N = 223)	Safinamide 100 mg/day (N = 224)	Placebo (N = 222)
Motor examination (UPDRS Section III)			
Study 018 baseline, n	223	224	222
Mean (SD)	27.3 (12.66)	28.3 (13.30)	28.7 (12.02)
Week 78, n	214	217	217
Change from baseline, mean (SD)	−5.1 (10.27)	−6.4 (10.96)	−4.7 (9.40)
LS mean change from baseline	−4.98	−6.06	−3.94
LS difference versus placebo (95% CI)	−1.05 (−2.58 to 0.48)	−2.13 (−3.65 to −0.60)	–
P value[a]	0.1791	0.0063	–
Change in ON time (ON + ON with minor dyskinesia)			
Study 018 baseline, n	215	217	214
Mean (SD)	9.373 (2.259)	9.520 (2.426)	9.301 (2.155)
Week 78, n	215	217	214
Change from baseline, mean (SD)	1.145 (2.751)	1.191 (2.881)	0.565 (2.510)
LS mean change from baseline	1.01	1.18	0.34
LS difference versus placebo (95% CI)	0.67 (0.23 to 1.11)	0.83 (0.39 to 1.27)	–
P value[b]	0.0031	0.0002	–
Dyskinesia Rating Scale			
Study 018 baseline, n	223	223	222
Mean (SD)	3.9 (3.89)	3.7 (4.07)	3.4 (3.93)
Week 78, n	69	70	64
Change from baseline, mean (SD)	−1.2 (2.88)	−1.1 (4.06)	0 (3.02)
LS mean change from baseline	−0.19	−0.28	0.32
LS difference versus placebo (95% CI)	−0.51 (−1.32 to 0.29)	−0.59 (−1.40 to 0.21)	–
P value[b]	0.2125	0.1469	–
Activities of daily living scale (UPDRS Section II)			
Study 018 baseline, n	223	224	222
Mean (SD)	11.8 (5.66)	12.1 (5.82)	12.3 (5.92)
Week 78, n	214	217	217
Change from baseline, mean (SD)	−2.1 (4.69)	−1.5 (4.80)	−1.1 (4.81)
LS mean change from baseline	−1.43	−1.97	−0.91
LS difference versus placebo (95% CI)	−0.52 (−1.29 to 0.25)	−1.06 (−1.83 to −0.29)	–
P value[a]	0.1857	0.0068	–

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention-to-treat; LS = least squares; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

Note: Baseline = Study 016 week 0 or last non-missing value before taking the study medication, unless otherwise specified.

[a] Treatments were compared using an ANCOVA with baseline as a covariate and treatment and centre as main effects

[b] Repeated measures model is based on the change from baseline with terms for baseline, treatment, pooled centre, visit, and treatment × visit interaction using the unstructured covariance structure.

Source: Clinical Study Report for Study 018.[8]

Harms

AEs arising in during Study 018 occurred more frequently in the placebo arm (85.1%) compared with the safinamide 50 mg/day arm (76.7%) and the safinamide 100 mg/day arm (78.3%) (Table 22). The most common AE was worsening of PD, which affected 21.1% of patients in the safinamide 100 mg/day arm compared with approximately 16% of patients in the placebo and safinamide 50 mg/day arms. Dyskinesia affected more patients in the placebo arm (15.4%) compared with the safinamide 50 mg/day arm (12.7%) and the safinamide 100 mg/day arm (13.3%).

SAEs occurred similarly between treatment arms (29.1% for safinamide 50 mg/day, 32.8% for safinamide 100 mg/day, 28.6% for placebo). SAEs did not occur in more than three patients in any single category in any treatment arm.

WDAEs occurred in 5.3% of patients in the safinamide 50 mg/day arm, 6.7% of patients in the safinamide 100 mg/day arm, and 5.7% of patients in the placebo arm. WDAEs did not occur in more than three patients in any single category in any treatment arm.

Eighteen patients died in Study 018 (four in the safinamide 50 mg/day arm, eight in the safinamide 100 mg/day arm, and six in the placebo arm). Causes of death included: leptospirosis and cardio-respiratory arrest, cardiac arrest, myocardial infarction, sudden death, pneumonia, pneumonia and cardio-respiratory arrest, and cardiopulmonary failure; none of the deaths were related to the study drug, according to the sponsor.

Notable harms identified in the protocol for this review included the following: constipation, dyskinesia, hallucinations, impulsive behaviour, insomnia, melanoma, nausea, postural/orthostatic hypotension, serotonin syndrome, and vomiting. Constipation occurred more frequently in both safinamide arms compared with placebo. Dyskinesia occurred more frequently in the placebo arm compared with both safinamide arms. Data were not reported for impulsive behaviour, melanoma, or serotonin syndrome.

Table 22: Harms

	Study 016		
	Safinamide 50 mg/day (N = 189)	Safinamide 100 mg/day (N = 180)	Placebo (N = 175)
AEs			
Patients with > 0 AEs, N (%)	145 (76.7)	141(78.3)	149 (85.1)
Most common AEs[a]			
Cataract	21 (11.1)	18 (10.0)	18 (10.3)
[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	10 (5.3)	16 (8.9)	13 (7.4)
Pyrexia	14 (7.4)	11 (6.1)	13 (7.4)
Fall	13 (6.9)	11 (6.1)	13 (7.4)
[redacted]	[redacted]	[redacted]	[redacted]
Back pain	9 (4.8)	14 (7.8)	9 (5.1)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Parkinson disease	32 (16.9)	38 (21.1)	29 (16.6)
Dyskinesia	24 (12.7)	24 (13.3)	27 (15.4)
Insomnia	18 (9.5)	6 (3.3)	7 (4.0)

