Tavapadon for Parkinson's Disease: Effectiveness and Value

Draft Evidence Report

JULY 29, 2026

Prepared for

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DATE OF PUBLICATION: July 29, 2026

How to cite this document: Tice JA, Winn AN, Fahim SM, Walton S, Lee W, Phillips M, Sarker J, Ollendorf D. Tavapadon for Parkinson's Disease: Effectiveness and Value; Draft Evidence Report. Institute for Clinical and Economic Review, July 29, 2026. https://icer-review.org/material/parkinsons-disease-draft-evidence-report/

Jeffrey A. Tice served as the lead author for the report. Shahariar Mohammed Fahim led the systematic review and authorship of the comparative effectiveness section of this report with assistance from Evan Amelchenko, Sol Sanchez, and Dmitriy Nikitin. Aaron Winn, Surrey Walton, and Jyotirmoy Sarker developed the cost-effectiveness model and authored corresponding sections of the report with support from Woojung Lee. Marie Phillips conducted the analysis for the budget impact model. Daniel A. Ollendorf provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Abigail Wright, Becca Piltch, and Anna Geiger for their contributions to this report.

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The funding for this report comes from non-profit foundations, with the largest single funder being the Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program (i.e., not relevant to the clinical or economic analysis in this draft report), with funding approximately equally split between insurers/PBMs and life science companies. A complete list of funders and more information on ICER's support is available on the funding page of the ICER website.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

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The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the initial draft evidence report:

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None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions or iterations of the report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.

To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.

For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit: https://icer.org/assessment/parkinsons-disease-2026/#overview.

Conflict of Interest Disclosures for the Report

Table 1. ICER Authors and External Collaborators Conflict of Interest Disclosures

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Table 2. Expert Reviewers of the Report Conflict of Interest Disclosures

Expert Reviewer	Conflict of Interest
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Rebecca Gilbert, MD, PhD, Chief Mission Officer, American Parkinson Disease Association	Dr. Gilbert is a full time employee of the American Parkinson Disease Association. The American Parkinson Disease Association receives less than 5% of financial support from health care companies.
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List of Acronyms and Abbreviations Used in this Report

AE	Adverse Event
AHRQ	Agency for Healthcare Research and Quality
COMT	catechol-O-methyltransferase
DA	Dopamine Agonist
DBS	Deep-brain stimulation
evLYs	Equal-value life years
FDA	Food and Drug Administration
HRQoL	Health-related quality of life
HY	Hoehn and Yahr
ICD	impulse control disorders
LYs	Life years
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
mg	Milligram
MAO-B	Monoamine oxidase-B
MCID	minimal clinically important difference
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire
PPMI	Parkinson's Precision Medicine Initiative
QALY	Quality-adjusted life year
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale
RCT	Randomized controlled trial
REM	Rapid eye movement
RoB 2	Risk of Bias Assessment Tool Version 2
SMRs	Standardized mortality ratios
SUCRA	Surface under the cumulative ranking curve
US	United States
WAC	Wholesale acquisition cost

Executive Summary

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by stiffness, slowed movement, tremor, instability, and a range of non-motor symptoms, including difficulties with thinking, depression, anxiety, and insomnia.[1] In the United States (US), approximately 1.2 million individuals are estimated to be living with PD or atypical Parkinsonism, with prevalence projected to increase significantly as the population ages.[2]

Patients described PD as a progressive condition characterized by a prolonged and often frustrating diagnostic journey, increasing functional impairment, and the need for continuous adjustment of therapy. The greatest burdens were the loss of motor function and the unpredictability of symptom control. Patients emphasized that relatively small changes in motor ability can substantially affect independence and quality of life. Difficulties performing routine tasks, such as tying shoes or walking safely, were highlighted as meaningful indicators of disease progression and treatment benefit.

Levodopa remains the most effective symptomatic therapy for motor symptoms.[1] However, long-term treatment is frequently associated with motor fluctuations and dyskinesias (involuntary muscle movements), and patients typically need to take pills three to five times a day to manage their symptoms. Dopamine agonists (e.g., pramipexole, ropinirole, rotigotine) are used as initial therapy in selected patients or as adjunctive therapy to levodopa in patients with motor fluctuations, but are associated with adverse effects, including sleepiness, low blood pressure when standing up, hallucinations, and impulse control disorders (e.g., pathological gambling, hypersexuality, compulsive buying or eating, etc.). Additional adjunctive options include monoamine oxidase-B (MAO-B) inhibitors, which block the enzyme that breaks down dopamine and catechol-O-methyltransferase (COMT) inhibitors, which block the enzyme that breaks down levodopa.[1]

Tavapadon (AbbVie Inc.) is an oral, once-daily, selective dopamine D1/D5 partial agonist under review by the Food and Drug Administration (FDA) for use as monotherapy in early-stage PD and as adjunctive therapy in patients experiencing motor fluctuations.[3] Unlike currently available dopamine agonists, which primarily target D2/D3 receptors, tavapadon selectively targets D1-like receptors. The side effects that limit the use of dopamine agonists (sleepiness, low blood pressure when standing up, hallucinations, and impulse control disorders [ICD]) are thought to be due to D2 and D3 receptor effects.

The greatest uncertainties arise because we lack head-to-head trials between tavapadon and other drugs, particularly versus levodopa alone and the combination of levodopa plus a dopamine agonist. Hence, our assessment of comparative effectiveness relies on indirect comparisons. Additional uncertainties are due to the relatively short follow-up time of the studies of tavapadon.

For example, impulse control disorder symptoms matter a lot to patients and their care partners. Observational studies suggest that the incidence of these symptoms increases steadily over several years. The relatively short follow-up time of the TEMPO trials could mask either a greater incidence over time or a flattening of the incidence curve that would demonstrate greater benefits of tavapadon compared with the older medications.

Among patients with early PD, tavapadon significantly improved scores on the Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III compared with placebo. However, quality-of-life measures improved only minimally. There were some patients with ICDs and hallucinations in the tavapadon group and none in the placebo group. However, the discontinuation rate due to adverse events (AEs) was much higher in the tavapadon group. Given the mix of benefits and harms and the lack of follow-up beyond six months for the primary outcomes, the comparative net health benefit compared with no pharmacologic treatment is comparable or better (C++).

The evidence comparing tavapadon with other comparators (dopamine agonists, MAO-B inhibitors) as monotherapies is less clear. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. In the network meta-analyses (NMAs), the evidence for the benefits of tavapadon on the UPDRS is mixed. There are no clear benefits in quality of life, and the within-trial discontinuation rates due to AEs were higher for tavapadon. Given the mixed results and low certainty of evidence, the net health benefit is promising, but inconclusive (P/I).

As expected, tavapadon also statistically significantly improved scores on the UPDRS Parts II and III compared with placebo in levodopa-treated patients with motor fluctuations. However, there were no significant improvements in quality of life. The overall discontinuation rate was significantly higher in the tavapadon group. Given the mix of benefits and harms and the lack of follow-up beyond six months for the primary outcomes, the comparative net health benefit compared to levodopa alone is comparable or better (C++).

The evidence comparing tavapadon with the other therapies (dopamine agonists, MAO-B inhibitors, COMT inhibitors) as an adjunct therapy to levodopa is less clear. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. Within-trial discontinuation rates due to AEs were significantly higher for tavapadon compared with each of the comparators. Given the lack of significant benefits, evidence of more discontinuations and low certainty, the net health benefit is promising, but inconclusive (P/I) for all three comparisons.

Table ES1. Evidence Ratings

Treatment	Comparator	Evidence Rating
Early PD		
Tavapadon	No pharmacologic treatment	C++
	Levodopa	P/I
	Dopamine Agonists	P/I
	MAO-B inhibitors	P/I
PD with Motor Fluctuations		
Tavapadon plus Levodopa	Levodopa alone	C++
	Dopamine Agonists plus levodopa	P/I
	COMT inhibitors plus levodopa	P/I
	MAO-B inhibitors plus levodopa	P/I

C++: "Comparable or Better" Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit; P/I: "Promising but Inconclusive" Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit

Using two semi-Markov models built with real-world Parkinson's disease data (Parkinson's Precision Medicine Initiative, Michael J Fox Foundation) and treatment effects from the TEMPO trials as well as the network meta-analyses (NMA), we estimated the cost-effectiveness of tavapadon for early Parkinson's disease (versus levodopa) and as an adjunct to levodopa for Parkinson's disease with motor fluctuations (versus other dopamine agonists added to levodopa). At the placeholder price of $15,000 per year, tavapadon was more costly and slightly less effective versus levodopa in early PD. The estimated cost-effectiveness for tavapadon compared with a market basket of dopamine agonists in patients already on levodopa was approximately $2.9 million per equal value life year (evLY) gained as well as per quality adjusted life year (QALY), based on a small estimate of overall benefit driven primarily by reductions in the rate of ICDs. These results were consistent under the health care sector and modified societal perspectives but varied substantially in sensitivity analyses, especially for the early PD population. The results were most sensitive to the estimates of the magnitude and durability of tavapadon's benefits. These estimates should be interpreted considering the placeholder price and other uncertainties in the model, as small changes in effectiveness estimates could markedly affect results.