	Study 016		
	Safinamide 50 mg/day (N = 189)	Safinamide 100 mg/day (N = 180)	Placebo (N = 175)
Hypertension	7 (3.7)	11 (6.1)	6 (3.4)
SAEs			
Patients with > 0 SAEs, N (%)	55 (29.1)	59 (32.8)	50 (28.6)
Most common SAEs[b]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, N (%)	10 (5.3)	12 (6.7)	10 (5.7)
Most common reasons[b]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Deaths, n	4	8	6
Notable harms			
Constipation	12 (6.3)	9 (5.0)	8 (4.6)
Dyskinesia	24 (12.7)	24 (13.3)	27 (15.4)
Hallucinations	6 (3.2)	3 (1.7)	4 (2.3)
Impulsive behaviour	NA	NA	NA
Insomnia	18 (9.5)	6 (3.3)	7 (4.0)
Melanoma	NA	NA	NA
Nausea	2 (1.1)	5 (2.8)	3 (1.7)
Postural/orthostatic hypotension	0	2 (1.1)	4 (2.3)
Serotonin syndrome	NA	NA	NA
Vomiting	2 (1.1)	6 (3.3)	1 (0.6)

AE = adverse event; NA = not applicable; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency > 5%.

[b] Frequency > 1.

Source: Clinical Study Report for Study 018.[8]

Critical Appraisal

Study 018 was an extension of Study 016 and was thus impacted by the same limitations. The exclusion criteria created an enriched study population that reduced the generalizability of the trials to the Canadian clinical population. Patient eligibility excluded patients with late -

stage PD and certain comorbidities (e.g., substance abuse or history of alcohol or drug abuse in the past three months; current clinically significant gastrointestinal, renal, hepatic, endocrine, pulmonary, or cardiovascular disease, including acute gastric ulcer, uncontrolled hypertension, asthma, COPD, and type I diabetes; history or current psychosis; depression). Further, to be eligible for participation in Study 018, patients from Study 016 could not have any dose-limiting side effects. They were also not eligible if they discontinued treatment or did not return for their scheduled efficacy evaluations at weeks 12 and 24. Patients were excluded if they experienced clinically significant AEs or showed clinically significant deterioration during participation in Study 016. These criteria contribute to the enriched population assessed in Study 018 and limit the external validity of the results compared with the Canadian clinical population.

Similar to Study 016, the doses of safinamide in Study 018 (50 mg/day, 100 mg/day) were associated with unique trials arms and were not representative of dose administration in a clinic setting, where patients would start at 50 mg/day and increase the dose, depending on tolerability.

The differential impact of dyskinesia (higher in safinamide arms) may have contributed to the unblinding of patients and investigators. Discontinuations in the trial were greater in the safinamide 50 mg/day arm (11.6%) compared with the safinamide 100 mg/day arm (5.0%). Discontinuations were most often related to withdrawal of consent. The reasons for withdrawal of consent were not available; it is also unclear why more patients in the safinamide 50 mg/day arm discontinued compared with the 100 mg/day arm.

The Health Canada indication for safinamide specifies that it is indicated as an add-on therapy to a regimen that includes levodopa. The majority of patients enrolled in Study 018 were concomitantly treated with medications for PD in addition to levodopa; therefore, the efficacy of safinamide compared with placebo remains unclear in patients treated only with levodopa.

Conclusion

Study 018 was an extension of Study 016 that presented efficacy and safety data for patients up to 78 weeks. Patients remained in their original treatment groups: safinamide 50 mg/day, safinamide 100 mg/day, or placebo. Generally, the efficacy results reflected the results from Study 016 for outcomes related to ON time for UPDRS sections II and III; although some numerical reductions in efficacy were observed for treatment with safinamide 50 mg/day for motor examination (UPDRS Section III) and ADL (UPDRS Section II) compared with the results from Study 016. Limitations of Study 018 include limited external validity to the Canadian population due to an enriched population, use of a dosing regimen inconsistent with the regimen specified in the Health Canada product monograph, and differential discontinuations. The efficacy outcomes should be considered exploratory, as Study 018 was not powered to detect statistical differences for any of the outcomes assessed. While no new safety signals arose over the course of Study 018, safety results should also be interpreted with caution.

Appendix 7: Summary of Indirect Comparisons

Introduction

Given the lack of head-to-head studies for safinamide, this review was conducted to summarize and appraise the indirect evidence comparing safinamide with other drugs approved for add-on therapy to a regimen that includes levodopa for the treatment of the signs and symptoms idiopathic PD.

Methods

One sponsor ITC was supplied.[9] CADTH conducted an independent literature search to identify relevant ITCs that included the patients, interventions, and outcomes as identified in the CDR Clinical Review protocol (Table 3); one ITC, by Binde et al. (2018),[10] met the criteria for inclusion.

Description of ITCs Identified

One ITC submitted by the sponsor[9] and one ITC identified from the literature (Binde et al., 2018)[10] were included for critical appraisal. Table 23 summarized the key aspects of the ITCs.

Table 23: Overview of Included ITCs

Population	Intervention	Comparators	Outcomes	Study Design
Adults (≥ 18 years of age) with idiopathic advanced PD[9]	Safinamide 50 mg/day or 100 mg/day	Levodopa in combination with: • entacapone • bromocriptine • ropinirole • rotigotine • pramipexole • selegiline • rasagiline • placebo	• Mean OFF-time reduction • AEs • Discontinuations due to AEs	RCT
Adults (≥ 18 years of age) with PD[10]	• Selegiline • Rasagiline • Safinamide	Alone or in combination with levodopa: • selegiline • rasagiline • safinamide • placebo	• UPDRS[a] • Mortality • SAE • Dropouts • Discontinuation of use	RCT

AE = adverse event; ITC = indirect treatment comparison; PD = Parkinson disease; RCT = randomized controlled trial; SAE = serious adverse event; UPDRS = Unified Parkinson's Disease Rating Scale.