Table ES2. Incremental Cost-Effectiveness Ratios

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*
Patients with Early Parkinson's Disease			
Tavapadon (Health System Perspective)	Levodopa	More Costly, Less Effective	More Costly, Less Effective
Tavapadon (Modified Societal Perspective)	Levodopa	More Costly, Less Effective	More Costly, Less Effective
Patients on Levodopa Experiencing Motor Fluctuations			
Tavapadon (Health System Perspective)	Other DAs	$2.9 million	$2.9 million
Tavapadon (Modified Societal Perspective)	Other DAs	$3.1 million	$3.1 million

DA: dopamine agonist, evLYs: equal-value life years, QALY: quality-adjusted life year

*Based on placeholder price for tavapadon

1. Background

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by stiffness, slowed movement, tremor, instability, and a range of non-motor symptoms, including difficulties with thinking, depression, anxiety, and insomnia.[1] PD is more common in non-Hispanic whites, though this may reflect underdiagnosis in populations with less access to care. It also occurs more commonly in men than in women.[1] The estimated global prevalence of PD has more than doubled over the past two decades.[4] In the United States (US), approximately 1.2 million individuals are estimated to be living with PD or atypical Parkinsonism, with prevalence projected to increase significantly as the population ages.[2]

PD is associated with substantial economic burden. Total annual US costs have been estimated at $82 billion in 2024, relatively evenly split between direct medical costs ($24 billion), indirect costs related specifically to lost productivity and informal caregiving ($26 billion), and other costs, including patient out-of-pocket expenses, other non-medical costs, and disability benefits ($32 billion).[2] Costs increase with disease progression and the development of motor complications, cognitive impairment, and institutional care needs.

Levodopa remains the most effective symptomatic therapy for motor symptoms.[1] However, long-term treatment is frequently associated with motor fluctuations and dyskinesias, and patients typically need to take pills three to five times a day to manage their symptoms. Dopamine agonists (e.g., pramipexole, ropinirole, rotigotine) are used as initial therapy in selected patients or as adjunctive therapy to levodopa in patients with motor fluctuations, but are associated with adverse effects, including sleepiness, low blood pressure when standing up, hallucinations, and impulse control disorders (e.g., pathological gambling, hypersexuality, compulsive buying or eating, etc.). Additional adjunctive options include monoamine oxidase-B (MAO-B) inhibitors, which block the enzyme that breaks down dopamine and catechol-O-methyltransferase (COMT) inhibitors, which block the enzyme that breaks down levodopa.[1]

Tavapadon (AbbVie Inc.) is an oral, once-daily, selective dopamine D1/D5 partial agonist under review by the Food and Drug Administration (FDA) for use as monotherapy in early-stage PD and as adjunctive therapy in patients experiencing motor fluctuations.[3] Unlike currently available dopamine agonists, which primarily target D2/D3 receptors, tavapadon selectively targets D1-like receptors. The side effects that limit the use of dopamine agonists (sleepiness, low blood pressure when standing up, hallucinations, and impulse control disorders [ICD]) are thought to be due to D2 and D3 receptor effects. In one cross-sectional study in the US and Canada, dopamine agonists were associated with a 2 to 3.5-fold higher odds of ICDs.[5] Tavapadon may avoid these potentially devastating side effects.

Table 1.1. Interventions of Interest

Intervention	Mechanism of Action	Delivery Route	Prescribing Information
Tavapadon	Selective dopamine D1/D5 partial agonist	Oral	5 or 15 mg once daily

mg: milligram

2. Patient and Other Stakeholder Perspectives

2.1. Patient Community Input

ICER engaged with patient advocacy organizations, clinical experts, and the manufacturer to better understand the treatment landscape for PD, unmet needs, and the potential role of tavapadon.

Representatives from patient advocacy organizations emphasized that PD affects both motor and non-motor functioning and that symptom burden varies substantially across individuals.

Motor symptoms, particularly bradykinesia, rigidity, tremor, and gait impairment, remain central to diagnosis and treatment decisions. However, stakeholders stressed that non-motor symptoms such as fatigue, depression, cognitive changes, hallucinations, and sleep disturbance are often underrecognized and may have equal or greater impact on quality of life.

A consistent theme was the unpredictability of motor fluctuations and medication response. Patients value consistent "ON" time, when their medications are working well and symptoms are at a minimum. They report that OFF time, when their symptoms return, significantly disrupts daily functioning.

Pill burden, particularly with levodopa, was a consistent theme in conversations with patients and clinical experts. The potential for a once daily therapy with fewer side effects is appealing to patients.

Interviews with Patients

Patients described PD as a progressive condition characterized by a prolonged and often frustrating diagnostic journey, increasing functional impairment, and the need for continuous adjustment of therapy. Several patients reported delays in diagnosis despite persistent symptoms, including evaluations by multiple neurologists before ultimately receiving a diagnosis at a movement disorders center or after symptoms became more pronounced. One patient noted that a family history of PD heightened concern but did not prevent several years of diagnostic uncertainty.

The greatest burden of disease was described as the loss of motor function and the unpredictability of symptom control. Patients emphasized that relatively small changes in motor ability can substantially affect independence and quality of life. Difficulties performing routine tasks, such as tying shoes or walking safely, were highlighted as meaningful indicators of disease progression and treatment benefit. One patient explained that participation in a clinical trial of tavapadon led to noticeable improvements in fine motor function and overall mobility, restoring the ability to perform daily activities that had previously become difficult.

Most patients described complex and individualized experiences with levodopa therapy. While levodopa was viewed as an essential treatment, patients characterized it as both a "blessing and a curse" because maintaining symptom control often required ongoing dose adjustments and careful timing. One patient described spending several years attempting to optimize therapy and continuing to adjust medication schedules based on anticipated daily activities. Another reported that the duration of benefit from each dose had shortened over time, with meaningful symptom control lasting only about an hour in the morning and evening. Patients also discussed medication sensitivity and treatment-related complications, including on-time dyskinesia, and expressed concern that conversations about emerging therapies sometimes focused primarily on the risk of adverse effects without sufficient consideration of potential benefits.

Patients emphasized that PD affects not only individuals living with the disease but also their care partners. One patient stressed that most people with PD are accompanied by care partners who share the daily burden of managing symptoms, medications, and functional limitations. This broader impact on families was viewed as an important consideration when evaluating new treatments.

Beyond motor symptoms, patients discussed nonmotor aspects of the disease that substantially influence quality of life. Sleep was identified as particularly important because better sleep was associated with improved daytime function and longer periods of effective symptom control. The vast majority of patients with PD report sleep disturbances (insomnia, nocturia, rapid eye movement [REM] sleep behaviors). Other common non-motor symptoms include gastrointestinal issues like constipation, mood disorders like depression and anxiety, autonomic dysfunction, cognitive impairment, and psychoses.

Patients also highlighted the importance of exercise programs, strength training, support groups, and other nonpharmacologic interventions in disease management.

When discussing future therapies, patients expressed interest in treatments that provide more consistent symptom control while allowing clinicians to safely adjust doses as the disease progresses. They emphasized the importance of understanding how new medications can be titrated over time and how long their benefits can be maintained. Patients also highlighted the need for accessible, trustworthy information about emerging therapies, noting that many in the community currently rely heavily on peer support groups and word-of-mouth recommendations to guide treatment decisions. Improving patient education and shared decision-making was viewed as an important unmet need alongside the development of more effective therapies.

Interviews with Care Partners

Care partners described PD as a condition that progressively transforms spouses and family members into full-time care partners, with responsibilities expanding substantially as motor and cognitive symptoms worsen. They emphasized that caregiving often evolves over many years, requiring increasing involvement in medication management, mobility assistance, health care coordination, financial planning, and emotional support. Care partners described assuming primary responsibility for nearly all aspects of daily care during the advanced stages of disease.

Disease progression, particularly the development of cognitive impairment, hallucinations, falls, and loss of mobility, was described as the greatest source of care partner impact. Care partners recounted that while motor symptoms initially predominated, cognitive decline eventually became equally or more challenging to manage. Behavioral symptoms, including agitation and hallucinations, led to repeated emergency department visits for one care partner, while another described recurrent fall resulting in multiple fractures despite constant supervision. Care partners emphasized that some safety risks cannot be fully prevented despite continuous vigilance, requiring them to adapt expectations while maintaining patient dignity and independence whenever possible.

Medication management represented a substantial and ongoing responsibility. Care partners described organizing complex medication regimens, monitoring adherence, coordinating prescription refills, and communicating with multiple clinicians and pharmacies. One reported managing approximately 30 medications each day, including antiparkinsonian therapies and medications for associated complications. Carbidopa/levodopa were described as the foundation of treatment over many years. One care partner also reported that deep brain stimulation substantially reduced dyskinesias (involuntary muscle movements) and improved the patient's and care partner's quality of life by reducing symptom burden and simplifying day-to-day management.

Care partners highlighted the extensive logistical demands of caregiving, including coordinating care across numerous specialists, arranging transportation, accompanying patients to appointments, documenting symptoms, and adapting to the home environment as disability progressed. Their families made significant modifications to their homes to improve accessibility, while one care partner described the challenges of arranging wheelchair-accessible transportation and the need to cancel medical appointments when transportation could not be secured. Care partners emphasized that they often serve as the primary coordinator of care across an increasingly fragmented health care system and noted that communication frequently overlooks the care partner despite their central role in managing treatment.

The physical, emotional, and financial consequences of caregiving were substantial. Caregiving was described as equivalent to a second full-time job that frequently resulted in burnout, physical injury, and social isolation. Providing transfers and mobility assistance led to chronic musculoskeletal

strain, while one care partner reported experiencing recurrent health problems related to prolonged caregiving stress. Care partners expressed difficulty taking time away from their loved ones because of concerns about safety, making respite care difficult even when assistance was available. As the disease progressed, social networks often diminished, leaving care partners increasingly isolated.

Care partners also described considerable financial burden associated with advanced PD. Out-of-pocket expenses included home modifications, paid home health aides, accessible transportation, and other supportive services that were not fully covered by insurance. They noted that disability insurance and financial planning substantially influenced families' ability to obtain needed care, while recognizing that many families may not have comparable resources. One care partner estimated that caregiving and associated expenses resulted in millions of dollars in lost income and expenditures over the course of the illness.

Care partners emphasized the need for education, practical support, and encouragement to prioritize their own well-being throughout the disease course. They recommended that newly diagnosed families recognize that every patient's trajectory is different and seek individualized guidance based on the patient's predominant symptoms rather than expecting a uniform disease course. Care partners also stressed the importance of exercise, support organizations, and community resources, while noting that identifying and accessing these services often requires significant personal effort. Overall, care partner support was seen as an essential component of high-quality PD care. Care partners also advised that effective therapies should be evaluated not only for their impact on patients' symptoms but also for their ability to reduce care partner impact, preserve independence, and improve quality of life for the entire family.

2.2. Clinical Input

Clinical experts reported that levodopa remains the most effective and commonly used first-line therapy, particularly for patients aged 60 years and older. Dopamine agonists and MAO-B inhibitors are used less frequently as initial therapy due to more modest efficacy or concerns about adverse effects.

Neuropsychiatric adverse events associated with dopamine agonists—including impulse control disorders, hallucinations, somnolence, and orthostatic hypotension—were identified as important limitations of current options. Several clinicians indicated that a similar therapy with a more favorable side effect profile could address an unmet need.

Motor fluctuations and dyskinesias were described as major drivers of treatment adjustments and consideration of advanced therapies such as deep-brain stimulation (DBS) or infusion pumps. Cognitive impairment was viewed as a key factor limiting eligibility for surgical intervention.

Several experts expressed interest in tavapadon as an additional option, particularly if it demonstrates improved tolerability relative to existing dopamine agonists and can be used both as monotherapy and adjunctive therapy.

2.3. Manufacturer Input

The manufacturer, AbbVie Inc., indicated that tavapadon is being developed for use in early PD and as adjunctive therapy in patients receiving levodopa who experience motor fluctuations. Comparators suggested including levodopa, dopamine agonists, MAO-B inhibitors, and other adjunctive agents.

The manufacturer emphasized the importance of evaluating adverse events including impulse control disorders, ON and OFF time, patient-reported outcomes, and care partner and societal impact measures.

3. Comparative Clinical Effectiveness

3.1. Methods Overview

Detailed methods for the systematic literature review assessing the evidence on tavapadon for the treatment of PD can be found in Supplement Section D1.

Scope of Review

We reviewed the clinical effectiveness of tavapadon as monotherapy in adults with early-stage PD (Population 1) and as adjunctive therapy in adults with PD taking levodopa who are experiencing motor fluctuations (Population 2). We searched for evidence on patient-important outcomes, including the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part II (motor experiences of daily living) scores, Part III (motor examination: e.g., tremor, rigidity, gait) scores, motor state durations (OFF time, ON time with troublesome dyskinesia, and ON time without troublesome dyskinesia), health-related quality of life (HRQoL), activities of daily living, and adverse events (e.g., discontinuations, serious events, impulse control disorders [ICD], dyskinesia, hypotension, hallucinations, and somnolence). The full scope can be found in Supplement Section D1.

Evidence Base

Population 1: Patients with Early PD

We updated the systematic literature review and network meta-analysis (NMA) published by Zhuo et al. (2016) to evaluate the effectiveness and safety of tavapadon in comparison to levodopa, other dopamine agonists, or MAO-B inhibitors as monotherapies in patients with early-stage PD.[6] Following pre-specified inclusion and exclusion criteria, 18 trials were included from Zhuo et al. (2016) in the NMA evidence for this report.[7-24] Details about these criteria are in Supplement Section D1. Our updated search identified five new studies: TEMPO-1, TEMPO-2, PD MED trial (early disease component), Zhang et al. (2016), and Hattori et al. (2019).[25-29] Using the Cochrane Risk of Bias Assessment Tool Version 2 (RoB 2), we rated 17 trials for the primary endpoints of UPDRS Part II and III scores. We rated five trials as "high" risk of bias, five trials as "some concerns" and seven trials as "low" risk of bias. Both TEMPO-1 and TEMPO-2 trials were rated as "some concerns" due to higher discontinuations rate (i.e., missing outcome data). See Table D1.6.

TEMPO-1 was a Phase III trial that randomized a total of 529 adults with early-stage PD to either tavapadon 5 mg or tavapadon 15 mg or placebo for 27 weeks, followed by a four-week of safety follow-up period.[25] TEMPO-2 was another Phase III, placebo-controlled, 27-weeks trial that enrolled 304 participants with early-stage PD to evaluate flexible doses of tavapadon (5-15 mg) as

monotherapies.[26] For both trials, the primary endpoint was change from baseline in MDS-UPDRS Part II and Part III combined score at week 26. The TEMPO trials used the MDS-UPDRS scale, but all earlier trials used the older UPDRS. To perform our NMAs, we converted the MDS-UPDRS Part II and Part III scores to their UPDRS equivalents using validated transformations.[30]

In the TEMPO-1 trial, the mean age was 64 years old and around 35% were female. Over 97% of the trial participants were White and had a mean disease duration of <1 year. All enrolled patients had stages I-II in the Hoehn and Yahr (HY) scale, a five-stage scale used to describe the progression of motor symptoms in PD (see Supplement Section A1 for details), and approximately 70% were at stage II. The mean MDS-UPDRS Part II and Part III scores were 7.4 and 24.4, respectively. More than a quarter of the trial participants (26%) were using MAO-B inhibitors during the trial.[25] At baseline, the mean age of TEMPO-2 trial participants was 63 years and 44% were female. The trial also predominantly included Whites (88%) and the mean MDS-UPDRS Part II and III combined score was 30.5. Around 30% of the trial participants used MAO-B inhibitors during the trial.[26]

Baseline characteristics of the other included trials were well-balanced across treatment arms and largely consistent with the TEMPO-1 and TEMPO-2 trial populations, except for their inclusion of Hoehn and Yahr (HY) stage III patients as an early-stage PD population. Details about design and baseline characteristics of these studies are available in Supplement Tables D2.1 and D2.3.

Population 2: Patients on Levodopa Experiencing Motor Fluctuations

We updated the systematic literature review and NMA published by Sako et al. (2023) to evaluate the comparative effectiveness and safety of tavapadon relative to other dopamine agonists, MAO-B inhibitors, or COMT inhibitors as adjuncts to levodopa in patients with PD experiencing motor fluctuations.[31] Following pre-specified inclusion and exclusion criteria, 21 trials from Sako et al. (2023) were included in the NMA for this report.[32,33] Details about these criteria are in Supplement Section D1. Our updated search identified two new studies: TEMPO-3 and the PD MED trial (adjuvant treatment component).[32,33] Using the Cochrane Risk of Bias Assessment Tool Version 2 (RoB 2), we rated 19 trials for the primary endpoints of motor state durations (OFF hours). We rated three trials as "high" risk of bias, eight trials as "some concerns" and eight trials as "low" risk of bias. TEMPO-3 trial was rated as "some concerns" due to higher discontinuations rate (i.e., missing outcome data). See Table D1.7.

TEMPO-3 was a Phase III trial in which 507 adults currently on a stable levodopa dose and experiencing motor fluctuations were randomized to either flexible dose tavapadon (5-15 mg) or placebo for 27 weeks, followed by a four-week safety follow-up period.[32]

In the TEMPO-3 trial, participants had a mean age of 73 years and 37% were female. Approximately 97% of the trial participants were White, with a mean disease duration of seven years. All enrolled patients had HY stages II-III disease, of whom around 22% were at stage III. The mean MDS-UPDRS

Part II and Part III scores were 12.9 and 32.5, respectively. More than 30% of the trial participants had a prior experience with MAO-B inhibitors. On average, participants had 5.5 hours of daily OFF time and a stable levodopa dose of around 815 mg per day.[32]

In the remaining included trials, baseline characteristics were balanced across treatment groups, and these trial populations were largely comparable to the TEMPO-3 trial population. Details about design and baseline characteristics of these studies are available in Supplement Tables D2.3 and D2.4.

Additional Evidence

TEMPO-4 was a Phase III, open label trial of tavapadon that combined both populations described above and reported data on safety outcomes over more than a year of follow-up. Participants were enrolled if they had completed any of the three prior TEMPO trials (N=468) or were new patients with PD on a stable levodopa dose (N=524). An interim analysis from this trial was presented as an abstract at a recent conference.[34]

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity (race/ethnicity, sex, and age) of the participants in the TEMPO-1, TEMPO-2, and TEMPO-3 trials using the ICER developed Clinical trial Diversity Rating (CDR) Tool (Agboola 2024). All three TEMPO trials achieved a "fair" rating for Race/Ethnicity, a "fair" rating for age, and achieved a "good" rating for sex. See Supplement D1 for full details of CDR methods and results.