[a] Responders were defined as the number of patients with at least a 20% reduction in UPDRS score from baseline to end of study (total UPDRS score was used where this was provided; sections II and III or only Section III scores were used where only these were provided).

Source: Sponsor-supplied ITC[9] and Binde et al., 2018.[10]

Review and Appraisal of ITCs

The ITCs were critically appraised using recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons as a guide.[81]

Review of Sponsor-Supplied ITC

Objectives and Rationale for the Sponsor-Supplied ITC

The main objective of the sponsor-supplied ITC was to compare the efficacy of safinamide 50 mg and safinamide 100 mg with the comparators: DAs (pramipexole, bromocriptine, rotigotine, ropinirole); COMT (entacapone); and MAO-B inhibitors (rotigotine, rasagiline, and selegiline) with respect to change in mean OFF time in idiopathic PD patients. The ITC was also used to assess the relative risk of AEs and discontinuations due to AEs.

Methods for the Sponsor-Supplied ITC

Study Eligibility, Selection Process, and Data Extraction

Studies included in the ITC were identified through a systematic literature search. The authors searched PubMed, MEDLINE, EMBASE, LILACS, Web of Science, and ClinicalTrials.gov on February 19, 2019. Prior to this date, the evidence base from the Cochrane review by Stowe et al. (2010) was reviewed. Additional information was included from reference lists of relevant articles.

Studies that met all of the following criteria were included, specifically, studies that:

- were composed of patients 18 years or older with idiopathic advanced PD
- investigated an orally administered DA therapy (bromocriptine, ropinirole, rotigotine, or pramipexole)
- investigated a MAO-B (selegiline, rasagiline, or safinamide 50 mg/day or 100 mg/day) or COMT inhibitor (entacapone) on a background of levodopa
- used an RCT design, were placebo-controlled, or compared two or more of the treatments from the comparator list
- evaluated OFF time or any AEs as outcomes
- published in English.

Studies were excluded if patients had early to mid-stage PD. Non-RCTs were also excluded.

Two investigators reviewed titles and abstracts for inclusion. A full-text review was performed on studies that met the inclusion criteria. The number of investigators who performed the full-text review was not specified. Data extraction was performed by an unspecified number of investigators following full-text review. The methods used for resolving discrepancies and quality control were not reported.

Comparators

The ITC included studies that compared the following:

- safinamide
- entacapone
- bromocriptine
- ropinirole
- rotigotine
- pramipexole
- selegiline
- rasagiline
- placebo

Outcomes

The ITC evaluated the following efficacy and safety outcomes:

- mean OFF time reduction, where OFF time was defined as patients experiencing motor fluctuations that may involve bradykinesia, rigidity, dystonia, tremor, or freezing in addition to problems breathing and swallowing
- discontinuations due to AEs
- AEs (headache, hallucinations, hypotension, insomnia, nausea, constipation, dizziness, worsening PD, and dyskinesia).

Quality Assessment of Included Studies

A specific tool was not used to assess the quality of the included studies. The quality of the included RCTs was assessed through the evaluation of key methodological components (i.e., random sequence generator, allocation concealment, blinding of participants, blinding of outcome assessment). The number of reviewers conducting the quality assessment was not reported, nor was the process for reconciling discrepancies. Characteristics of the studies were reported when available (e.g., duration of PD, average treatment dose).

Indirect Comparison Methods

The ITC was performed using a Bayesian approach. The ITCs were based on burn-in and sampling of 50,000 iterations. Model convergence was assessed by inspecting the trace plots and Monte Carlo SE of parameter estimates from the Markov chain Monte Carlo analysis.

The OFF-time ITC was modelled using vague prior distributions (normal with a mean of 0 and precision of 0.0001 or a variance of 100^2) and vague prior distributions for between-trial variance (uniform with a mean of 0 and precision of 5) for both the fixed- and random-effects models. Model selection was based on the deviance information criterion (DIC) to assess model fit. Uncertainty was presented using 95% CrIs. A Bayesian fixed-effects model was chosen based on an evaluation of posterior residual deviance and the DIC goodness-of-fit criteria. Heterogeneity assessment was performed using I^2. An additional model was run that was adjusted for baseline risk, as it was expected to act as a proxy measure for potential confounding factors.

The safety outcome ITCs (discontinuations due to AEs, headache, hallucinations, hypotension, insomnia, nausea, constipation, dizziness, worsening PD, and dyskinesia) were modelled using the same vague prior distributions as previously specified. Risk ratios and corresponding 95% CrIs were reported. Random-effects models were chosen based on an evaluation of posterior residual deviance and the DIC goodness-of-fit criteria.

No relevant subgroup analysis was performed on the ITC.

Results

The systematic review identified a total of 1,388 publications. Overall, 42 trials met the criteria for inclusion. An overview of study and patient characteristics included in the ITCs is provided in Table 24. The included studies took place in Japan, the US, the UK, Europe, Canada, and China. The included patients in the trials were adults with advanced PD (not defined) on a background of levodopa that was stabilized prior to study initiation.

For the ITC, comparisons were made for the following treatments: bromocriptine, ropinirole, rotigotine, pramipexole, selegiline, rasagiline, safinamide 50 mg/day or 100 mg/day, and entacapone. Individual studies included in the ITC inconsistently reported the dose of each comparator. The duration of follow-up ranged from eight to 24 weeks. Baseline characteristics were sparsely reported. The mean age ranged from 57 to 67 years. Male patients ranged from 38% to 72%. The duration of advanced PD ranged from 4.4 to 13.4 years. The results of the ITC did not report the doses that corresponded to the comparators, with the exception of safinamide (50 mg/day, 100 mg/day).

A specific tool was not used to assess the quality of the included studies. The quality of the included RCTs was assessed by the authors through the evaluation of key methodological components (i.e., random sequence generator, allocation concealment, blinding of participants, and blinding of outcome assessment). The authors reported that the overall risk of bias of the included RCTs was low based on their assessment of key methodological components. Many of the studies did not provide sufficient detail on randomization or allocation concealment for those factors to be assessed (12 of the 42 trials reported allocation concealment; 30 of the 42 eligible trials described the method of randomization).

Table 24: Study and Patient Characteristics for Sponsor-Supplied ITC[9]

Study[a]	Participants	Males, n (%)	Age, mean years	Duration of PD, mean years	Average dose of treatment	Duration of study
Entacapone						
COMTI (E): Celomen	Idiopathic PD patients with motor complications	129 (43%)	61	8.9	200 mg/dose levodopa	24 weeks
COMTI (E): ComQol	Idiopathic PD patients with motor complications	151 (56%)	67	7.3	200 mg/dose levodopa	13 weeks
COMTI (E): Filomen	Idiopathic PD patients needing enhancement and/or smoothing of levodopa effects; fluctuating and non-fluctuating patients	216 (66%)	62	6.1	200 mg/dose levodopa; 824 mg at baseline, 720 mg at 12 months	12 months
COMTI (E): INT-02	Idiopathic PD patients with motor fluctuations	101 (62%)	64	NR	200 mg/dose levodopa	12 weeks
COMTI (E): Japan	Idiopathic PD patients with motor fluctuations	127 (45%)	63	10.2	200 mg/dose levodopa	8 weeks
COMTI (E): Interntl	Idiopathic PD patients with motor complications	16 (53%)	55	4.8	200 mg/dose levodopa; 683.3 mg at 2 years	2 years
COMTI (E): LARGO	Idiopathic PD patients with motor fluctuations	271 (59%)	64	9	Entacapone: 200 mg/dose levodopa Rasagiline: 1 mg/day	18 weeks
COMTI (E): Nomecomt	Idiopathic PD patients with motor fluctuations	94 (55%)	63	10.8	200 mg/dose levodopa	24 weeks
COMTI (E): Seesaw	Idiopathic PD patients with motor fluctuations	133 (65%)	63	11.1	200 mg/dose levodopa	28 weeks
COMTI (E): South Korea	Idiopathic PD patients with end-of-dose deterioration	79 (40%)	57	7.9	200 mg/dose levodopa	8 weeks
COMTI (E): UK/Irish	Idiopathic PD patients; fluctuating and non-fluctuating patients	109 (63%)	65	9.4	200 mg/dose levodopa	24 weeks
Bromocriptine						
DA (B): Germany	Idiopathic PD patients not optimally controlled with levodopa	23 (57.5%)	65	9.1	30 mg to 40 mg	4 weeks
DA (B): Japan	Idiopathic PD patients not optimally controlled with levodopa	109 (49%)	63	6.6	16.7 mg	8 weeks
DA (B): South Africa	Idiopathic PD patients with Hoehn and Yahr stage 2 to 4	21 (52.5%)	65	13.4	NR	5 weeks
DA (B): Rotterdam	Idiopathic PD patients not optimally controlled with levodopa	10 (43%)	59	8.7	71 mg	5 months
Pramipexole						
DA (Pr): Aust/Germ	Idiopathic PD patients with motor fluctuations	51 (65%)	60	8.2	3.59 mg	11 weeks

Study[a]	Participants	Males, n (%)	Age, mean years	Duration of PD, mean years	Average dose of treatment	Duration of study
DA (Pr/Rot): CLEOPATRA	Idiopathic PD patients with motor fluctuations in Hoehn and Yahr stage 2 to 4	183 (61%)	64	8.5	Rotigotine: 12.95 mg/d Pramipexole: 3.1 mg	24 weeks
DA (Pr): Denmark	Idiopathic PD patients with motor fluctuations	40 (58%)	63	10	NR	12 weeks
DA (Pr): Europe	Idiopathic PD patients with motor fluctuations	230 (65%)	64	7.8	3.7 mg	32 weeks
DA (Pr): Hong Kong/ Taiwan	Idiopathic PD patients with Hoehn and Yahr stage 1 to 4	104 (69%)	60	4.4	NR	15 weeks
DA (Pr): US/Canada	Idiopathic PD patients with motor fluctuations	235 (65%)	63	9.2	NR	32 weeks
PREPARED	Idiopathic PD treated with levodopa	Placebo: 94 (52.8%) Pramipexole ER: 92 (56.1%) Pramipexole IR: 98 (56%)	Placebo: 60.9 Pramipexole ER: 61.6 Pramipexole IR: 62.0	Placebo: 5.9 Pramipexole ER: 6.1 Pramipexole IR: 6.6	Placebo: 3.1 mg/day Pramipexole ER: 2.7 mg/day Pramipexole IR: 2.8 mg/day	33 weeks
Ropinirole						
DA (R): EASE-PD	Idiopathic PD patients with motor fluctuations	246 (63%)	66	8.6	NR	24 weeks
DA (R): France/ England	Idiopathic PD patients not optimally controlled with levodopa	28 (61%)	63	8	6.7 mg	12 weeks
DA (R): UK/Israel	Idiopathic PD patients not optimally controlled with levodopa	41 (60%)	63	NR	NR	12 weeks
DA (R): US	Idiopathic PD patients with predictable motor fluctuations	NR	NR	9	NR	26 weeks
Zesiewicz, 2017	Idiopathic PD demonstrating a lack of control with levodopa	184 (53%)	35 to 85	NR	NR	4 weeks
Rotigotine						
SP921	Idiopathic PD of longer than 3 years' duration presenting with bradykinesia plus at least one of the following: resting tremor, rigidity, or impairment of postural reflexes judged by the treating physician to be inadequately controlled on levodopa	56 (40%)	63.2	7.49	8 mg/day	12 weeks
Nomoto, 2014	Japanese patients with advanced PD and presence of motor complications and a stable levodopa dose for ≥ 28 days	Placebo: 44 (51.2%) Rotigotine: 34 (39.5%)	Placebo: 66.8 Rotigotine: 67.0	Placebo: 5.4 Rotigotine: 7.5	NR	12 weeks