3.2. Results

Clinical Benefits

Clinical benefits are summarized first for patients with early PD (Population 1) and then for patients with PD on levodopa who are experiencing motor fluctuations (Population 2). We performed random-effects unadjusted NMAs for outcomes reported similarly in sufficient numbers of trials. Details about NMA methods are available in Supplement Section D. Data on HRQoL measures from key trials are summarized for each population as there was not sufficient data to perform NMAs.

Population 1: Patients with Early PD

UPDRS Scores

Seventeen trials contributed data on UPDRS Part III scores.[7-12,14-17,19-21,23,25,26,28,29] All treatments were significantly better than placebo (mean difference -2.7 to -7.2 vs. placebo). Only tavapadon and levodopa met the reported minimal clinically important difference (MCID) thresholds for improvement (-4.8 to -6.2).[35,36] There were no statistically significant differences between tavapadon and levodopa. However, tavapadon was superior to both dopamine agonists and MAO-B inhibitors. See Table 3.1. There were no meaningful changes when studies rated as having a "high" risk of bias were excluded from the NMA (see Supplement Table D1.18).

Table 3.1. NMA Results for UPDRS Part III Scores Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives

Tavapadon				
-0.86 (-3.58, 1.93)	Levodopa			
-2.80 (-4.81, -0.80)	**-1.95 (-3.84, -0.09)**	Dopamine Agonists		
-4.52 (-6.50, -2.46)	**-3.66 (-6.07, -1.25)**	**-1.72 (-3.20, -0.17)**	MAO-Bs	
-7.17 (-8.86, -5.46)	**-6.31 (-8.49, -4.19)**	**-4.37 (-5.43, -3.30)**	**-2.65 (-3.76, -1.60)**	Placebo

MAO-Bs: monoamine oxidase-B inhibitors

Each box represents the estimated relative mean difference and 95% credible interval. Values less than 0 indicate greater benefit. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect surface under the cumulative ranking curve (SUCRA).

Fourteen trials contributed data on UPDRS Part II scores.[9,11,12,14-16,19-21,23,25,26,28,29] All treatments were significantly more likely to reduce the UPDRS Part II scores compared to placebo (mean difference -1.2 to -1.9 vs. placebo), except for levodopa, which demonstrated a reduction (mean difference -2.7) that did not reach statistical significance. Only one small trial comparing levodopa with dopamine agonists contributed data to this NMA.[9] Hence, the comparison between levodopa and placebo is based on indirect evidence with wide credible intervals. The reported MCID for Part II score ranges from -1.8 to -3.05.[36,37] There were no statistically significant differences between tavapadon, levodopa, dopamine agonists, and MAO-B inhibitors. See Table 3.2. There were no

meaningful changes when studies that a "high" risk of bias had were excluded from the NMA (see Supplement Table D1.19).

Table 3.2. NMA Results for UPDRS Part II Scores Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives

Tavapadon				
0.80 (-3.51, 5.13)	Levodopa			
-0.02 (-0.87, 0.83)	-0.85 (-5.06, 3.45)	Dopamine Agonists		
-0.69 (-1.54, 0.17)	-1.51 (-5.78, 2.82)	-0.67 (-1.31, 0)	MAO-Bs	
-1.86 (-2.59, -1.15)	-2.67 (-6.92, 1.56)	**-1.84 (-2.29, -1.38)**	**-1.18 (-1.64, -0.72)**	Placebo

MAO-Bs: monoamine oxidase-B inhibitors

Each box represents the estimated relative mean difference and 95% credible interval. Values less than 0 indicate greater benefit. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect SUCRA.

Health-Related Quality of Life (HRQoL)

Data from two HRQoL instruments were available for five trials.[14,16,25,27,29] The Parkinson's Disease Questionnaire (PDQ-39) is a disease-specific instrument to assess the effect of Parkinson's on the quality of life and the EQ-5D is a widely validated measure of health utility.

In the TEMPO-1 trial, there were no significant differences in PDQ-39 total scores or in EQ-5D VAS scores between tavapadon and placebo at week 26. There was a statistically significant improvement in the EQ-5D index score for participants receiving tavapadon compared to placebo (tavapadon 15 mg vs. placebo treatment difference 0.03, 95% CI: 0.01 to 0.05) at week 26.[25] The MCID for EQ-5D index scores among PD patients is approximately 0.10.[38] In the TEMPO-2 trial, tavapadon showed numerical improvements in both EQ-5D VAS and index scores compared to placebo at week 26; however, treatment differences were not significant.[26]

The PD MED trial provided data on long-term quality of life comparing levodopa versus levodopa-sparing therapy (combining patients using either dopamine agonists or MAO-B inhibitors) as monotherapy in early-stage PD. After seven years of follow-up, patients treated with levodopa had significantly greater improvement in PDQ-39 mobility scores compared with those treated with either a dopamine agonist or an MAO-B inhibitor (mean difference 1.8; 95% CI: 0.5 to 3.0). The MCID for the PDQ-39 mobility domain is -3.2.[39] There was also a significant improvement in EQ-5D index scores for levodopa compared to levodopa-sparing agents (mean difference 0.03; 95% CI: 0.01 to 0.05), although this is also below the MCID threshold stated above. There were no significant differences between dopamine agonists and MAO-B inhibitors for any of the quality-of-life measures.[27]

Finally, three additional trials comparing individual treatments to placebo also showed greater improvements on these scales, favoring the treatments, but not all comparisons reached statistical significance or met the MCID thresholds described in the Supplement Section D1. Details of these results are in Supplement Section D2.

Population 2: Patients on Levodopa Experiencing Motor Fluctuations

Motor State Durations

Data on overall ON-time and ON-time with troublesome dyskinesias were not available from the TEMPO trials. The NMA results for daily OFF times and ON times without troublesome dyskinesia are summarized below. Shorter OFF times (hours) and longer ON times (hours) indicate better treatment response.

Nineteen trials reported data on daily OFF hours.[19,32,40-57] All adjunct therapies were significantly better than levodopa alone for OFF times (mean difference -0.75 to -1.41 vs. placebo). There were no differences between tavapadon and other therapeutic alternatives, but dopamine agonists were superior to both COMT inhibitors and MAO-B inhibitors when added to levodopa. The MCIDs for OFF time ranges from 1 to 1.3 hour.[36] See Table 3.3. There were no meaningful changes when studies that had a "high" risk of bias were excluded from the NMA (see Supplement Table D1.20).

Table 3.3. NMA Results for Daily OFF Times (Hours) Comparing Tavapadon with Other Therapeutic Alternatives as Adjunct to Levodopa

Tav + Lev				
0.46 (-0.24, 1.16)	**DA + Lev**			
-0.18 (-0.84, 0.48)	**-0.64 (-1.08, -0.20)**	**COMTs + Lev**		
-0.20 (-0.87, 0.47)	**-0.66 (-1.10, -0.22)**	-0.02 (-0.37, 0.33)	**MAO-Bs + Lev**	
-0.95 (-1.55, -0.34)	**-1.41 (-1.75, -1.06)**	**-0.77 (-1.03, -0.49)**	**-0.75 (-1.03, -0.47)**	**Pbo + Lev**

COMTs: Catechol-O-methyltransferase inhibitors, DAs: dopamine agonists, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, Tav: tavapadon

Each box represents the estimated relative mean difference and 95% credible interval. A negative mean difference is favorable. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect SUCRA.

Ten trials reported ON time without troublesome dyskinesia data.[32,40,41,43,48,50-53,57] All adjunct therapies were significantly better than levodopa alone for ON times without troublesome dyskinesia (mean difference 0.82 to 1.61 vs. placebo). There were no differences between tavapadon and other therapeutic alternatives, but dopamine agonists were superior to both COMT inhibitors and MAO-B inhibitors when added to levodopa. No MCID threshold was found for daily ON times or ON times without troublesome dyskinesia. See Table 3.4.

Table 3.4. NMA Results for Daily ON Times (Hours) Without Troublesome Dyskinesia Comparing Tavapadon with Other Therapeutic Alternatives as Adjunct to Levodopa

Tav + Lev				
-0.51 (-1.45, 0.40)	**DA + Lev**			
0.29 (-0.59, 1.17)	**0.80 (0.14, 1.48)**	**COMTs + Lev**		
0.28 (-0.60, 1.14)	**0.79 (0.14, 1.45)**	-0.01 (-0.54, 0.52)	**MAO-Bs + Lev**	
1.10 (0.33, 1.87)	**1.61 (1.11, 2.13)**	**0.81 (0.38, 1.25)**	**0.82 (0.42, 1.24)**	**Pbo + Lev**

COMTs: Catechol-O-methyltransferase inhibitors, DAs: dopamine agonists, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, Tav: tavapadon

Each box represents the estimated relative mean difference and 95% credible interval. A positive mean difference is favorable. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect SUCRA.