Study[a]	Participants	Males, n (%)	Age, mean years	Duration of PD, mean years	Average dose of treatment	Duration of study
SP1037	Chinese patients with advanced-stage PD (idiopathic and of > 3 years' duration) inadequately controlled on levodopa	203 (58.7%)	62.2	6.62	11.8 mg	12 weeks
Mizuno, 2014	Japanese PD patients on concomitant levodopa therapy whose motor symptoms were not well controlled	Placebo: 42 (50%) Rotigotine: 61 (37.2%) Ropinirole: 68 (41%)	Placebo: 65.3 Rotigotine: 64.8 Ropinirole: 67.0	Placebo: 7.0 Rotigotine: 7.0 Ropinirole: 6.8	Rotigotine: 12.9 mg/24 hours Ropinirole: 9.2 mg/day	4 weeks
Rascol, 2016	Patients with advanced PD (idiopathic and on levodopa) and at least moderate PD associated chronic pain	Placebo: 17 (52%) Rotigotine: 19 (54%)	Placebo: 65.3 Rotigotine: 66.5	Placebo: 5.6 Rotigotine: 5.9	14.7 mg	13 to 19 weeks
Rasagiline						
MAOBI (R): PRESTO	Idiopathic PD patients with motor fluctuations	305 (65%)	64	9.4	1 mg/day	26 weeks
Zhang 2013	Chinese idiopathic PD patients treated with levodopa	Placebo: 67 (53.6%) Rasagiline: 64 (53.8%)	Placebo: 61.56 Rasagiline: 61.64	Placebo: 5.4 Rasagiline: 5.57	1 mg/day	12 weeks
Hattori 2018	Japanese PD patients with wearing-off phenomena while receiving levodopa	157 (38.9%)	66	9	Rasagiline 0.5 mg/day Rasagiline 1 mg/day	28 weeks
Zhang, 2018	Chinese patients with idiopathic PD and motor fluctuations who are receiving treatment with levodopa	212 (66%)	62	7	1 mg/day	16 weeks
Selegiline						
MAOBI (S): Norway/ Finland	Idiopathic PD patients under continuous stabilized treatment with levodopa	20 (53%)	66	10.3	10 mg	8 weeks
MAOBI (S): US	Idiopathic PD patients with motor complications	NR	62	9.2	10 mg	8 weeks
MAOBI (ZS): US	Idiopathic PD patients with predictable motor complications	89 (64%)	65	6.9	2.5 mg	12 weeks
MAOBI (ZS): US/UK	Idiopathic PD patients taking stable doses of levodopa and with minimum 3 hours of OFF time per day	NR	NR	NR	2.5 mg	12 weeks
Safinamide						

Study[a]	Participants	Males, n (%)	Age, mean years	Duration of PD, mean years	Average dose of treatment	Duration of study
ONSTRYV 016	Idiopathic PD patients taking stable doses of levodopa and with Hoehn and Yahr stage of I-IV during an OFF phase; motor fluctuations (> 1.5 hours of OFF time/day)	480 (72%)	60	8.1	100 mg/day 50 mg/day	24 weeks
SETTLE	Patients with idiopathic PD, levodopa-responsive, and following an oral levodopa regimen; patients' PD pharmacotherapy could include a dopamine agonist, anticholinergic, COMT inhibitor, and/or amantadine at stable dosage	334 (60.8%)	61.9	8.9	100 mg/day	24 weeks

ER = extended release: IR = immediate release; ITC = indirect treatment comparison; NR = not reported; PD = Parkinson disease.

a All studies included in this ITC were parallel group double-blind trials.

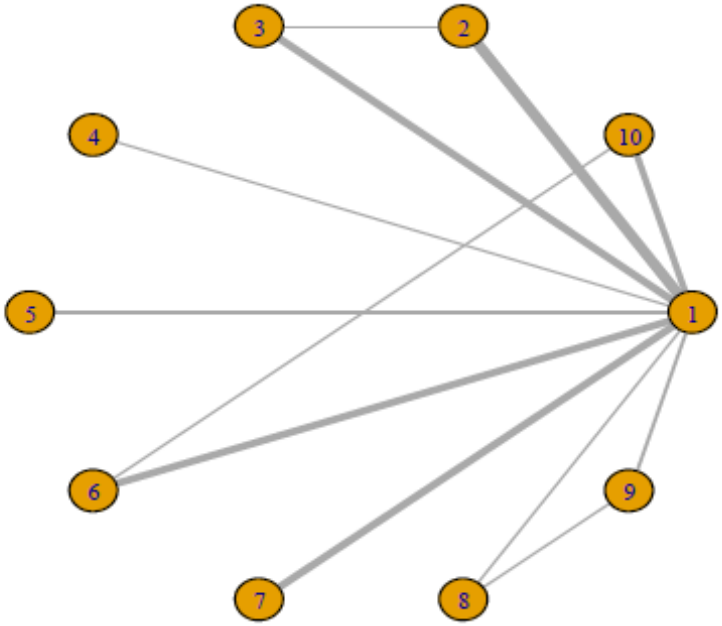
Source: Sponsor-supplied ITC.[9]

OFF Time

For the analysis related to the mean change difference in OFF time, 28 trials contributed data. The network of evidence for the mean change difference in OFF time is presented in Figure 2. The I^2 for the model was 8%; this indicates low statistical heterogeneity and suggests a statically homogenous population.