UPDRS Scores

UPDRS scores were measured as secondary endpoints in the trials of patients on levodopa experiencing motor fluctuations. A total of 20 trials reported data on UPDRS scores. There were no significant differences between tavapadon and any of its therapeutic alternatives as adjunct therapies to levodopa in either Part III or Part II scores. Dopamine agonists demonstrated statistical superiority in both parts over COMT inhibitors as adjunct therapies as well as over levodopa alone. Additional details are available in the Supplement Section D2 (Additional Clinical Benefits) and Tables D1.21 and D1.22.

Health-Related Quality of Life (HRQoL)

Data on HRQoL outcomes were reported across 11 trials in this population.[33,43-45,47-51,54,57] Of these, the PD MED trial (adjuvant treatment part) compared dopamine agonists, MAO-B inhibitors, and COMT inhibitors directly while the remaining ten compared individual treatments against either placebo or active comparators.

In the TEMPO-3 trial, there were no statistically significant differences between tavapadon and placebo in PDQ-39 mobility scores, EQ-5D index scores, and EQ-5D VAS scores.[32] After five years of follow-up, there were no significant differences in these QoL measures between those treated with dopamine agonists plus levodopa and those treated with dopamine reuptake inhibitors (i.e., either MAO-B inhibitors plus levodopa or COMT inhibitors plus levodopa) in the PD MED trial. However, MAO-B inhibitors as an adjunct treatment to levodopa demonstrated significantly higher mobility scores on the PDQ-39 (mean difference 4.2 points; 95% CI: 0.4 to 7.9) and higher EQ-5D index scores (mean difference 0.05; 95% CI: 0.003 to 0.09) compared to COMT inhibitors plus levodopa, although this fell short of the published MCID of 0.10.[33]

Finally, trials comparing individual treatments in combination with levodopa also showed some improvements in these HRQoL outcomes when compared to levodopa alone therapy and are presented in detail with their MCID thresholds in the Supplement Section D1.

Harms

For each population, we summarize harm evidence from the NMAs in two sections: discontinuation rates and adverse events of interest, including ICDs, dyskinesia, somnolence, hypotension, and hallucinations. We also report trial-specific results in the absence of NMA data. We then present findings from an interim analysis of the TEMPO-4 trial as supplemental information on the long-term safety of tavapadon at the end of this section.

Population 1: Patients with Early PD

Discontinuation Rates

In the TEMPO-1 trial, 29% of the trial participants treated with tavapadon discontinued the study compared with 15% in the placebo arm. The tavapadon arm also had higher discontinuations than in the placebo arm (38% vs. 15%) in the TEMPO-2 trial. Discontinuations due to adverse events (AEs) were also substantially higher in the tavapadon group (18% and 24%) than those treated with placebo (3% and 4%) in these two TEMPO trials, respectively, although discontinuations due to AEs decreased substantially after the titration period.[25,26]

Nineteen trials separately contributed data on all-cause discontinuations and discontinuations due to AEs.[7-17,19-26,28,29] Participants treated with tavapadon were twice as likely to discontinue therapy compared with MAO-B inhibitors (relative risk [RR] 2.27; 95% CrI: 1.03, 4.82) and placebo. There were no significant differences in all-cause discontinuations between tavapadon and either levodopa or dopamine agonists. See Table 3.5.

Table 3.5. NMA Results for All Cause Discontinuations Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives

Tavapadon				
2.03 (0.79, 5.12)	Levodopa			
1.96 (0.94, 4.06)	0.97 (0.54, 1.72)	Dopamine Agonists		
2.27 (1.03, 4.82)	1.12 (0.50, 2.46)	1.16 (0.66, 1.99)	MAO-Bs	
2.11 (1.12, 4.04)	1.04 (0.53, 2.07)	1.08 (0.76, 1.55)	0.93 (0.62, 1.45)	Placebo

MAO-Bs: monoamine oxidase-B inhibitors

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Treatment order does not reflect SUCRA.

Tavapadon had almost a threefold higher discontinuation rates due to AEs than those treated with dopamine agonists (RR 2.83; 95% CrI: 1.02, 8.34) and five times higher discontinuation due to AEs than those treated with MAO-B inhibitors (RR 4.94; 95% CrI: 1.74, 15.83) or placebo. The wider credible intervals may have been resulted because these indirect comparisons relied on fewer tavapadon trials. Finally, there was no significant difference between tavapadon and levodopa. See Table 3.6.

Table 3.6. NMA Results for Discontinuations due to AEs Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives

Tavapadon				
3.50 (0.89, 15.61)	Levodopa			
2.83 (1.02, 8.34)	0.81 (0.29, 2.04)	Dopamine Agonists		
4.94 (1.74, 15.83)	1.41 (0.43, 4.67)	1.74 (0.90, 3.64)	MAO-Bs	
5.07 (2.03, 13.34)	1.46 (0.47, 4.08)	**1.79 (1.11, 2.85)**	1.03 (0.55, 1.75)	Placebo

MAO-Bs: monoamine oxidase-B inhibitors

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. The treatment order does not reflect SUCRA.

The NMA showed no significant differences in the incidence of serious adverse events between tavapadon and any of its therapeutic alternatives, with RRs across comparisons ranges from 0.61 to 1.49. See Supplement Table D1.23. There was one death in the tavapadon 5 mg arm of the TEMPO-1 trial, but it was deemed unrelated to the study drug, whereas no deaths occurred in the TEMPO-2 trial.[25,26]

In the PD MED trial (early disease), patients randomized to dopamine agonists and MAO-B inhibitors had higher discontinuation rates than those on levodopa. At seven-years follow-up, the all-cause discontinuation rates were 7%, 50%, and 72% for levodopa, dopamine agonists, and MAO-B inhibitors, respectively. The estimated discontinuations due to AEs were 2% for levodopa, 28% for dopamine agonists, and 23% for MAO-B inhibitors.[27]

Adverse Events of Interest

Only three trials reported data on impulse control disorders (ICD) in this population. Both the TEMPO-1 and TEMPO-2 trials found no difference in changes from baseline scores in the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) between tavapadon and placebo at week 26.[25,26] In the TEMPO-1 trial, three tavapadon participants experienced ICD-related AEs during the maintenance phase compared to none in the placebo group.[25] Two participants in the TEMPO-2 trial experienced ICD-related AEs during the titration period compared to none in the placebo group.[26] All events were mild or moderate in severity. Additionally, two other trials evaluating individual treatments suggested a numerically higher proportion of participants treated with dopamine agonist (2-34%) experiencing ICD-related AEs compared to either placebo (1%) or an MAO-B (13%).[14,22] The small trial (N=109) that showed elevated ICD events for dopamine agonists (34%) versus MAO-B inhibitors (13%) reported data by three subcategories of ICDs and combining them was necessary to obtain an overall rate, which may have double-counted patients who reported more than one behavior.[22]

There were no differences in the risk of hypotension or somnolence between tavapadon and any of the comparators of interest. We were unable to conduct NMAs for hallucinations or dyskinesias due to limited data. A total of 17 participants (3%) experienced hallucinations in the tavapadon arms

compared to none in placebo arm in the two TEMPO trials. The TEMPO-2 trial reported zero dyskinesia events in both arms whereas no data were presented in the TEMPO-1 trial.[25,26] The PD MED trial found that participants treated with levodopa were more likely to develop dyskinesias than those treated with either a dopamine agonist or an MAO-B inhibitor (hazard ratio, HR 1.52; 95% CI: 1.16 to 2.00) at year 7, but rates of dyskinesia were similar between dopamine agonists and MAO-B inhibitors.[27]

Population 2: Patients on Levodopa Experiencing Motor Fluctuations

Discontinuation Rates

In the TEMPO-3 trial, 37% of the trial participants treated with tavapadon plus levodopa discontinued the study compared with 19% in the placebo plus levodopa arm. Discontinuations due to AEs were also substantially higher in the tavapadon plus levodopa group (17%) than those treated with placebo plus levodopa (9%), although most had occurred during the titration period.[32]

A total of 22 trials reported data on all-cause discontinuations and 21 trials on discontinuations due to AEs.[19,32,40-59] Participants treated with tavapadon plus levodopa were three times more likely to discontinue the trial compared to dopamine agonists plus levodopa (RR 2.71; 95% CrI: 1.46, 5.08) and twice as likely to discontinue compared to MAO-B inhibitors plus levodopa (RR 2.06; 95% CrI: 1.06, 4.04). See Table 3.7.

Table 3.7. NMA Results for All Cause Discontinuations Comparing Tavapadon with Other Therapeutic Alternatives as Adjunct to Levodopa

Tav + Lev				
2.71 (1.46, 5.08)	**DAs + Lev**			
1.58 (0.83, 2.96)	**0.58 (0.41, 0.82)**	**COMTs + Lev**		
2.06 (1.06, 4.04)	0.76 (0.51, 1.15)	1.31 (0.88, 1.97)	**MAO-Bs + Lev**	
1.90 (1.07, 3.40)	**0.70 (0.55, 0.88)**	1.20 (0.93, 1.57)	0.92 (0.65, 1.29)	**Pbo + Lev**

COMTs: Catechol-O-methyltransferase inhibitors, DAs: dopamine agonists, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, Tav: tavapadon

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. The treatment order does not reflect SUCRA.

There were no significant differences in discontinuations due to AEs between tavapadon and the comparators when added to levodopa. See Table 3.8.

Table 3.8. NMA Results for Discontinuations due to AEs Comparing Tavapadon with Other Therapeutic Alternatives as Adjunct to Levodopa

Tav + Lev				
2.06 (0.96, 4.35)	DAs + Lev			
1.28 (0.60, 2.78)	**0.62 (0.40, 0.96)**	COMTs + Lev		
1.78 (0.78, 4.39)	0.86 (0.50, 1.61)	1.39 (0.81, 2.52)	MAO-Bs + Lev	
1.83 (0.91, 3.71)	0.89 (0.66, 1.19)	**1.43 (1.04, 1.96)**	1.03 (0.60, 1.65)	Pbo + Lev

COMTs: Catechol-O-methyltransferase inhibitors, DAs: dopamine agonists, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, Tav: tavapadon

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. The treatment order does not reflect SUCRA.

The NMA showed no significant differences in serious adverse events between tavapadon and any of its therapeutic alternatives as an adjunct therapy to levodopa, with RRs across comparisons ranges from 0.75 to 1.39. See Supplement Table D1.26. There was one death in the tavapadon plus levodopa arm of TEMPO-3 trial, but it was deemed unrelated to the study drug.[32]

The PD MED trial (adjuvant treatment part) suggested higher discontinuations with long-term use of our comparators of interest for this Population 2. At five-years follow-up, the estimated all-cause discontinuation probabilities reached 55%, 56%, and 58% for dopamine agonists, COMT inhibitors, and MAO-B inhibitors as adjunct therapies to levodopa, respectively. The estimated discontinuations due to AEs were 46% for dopamine agonists, 34% for COMT inhibitors, and 40% for MAO-B inhibitors as adjunct therapies to levodopa.[33]

Adverse Events of Interest

Five trials reported ICD data in this population. The TEMPO-3 trial found no difference in changes from baseline scores in the QUIP-RS between tavapadon plus levodopa and levodopa alone at week 26. Six participants (2%) experienced ICD-related AEs during the maintenance phase compared with three (1%) in the placebo group; however, all events were non-serious.[32] Four other trials evaluating individual treatments suggested a numerically higher proportion of participants treated with dopamine agonists plus levodopa (0-5%) or with COMTs plus levodopa (8%) experiencing ICD-related AEs compared to levodopa alone (0-4%).[41,42,44,48] A fixed effects NMA including these five trials showed no difference between tavapadon plus levodopa and its therapeutic alternatives.

There were no differences in the risk of hypotension or somnolence or hallucinations between tavapadon and any of the comparators of interest as an adjunct therapy to levodopa. The NMA also showed no differences in the risk of dyskinesia between tavapadon, dopamine agonists, and COMT inhibitors when added to levodopa therapy. However, tavapadon plus levodopa demonstrated a statistically significant higher risk of dyskinesia (RR 3.84; 95% CrI: 1.20 to 14.29) compared to MAO-B inhibitors plus levodopa. The wider credible intervals may have been resulted because these

indirect comparisons relied on fewer tavapadon trials. Additional details are available in Supplement Section D (Additional Harms) and in Supplement Table D1.30.

TEMPO-4

In the TEMPO-4 trial, previously untreated participants (placebo rollover from previous TEMPO trials and de novo participants, N=523) consistently showed higher rates of AEs compared to those already on tavapadon (N=468), particularly for discontinuations due to AEs (19% vs. 9%), serious AEs (10% vs. 6%), and hallucinations (8% vs. 4%), respectively, suggesting the incidence of AEs may plateau during long-term treatment with tavapadon. Rates were similar for somnolence (5% vs. 5%), orthostatic hypotension (4% vs. 4%), and ICDs (2% vs. 1%). No new safety issues related to tavapadon were reported in this trial.[34]

Subgroup Analyses and Heterogeneity

In both TEMPO-1 and TEMPO-2 trials, subgroup analyses by baseline characteristics including age, sex, HY stages, and disease duration did not identify any effect modification.[25,26] No subgroup analyses were presented for the TEMPO-3 trial results.

Uncertainty and Controversies

The greatest uncertainties arise because we lack head-to-head trials between tavapadon and other drugs, particularly the dopamine agonists. Hence, our assessment of comparative effectiveness relies on indirect comparisons through NMAs. Some of the findings are counterintuitive. Specifically, the hope is that tavapadon will have fewer important side effects than earlier dopamine agonists because it targets the relevant dopamine receptors more precisely. However, tavapadon had markedly more discontinuations due to adverse events in our indirect comparisons.

Similarly, since levodopa is the preferred first-line therapy in early PD, head-to-head trials between tavapadon and levodopa would be illustrative. Head-to-head trials are needed to provide greater certainty about the potential value of tavapadon as both first-line therapy in early PD and for managing levodopa-treated patients with motor fluctuations.

Impulse control disorder symptoms matter a lot to patients and their care partners. Observational studies suggest that the incidence of these symptoms increases steadily over several years. The relatively short follow-up time of the TEMPO trials could mask either a greater incidence over time or a flattening of the incidence curve that would demonstrate greater benefits of tavapadon compared with the older medications. For example, in the TEMPO-4 results (non-randomized data from an abstract), the ICD-related AEs were higher among patients newly started on tavapadon (1.9%) compared to those patients continuing tavapadon therapy (0.9%).

The Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP-RS) may be insensitive to changes leading to ICDs. In both the TEMPO-1 and TEMPO-3 trials, there were no between-group differences in the QUIP-RS, but there were more ICD-related AEs in the tavapadon groups than in the placebo group for both trials.

Other uncertainties arise because the instruments used to measure key outcomes in patients with Parkinson's disease have evolved over time. The TEMPO trials used the MDS-UPDRS, while the older trials all used the original UPDRS. New trials use the Hauser diary to assess OFF and ON time, while older trials use other instruments to measure approximately the same outcomes.

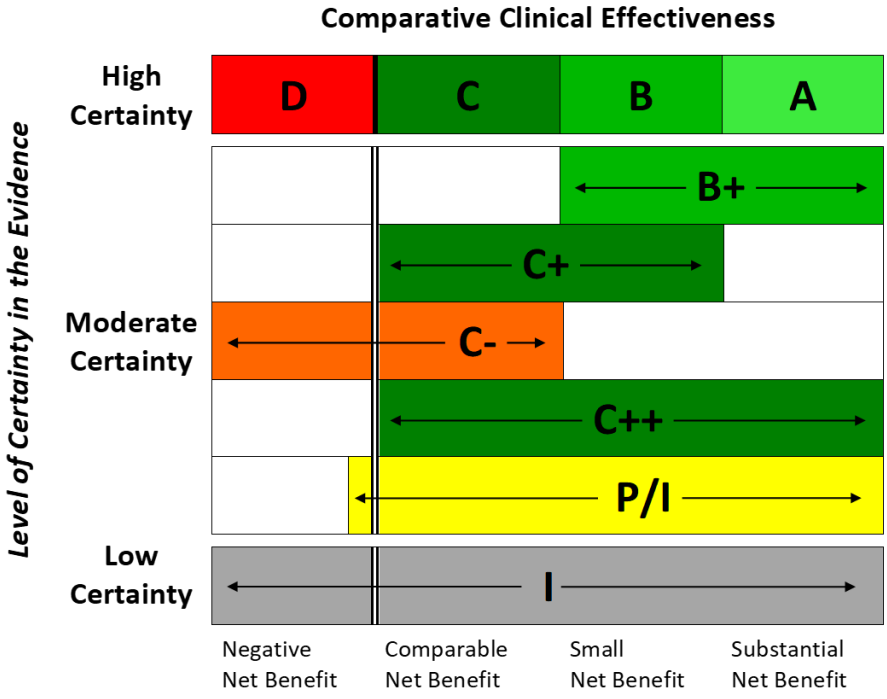
A related uncertainty is the wide range of reported MCIDs for the UPDRS Part II and Part III subscales.[60] This complicates the interpretation of statistically significant and clinically significant improvements in the subscales. For the MDS-UPDRS, only a group in Hungary has assessed the MCID for the Part II and Part III subscales,[37,61] so there may be variability here as well once more groups assess the MCIDs.

Finally, the TEMPO-1 and TEMPO-2 trials in early Parkinson's disease allowed participants taking MAO-B inhibitors to be eligible for enrollment. This was also true for most of the earlier trials included in our NMAs. The studies did not assess for effect modification by use of MAO-B inhibitors, so it is unclear whether results may differ in patients on true monotherapy.

3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

Figure 3.1. ICER Evidence Rating Matrix



A = "Superior" - *High certainty of a substantial (moderate-large) net health benefit*
B = "Incremental" - *High certainty of a small net health benefit*
C = "Comparable"- *High certainty of a comparable net health benefit*
D= "Negative"- *High certainty of an inferior net health benefit*
B+= "Incremental or Better" – *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+ = "Comparable or Incremental" - *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
C- = "Comparable or Inferior" – *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
C++ = "Comparable or Better" - *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I = "Promising but Inconclusive" *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
I = "Insufficient" – *Any situation in which the level of certainty in the evidence is low*

Population 1: Patients with Early PD

As expected, tavapadon significantly improved scores on the UPDRS Parts II and III compared with placebo among patients with early PD. However, quality-of-life measures improved only minimally. There were some patients with ICDs and hallucinations in the tavapadon group and none in the placebo group, but none were severe, and they were uncommon. However, the discontinuation rate due to AEs was much higher in the tavapadon group. The TEMPO-1 and -2 trials do provide

direct comparisons between tavapadon and placebo, so the level of certainty is moderate to high. Given the mix of benefits and harms and the lack of follow-up beyond six months for the primary outcomes, the comparative net health benefit compared to no pharmacologic treatment is comparable or better (C++).