Using a fixed-effects model (DIC = 113.2), treatment with safinamide 50 mg/day was more efficacious than treatment with placebo. Treatment with rotigotine, bromocriptine, and pramipexole was more efficacious than treatment with safinamide 50 mg/day (Table 25). Similarly, treatment with safinamide 100 mg/day was also more efficacious than treatment with placebo, while treatment with bromocriptine and pramipexole was more efficacious than treatment with safinamide 100 mg/day. The results for both 50 mg/day and 100 mg/day safinamide doses were consistent when the model was run with adjustment for baseline risk (Table 26).

Figure 2: Evidence Network for OFF Time (Hours)



Note: 1 = placebo, 2 = entacapone, 3 = rasagiline, 4 = selegiline, 5 = bromocriptine, 6 = pramipexole, 7 = ropinirole, 8 = safinamide 50 mg, 9 = safinamide 100 mg, 10 = rotigotine. Connecting lines indicate treatment comparisons that were available from included studies; darker lines indicate a greater number of comparisons.

Source: Sponsor-supplied indirect treatment comparison.[9]

Table 25: ITC Estimate of OFF Time (Hours)

Treatment	Relative to safinamide 50 mg/day, mean change difference (95% CrI)	Relative to safinamide 100 mg/day, mean change difference (95% CrI)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	−0.096 (−0.45 to 0.26)

Treatment	Relative to safinamide 50 mg/day, mean change difference (95% CrI)	Relative to safinamide 100 mg/day, mean change difference (95% CrI)
[redacted]	[redacted]	0.74 (−0.17 to 1.67)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CrI = credible interval; ITC = indirect treatment comparison.

Source: Sponsor-supplied ITC.[9]

Table 26: ITC Estimate of OFF Time (Hours), Adjusted Model

Treatment	Relative to safinamide 50 mg/day, mean change difference (95% CrI)	Relative to safinamide 100 mg/day, mean change difference (95% CrI)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CrI = credible interval; ITC = indirect treatment comparison.

Source: Sponsor-supplied ITC.[9]

AEs

For the analysis related to discontinuations due to AEs, 35 trials contributed data (I^2 = 0%) (Table 27). For the specific AE networks: 16 trials contributed data for the headache network (I^2 = 19%); 19 trials contributed data for the hallucination network (I^2 = 10%); 18 trials contributed data for the hypotension network (I^2 = 17%); 16 trials contributed data for the insomnia network (I^2 = 25%); 30 trials contributed data for the nausea network (I^2 = 25%); 26 trials contributed data for the dizziness network (I^2 = 21%); 13 trials contributed data for the worsening PD network (I^2 = 15%); and 32 trials contributed data for the dyskinesia network (I^2 = 14%).

No network of evidence was available for any of the AE outcomes. Random-effects models were used for the AE outcomes but DIC values were not provided.

Treatment with safinamide 100 mg/day was associated with an increased risk of dyskinesia compared with selegiline and placebo. All other comparisons with safinamide 50 mg/day and 100 mg/day were not statistically significantly different for AEs based on the 95% CrIs.

Table 27: ITC Estimate of Discontinuations Due to AEs

	Safinamide 50 mg/day		Safinamide 100 mg/day	
Treatment	RR	95% CrI	RR	95% CrI
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Safinamide 50 mg/day		Safinamide 100 mg/day	
Treatment	RR	95% CrI	RR	95% CrI
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

	Safinamide 50 mg/day		Safinamide 100 mg/day	
Treatment	RR	95% CrI	RR	95% CrI
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
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AE = adverse event; CrI = credible interval; ITC = indirect treatment comparison; RR = relative risk.

Source: Sponsor-supplied ITC.[9]

Critical Appraisal

The methods used to conduct the systematic review generally appear to be appropriate. The systematic review included a search of multiple databases and title and abstract screening completed by two independent reviewers; however, the method for resolving discrepancies was not reported. The number of investigators that performed the full-text review and data extraction was not specified. The methods used for resolving discrepancies and quality control were not reported. While the reference lists of relevant publications were searched, a search of grey literature was not performed. The number of reviewers carrying out the quality assessment was not reported, nor was the process for reconciling discrepancies. The authors provided detailed summary tables of relevant data from the included trials, which facilitated the assessment of the similarity between trials. The treatments included were generally relevant to this CDR review, and the dosages for safinamide were clinically relevant. The ITC did not include amantadine (which is used beyond the Health Canada indication for Canadian patients with PD) or apomorphine, which were both considered relevant comparators in the CDR review.

A specific tool was not used to assess the quality of the included studies. However, the authors considered all trials to have a low risk of bias based on the assessment of key methodological components (i.e., random sequence generator, allocation concealment, blinding of participants, blinding of outcome assessment). The number of reviewers carrying out the assessment was not reported, nor was the process for reconciling discrepancies. Characteristics of the studies were reported when available (e.g., duration of PD, average treatment dose of comparator).

The outcomes for OFF time and AEs were assessed and were deemed clinically relevant. Outcomes related to ON time, mobility, symptoms, and HRQoL outcomes were not assessed; these outcomes are generally a priority for patients.