The evidence comparing tavapadon with levodopa is less clear. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. In the NMAs, tavapadon was non-significantly better on the UPDRS Part III but showed a non-significant trend towards worse scores on Part II. There are no clear benefits in quality of life, and the discontinuation rates due to AEs were 3.5 times higher for tavapadon, although this was not statistically significant. Given the mixed results and low certainty, the net health benefit is promising, but inconclusive (P/I).

The evidence comparing tavapadon with other dopamine agonists is similar. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. In the NMAs, tavapadon was significantly better on the UPDRS Part III but showed a non-significant trend towards worse scores on Part II. There are no clear benefits in quality of life, and the discontinuation rates due to AEs were significantly higher for tavapadon. It remains unclear whether psychiatric side effects, like ICDs and hallucinations, will be lower with tavapadon. Given the mixed results and low certainty of evidence, the net health benefit is promising, but inconclusive (P/I).

The evidence comparing tavapadon with other MAO-B inhibitors is mixed. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. In the NMAs, tavapadon was significantly better on both the UPDRS Part III and Part II, though the magnitude of the benefits were smaller than those seen compared with placebo. There are no clear benefits in quality of life, and the discontinuation rates were significantly higher for tavapadon compared with MAO-B inhibitors, though the discontinuation rate due to AEs was not significant. Given the mixed results and low certainty of evidence, the net health benefit is promising, but inconclusive (P/I).

Table 3.9. Evidence Ratings

Treatment	Comparator	Evidence Rating
Early PD		
Tavapadon	No pharmacologic treatment	C++
	Levodopa	P/I
	Dopamine Agonists	P/I
	MAO-B inhibitors	P/I
PD with Motor Fluctuations		
Tavapadon plus Levodopa	Levodopa alone	C++
	Dopamine Agonists plus levodopa	P/I
	COMT inhibitors plus levodopa	P/I
	MAO-B inhibitors plus levodopa	P/I

C++: "Comparable or Better" Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit; P/I: "Promising but Inconclusive" Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit

Population 2: Patients on Levodopa Experiencing Motor Fluctuations

As expected, tavapadon significantly improved scores on the UPDRS Parts II and III compared with placebo in patients on levodopa who are experiencing motor fluctuations. However, there were no significant improvements in quality of life measures. In the TEMPO-3 trial, there were no differences in the QUIP-RS between tavapadon and placebo, but six patients treated with tavapadon experienced ICD-related AEs compared to three in the placebo group. In addition, the overall discontinuation rate was significantly higher in the tavapadon group. Finally, there is only one trial in this population (TEMPO-3). Given the mix of benefits and harms and the lack of follow-up beyond six months for the primary outcomes, the comparative net health benefit compared to levodopa alone is comparable or better (C++).

The evidence comparing tavapadon with the other comparators (dopamine agonists, MAO-B inhibitors, COMT inhibitors) is less clear. The comparisons are indirect, so there is greater uncertainty about the magnitude of the net health benefits. Discontinuation rates due to AEs were significantly higher for tavapadon compared with each of the comparators. Given the lack of significant benefits, evidence of more discontinuations and low certainty, the net health benefit is promising, but inconclusive (P/I) for all three comparisons.

4. Long-Term Cost Effectiveness

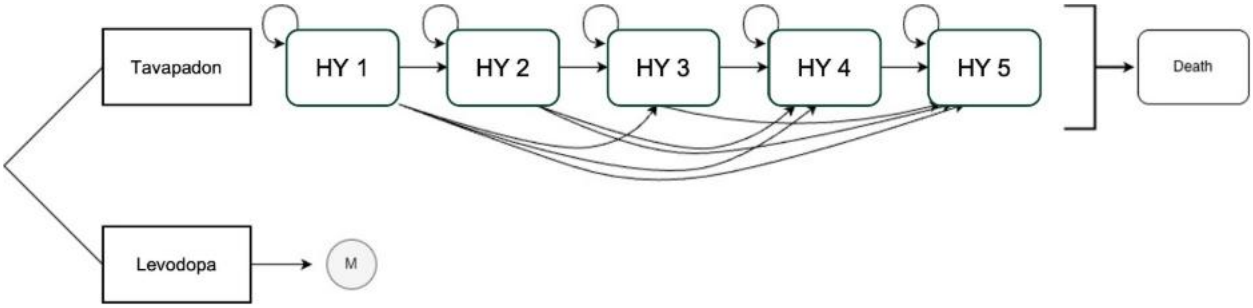
4.1. Methods Overview

We developed two *de novo* decision analytic models for this evaluation, informed by key clinical trials and prior relevant economic models. Both models are semi-Markov models meaning that some of the transition rates across health states change across cycles. Specifically, background mortality varies with the age of the cohort as it advances through the model, so the probability of death depends on time elapsed rather than on health state alone. This framework for both models was selected to best follow available data on progression and treatment effects, focus on best characterizing mean treatment effects from available data, and for transparency. Costs and outcomes were discounted at 3% per year. Each model focused on an intention-to-treat analysis of a hypothetical cohort of patients with Parkinson's disease. The first model (Model 1) evaluated patients with early Parkinson's disease initiating first-line therapy, and compared tavapadon with levodopa. The second model (Model 2) evaluated patients with Parkinson's disease receiving levodopa and experiencing motor fluctuations, and compared tavapadon with other dopamine agonists as add-on therapy. In both models, the cycle length was six months, based on prior published economic models and the available clinical data. Patients cycled through the health states based on transition rates fitted to real-world data from the Parkinson's Precision Medicine Initiative (PPMI).[62]

The modified Hoehn and Yahr scale stages Parkinson's disease from unilateral motor involvement (Stage 1) through bilateral involvement (Stage 2), postural instability with preserved independence (Stage 3), and severe disability requiring assistance (Stage 4), to confinement to a wheelchair or bed (Stage 5). Patients in both treatment arms in each model cycled through the same health states based on HY stages, as depicted in Figures 4.1a and 4.1b. Hoehn and Yahr stage was assessed in the ON state, so that stage assignment reflected motor function during medication response and was not confounded by transient worsening during OFF periods; the proportion of waking hours spent in the OFF state was tracked separately and applied to utilities through the HY-by-OFF-time matrix. HY stages were used as they represent the best available markers of progression in real-world data, although we recognize they may lack sensitivity in fully describing disease impacts. Within each HY health state, additional clinical measures, including the MDS-UPDRS score and amount of daily OFF-time were tracked to add precision as well as capture differences in symptom burden and treatment effects, as shown in Figure 4.1c. These measures were not used to define separate health states but were used within the HY stage-based health states to inform model outcomes, including health-related quality of life, costs, and other clinical outcomes. Patients remain in the model until they die. All patients can transition to death from all causes from any of the alive health states. Mortality rates were based on US averages by age and sex and modified by an excess hazard ratio derived from the PPMI data associated with Parkinson's disease and each HY stage. Note that

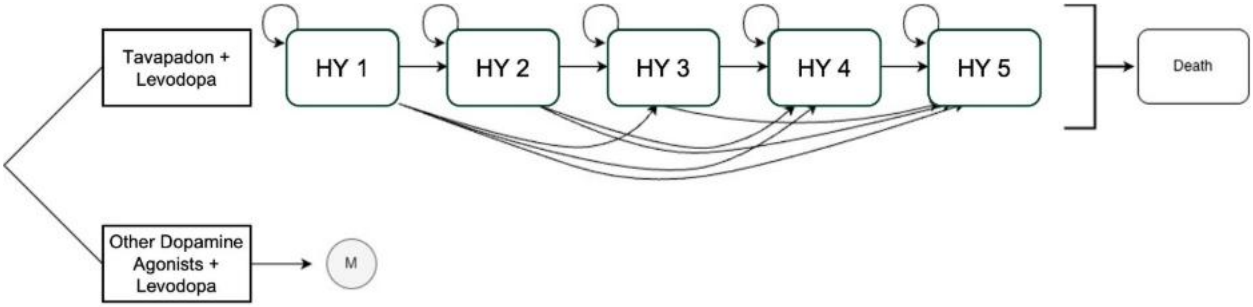
because the treatments being compared address symptom burden only, we did not assume any effect on disease progression as tracked by HY stage in the model or on mortality, so each of the models and each of the arms have the same health states and transition rates across those states. However, the costs, utilities, MDS-UPDRS scores, OFF-time, and other outcomes in the model vary across the arms according to treatment-specific effects and patient characteristics (see Figure 4.1c).