Sensitivity analyses were not performed based on the findings of the quality assessment. Heterogeneity assessments were performed using the I^2 statistic. The evidence networks for OFF time and AEs did not demonstrate concerning levels of statistical heterogeneity; however, based on the sparse reporting of baseline characteristics, the level of clinical heterogeneity is unclear.

The included studies were of similar design (RCTs) and had reportedly included patients with advanced PD. However, a definition for advanced PD was not specified, so it is unclear if the individual trials truly had a homogenous population based on PD stage. Data relating to the dose of treatments was not consistently reported in the individual trials. It is unclear if the doses of comparators would be comparable to the Canadian population. The results for the ITC compare safinamide 50 mg/day and safinamide 100 mg/day with a number of comparators without specifying the doses of the comparators. Although, statically, heterogeneity was not observed for the OFF-time assessment, the absence of dose information may contribute to clinical heterogeneity. It is unclear if optimal doses of comparators were used in the studies. This limits the ability to interpret the comparative results and assess their generalizability to the Canadian population.

For the OFF-time assessment, assumptions for similarity, transitivity, and consistency were reported to have been addressed. The OFF-time ITC was conducted using a fixed-effects model. It was reported that both fixed- and random-effects models were run; however, the results were reported only for the fixed-effects model based on a smaller DIC value compared with the random-effects model (113.2 versus 113.9). The difference in DIC values is small (0.7) and, on its own, may not be sufficient to justify the use of a fixed-effects model over a random-effects model, the use of which would have accounted for more between-study variance. It is unclear if the results using the random-effects model were consistent with the results reported for the fixed-effects model. The primary model for the OFF-time ITC was not adjusted for any covariates. In an additional model, OFF time was assessed with adjustment for baseline risk, which was assumed to act as a proxy measure for potential confounding factors. The details for determining baseline risk were not provided.

For the AE outcomes, trials inconsistently reported data; the resulting sparse networks prevented statistical adjustment for potential outcomes.

Review of Binde et al., 2018

Objectives and Rationale for Binde et al., 2018

The main objective of the Binde et al., 2018 ITC was to perform a drug class review comparing all available MAO-B inhibitors.

Methods for Binde et al., 2018

Study Eligibility, Selection Process, and Data Extraction

Studies included in the ITC were identified via systematic literature search. The authors searched MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials. The

search was performed on June 26, 2017 and was updated in November 2017. Reference lists of included publications were also searched.

Studies with the following criteria were included: DB RCTs of patients with PD who were 18 years of age or older, interventions of interest (selegiline, rasagiline, safinamide) as monotherapy or combined with levodopa or other drugs (DAs, COMT) compared with each other or placebo, evaluating efficacy or safety.

Title and abstract screening were not specified. Two authors independently reviewed the full-text publications based on the pre-specified inclusion criteria. The method for resolving discrepancies was not reported.

Comparators

The ITC included studies that compared the following as monotherapy or with levodopa, DAs, or COMT:

- safinamide
- selegiline
- rasagiline
- placebo

Outcomes

The ITC evaluated the following efficacy and safety outcomes:

- UPDRS responders, where responders were defined as the number of patients with at least a 20% reduction in the UPDRS score from baseline to end of study (total UPDRS score was used where this was provided; scores for sections II and III or Section III only were used where only those scores were provided).
- SAEs.

Quality Assessment

A quality assessment of the included studies was not reported.

ITC Methods

The ITC for the comparison of rasagiline, safinamide, selegiline, and entacapone with levodopa compared with placebo and levodopa was performed with and without explanation variables (disease duration, dose level). A Bayesian approach was used to perform the network meta-analyses. The models were run using non-informative priors and a burn-in of 1,000,000 iterations. The parameter estimates were provided with corresponding 95% CrIs. It is unclear whether a random- or fixed-effects model was used. It was unclear how the model was selected or if goodness of fit was assessed. It was unclear if a heterogeneity assessment was performed. No relevant subgroup analysis was performed in the ITC.

Results

The systematic review identified a total of 249 publications. Overall, 27 trials met the criteria for inclusion.

An overview of the study and the patient characteristics included in the ITCs is provided in Table 28. The location of the included studies was not reported. The patients included in the trials were adults with PD.

For the ITC relevant to this review (required levodopa), comparisons were made for the following treatments: safinamide, selegiline, rasagiline, entacapone, and placebo. The doses of each comparator were categorized as high or low. Disease duration was categorized as greater than or equal to three years, or less than three years. Other study design and patient characteristics were not reported.

No quality assessment of included studies was reported.

Table 28: Study Characteristics for Binde et al., 2018

Study	Comparator	Dose	Disease duration
Rabey et al. 2000	Rasagiline + levodopa	Low (treatment arm 1, treatment arm 2) High (treatment arm 3)	≥ 3 years
Parkinson study group	Rasagiline + levodopa	Low	≥ 3 years
Rascol et al., 2005	Rasagiline + levodopa Entacapone + levodopa	Low	≥ 3 years
Zhang et al., 2013	Rasagiline + levodopa	Low	≥ 3 years
Barone et al., 2015	Rasagiline + levodopa	Low	≥ 3 years
Hanagasi et al., 2011	Rasagiline + levodopa	Low	≥ 3 years
Frakey and Friedman, 2017	Rasagiline + levodopa	Low	< 3 years
Lim et al., 2015	Rasagiline + levodopa	Low	≥ 3 years
Hauser et al., 2015	Rasagiline + levodopa	Low	≥ 3 years
Olanow et al., 1995	Selegiline + levodopa	High	≥ 3 years (reference arm) < 3 years (treatment 1 arm)
Shoulson et al., 2002	Selegiline + levodopa	High	≥ 3 years
Larsen et al., 1999	Selegiline + levodopa	High	≥ 3 years
Pålhagen et al., 2006	Selegiline + levodopa	High	< 3 years (reference arm) ≥ 3 years (treatment arm)
Takahashi et al., 1994	Selegiline + levodopa	High	< 3 years
Borgohain et al., 2014	Safinamide + levodopa	Low	≥ 3 years

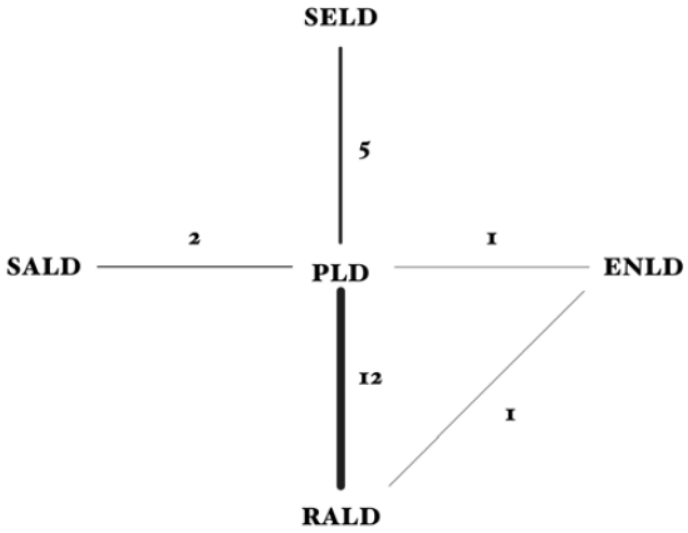
Note: The dose level used was defined as either low (< 1 mg/day of rasagiline; < 10 mg/day of selegiline; < 100 mg/day of safinamide) or high.

Source: Binde et al., 2018.[10]

Evidence Network

Figure 3 presents the evidence network for the relative effect of each MAO-B inhibitor versus the comparator drugs.

Figure 3: Evidence Network for Drug Effect



ENLD = entacapone + levodopa; PLD = placebo + levodopa; SALD = safinamide + levodopa; SELD = selegiline + levodopa; RALD = rasagiline + levodopa.

Source: Binde et al.[10]

UPDRS Responders

For the analysis of UPDRS responders, 15 trials contributed data. The evidence network is presented in Figure 3. Other characteristics of the model were not reported.

Treatment with safinamide (less than 100 mg/day) plus levodopa was more efficacious than treatment with placebo plus levodopa. The results were consistent when the model was run with adjustment for disease duration. Comparisons between safinamide plus levodopa and other active comparators plus levodopa were not reported.

Table 29: ITC Estimates of UPDRS Responders

Treatment	Unadjusted model relative to placebo + levodopa, relative risk (95% CrI)	Adjusted model relative to placebo + levodopa, relative risk (95% CrI)
Safinamide + levodopa	1.18 (1.03 to 1.35)	1.31 (1.13 to 1.51)

CrI = credible interval; ITC = indirect treatment comparison; UPDRS = Unified Parkinson's Disease Rating Scale.

Source: Binde et al., 2018.[10]

SAEs

For the analysis of SAEs, 15 trials contributed data. The evidence network is presented in Figure 3. Other characteristics of the model were not reported.

Treatment with safinamide (less than 100 mg/day) plus levodopa showed no difference in the occurrence of SAEs compared with placebo plus levodopa, based on 95% CrIs (Table 30). The results were consistent when the model was run with adjustment for disease duration. Comparisons between safinamide plus levodopa and other active comparators plus levodopa were not reported.

Table 30: ITC Estimates of SAEs

Treatment	Unadjusted model relative to placebo + levodopa relative risk (95% CrI)	Adjusted model relative to placebo + levodopa relative risk (95% CrI)
Safinamide + levodopa	1.07 (0.82 to 1.47)	0.97 (0.72 to 1.27)

CrI = credible interval; ITC = indirect treatment comparison; SAE = serious adverse event.

Source: Binde et al., 2018.[10]

Critical Appraisal of Binde et al., 2018[10]

The methods used to conduct the systematic review were not reported sufficiently. While a search of multiple databases was performed and two authors independently reviewed the full-text publications, it is unclear if a title and abstract screening was performed. The number of authors who performed the title and abstract screening and data extraction was not specified. The method for resolving discrepancies was not reported. While the reference lists of included publications were searched, no search of grey literature was performed.

It is unclear if a quality assessment of included studies was performed and if the methods were appropriate. The authors provided minimal study design and patient characteristic data from included trials. This reduced the ability to assess the similarity between trials and the applicability to the Canadian population. The minimal reporting of dosages reduced the ability to determine the external validity of the results.

The reporting of the ITC methodology was sparse. Important information about the type of model (random or fixed) and heterogeneity were not reported. It is unclear if any assumptions of the models were tested.

While the ITC included relevant comparators in its design, no comparisons between safinamide and active comparators were reported.

Conclusion

Two ITCs met the inclusion criteria for this review.

[redacted]

Evidence from the Binde et al., 2018 ITC suggests improved efficacy in UPDRS compared with placebo. No difference compared with placebo in the occurrence of SAEs was determined based on 95% CrIs. The utility and quality of the Binde et al., 2018 ITC is limited due to poor reporting of methods. Limitations of this ITC include inadequate reporting of study and patient characteristics, which prevent the ability to assess generalizability to the Canadian clinical population. Definitive conclusions regarding the efficacy and safety of safinamide compared with placebo cannot be made based on the Binde et al., 2018 ITC.

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