Figure 4.1a Model 1 Schematic



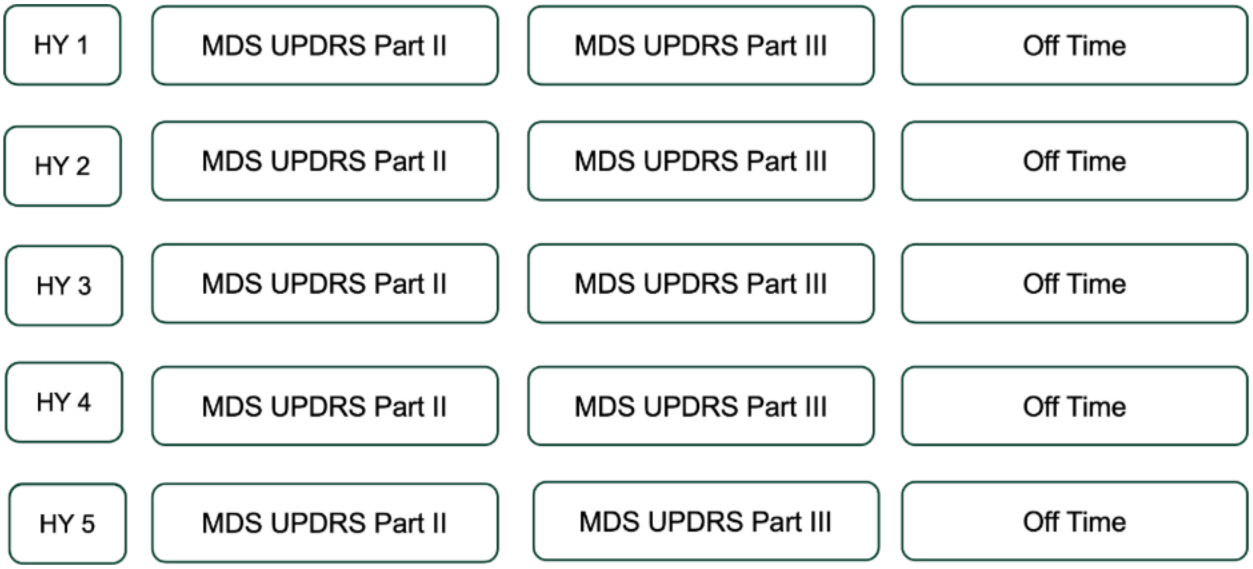
Note: The circled M (Ⓜ) indicates entry into the Markovian component of the model. Within this component, patients occupy mutually exclusive health states defined by HY stage and transition between states at each model cycle according to estimated transition probabilities derived from the PPMI cohort. Each health state captures the following parameters: motor severity (MDS-UPDRS Parts II and III), OFF-time burden (proportion of waking day in OFF), health-related quality of life, direct medical costs, informal care partner costs, and adverse event rates and associated disutility and costs.

Figure 4.1b Model 2 Schematic



Note: The circled M (Ⓜ) indicates entry into the Markovian component of the model. Within this component, patients occupy mutually exclusive health states defined by HY stage and transition between states at each model cycle according to estimated transition probabilities derived from the PPMI cohort. Each health state captures the following parameters: motor severity (MDS-UPDRS Parts II and III), OFF-time burden (proportion of waking day in OFF), health-related quality of life, direct medical costs, informal care partner costs, and adverse event rates and associated disutility and costs.

Figure 4.1c Model Schematic of Functional and Motor Fluctuation Status Within Health State



4.2. Key Model Assumptions and Inputs

HY stage-based health states were used to model disease progression over time. Although HY stage does not fully capture all dimensions of Parkinson's disease progression, it was selected because it provides a practical structure for tracking disease progression in an evidence-based manner as well as for linking disease severity to health-related quality of life, costs, and mortality. In addition, the HY stage-based structure allows the models to incorporate variation in MDS-UPDRS scores and OFF-time within each disease stage, which is important for capturing differences in treatment effects across the therapies being evaluated. HY stage-based health states have also been commonly used in prior economic models of Parkinson's disease, supporting their use as a transparent and comparable framework for this evaluation.[63-67] Mortality and the underlying rate of disease progression are not impacted by the treatments of interest, which have evidence of symptomatic effects only. Based on clinical expert opinion and the progressive nature of Parkinson's disease, transitions across HY stage-based health states were restricted to forward movement only. While patients remain on the same treatment regimen, underlying disease severity as captured by HY stage was not expected to improve over time; rather, patients were expected to remain in the same HY stage or progress to a more severe HY stage. Based on observed transitions in the data, a small percentage of patients can jump more than one stage of progression in a cycle. Any symptomatic improvements associated with treatment initiation or escalation were captured through changes in MDS-UPDRS scores and OFF-time, rather than through backward transitions to less severe HY stages.

All key assumptions and their associated rationale are listed in Table 4.1 below.

Table 4.1. Key Model Assumptions

Assumption	Rationale
In each model cycle, patients may either remain in their current HY stage-based health state or transition to a more advanced HY stage-based health state.	Based on input from clinical experts and general patient experiences with the disease we believe Parkinson's disease is best modeled as a purely "progressive" disease. Transition probabilities are based on real world patterns from the PPMI data (using patients in the system for at least two years) based on clinical input to best represent patients when they would typically be diagnosed.
HY stages directly impact MDS-UPDRS scores.	There is a quantitatively demonstrated connection between HY stage and MDS-UPDRS in available data. Using the PPMI data, we calculated the mean of the Part II and Part III scores seen across HY stages.[62] Further, in scenario analyses we estimated MDS-UPDRS scores as a categorical variable within HY stages based on the PPMI data.
HY stages directly impact OFF-time.	Identical to above. Using PPMI data, we calculated the means of OFF-time hours seen across HY stages.[62] In scenario analyses, we modified the model to examine the distribution of OFF time within HY stages seen in the PPMI data. This approach captures the heterogeneity of OFF time with a HY stage.
Dyskinesia rates in Model 1 for levodopa and ICD rates for DAs in Model 2 are based on real world data across longer time horizons than those seen in clinical trials.	These are known important effects of these drugs and the real world patterns are different than those seen in the limited number of trials available for a network meta-analysis.
Treatment effects as measured from the relevant clinical trials are constant across HY states for as long as patients are on the medication.	There is no data available that allows a different treatment effect to be associated with HY stages.
Adverse event rates in general for tavapadon are based on clinical trial data and are assumed to reflect real-world adverse event experience.	Clinical trial data for tavapadon represents the best available evidence at this time, as the product is not yet established in real-world practice.
Discontinuation rates for tavapadon are derived from randomized controlled trial (RCT) data and modeled in part on discontinuation seen in other DAs.	Long-term real-world discontinuation data for tavapadon are not yet available given its stage of development. Discontinuation rates available in the trials appear to decline over time, which is also a general pattern seen in other DAs. Hence we use available early discontinuation in the trials and model declines in discontinuation in later cycles as parallel changes to those seen in DAs.
MDS-UPDRS scores from the TEMPO trials are converted to original (pre-2008) UPDRS equivalents using published crosswalk equations before being applied to the National Institute for Health and Care Excellence (NICE) utility mapping.	The TEMPO trials report motor and functional severity using the MDS-UPDRS, whereas the NICE utility equation used to derive health-state utilities is based on the original UPDRS.[68,69] Converting the trial-reported MDS-UPDRS scores to UPDRS units allows the trial data to be applied to the NICE mapping on a consistent scale.

Assumption	Rationale
Patients in Model 1 starting on tavapadon switch to levodopa upon discontinuation, and patients on levodopa remain on levodopa. Patients in Model 2 on tavapadon or DAs along with levodopa each switch to a common representative market basket upon discontinuation.	These are simplifying assumptions, as in reality, patients may attempt therapy with multiple other classes of drugs. However, in Model 1 we wish to focus on the incremental effects of tavapadon compared to levodopa as a first line therapy. In Model 2, we wish to focus on tavapadon relative to DAs as add on therapy to levodopa. Available evidence suggests there are high discontinuation rates, and the main focus of attention is on the incremental effects of initial treatment rather than the sequence. Because there is no evidence to suggest differential switching patterns based on initial therapy, a reasonable market basket was considered a viable alternative.

Unless otherwise specified, all input parameters are consistent across Model 1 and 2. The two models differ only in the input population and treatment effectiveness, reflected in model-specific inputs for MDS-UPDRS score changes and OFF-time distributions by HY stage. Where inputs differ between models, they are reported separately; where a single value is reported, it applies to both models.

Clinical Inputs

The relative treatment effectiveness of tavapadon compared to the comparators was obtained from NMAs using relevant trials for the intervention and the comparators. For Model 1, treatment effectiveness was based on differences in MDS-UPDRS (converted to UPDRS for NMA purposes) scores between tavapadon and the comparator, mirroring the endpoints in the TEMPO-1 and TEMPO-2 trials. For Model 2, treatment effectiveness was based on differences in OFF-time experienced between groups, mirroring the TEMPO-3 trial endpoints. The NMA was also used to account for differences in adverse events and treatment discontinuations across treatments.

Baseline HY States

The baseline distribution of HY stages for patients entering the model cohort differed between models. For Model 1, baseline patient characteristics were based on the TEMPO-1 trial population. The TEMPO-2 population was broadly similar, though slightly younger (mean age 62.9 vs. 63.7 years), less predominantly male (56% vs. 64.7%), and weighted toward earlier disease stages. Because model conclusions were qualitatively similar when the TEMPO-2 population was simulated, we modeled the TEMPO-1 population alone, as simulating a single cohort is more tractable. For Model 2, baseline patient characteristics were derived from the TEMPO-3 trial population.[25,32]

Table 4.2. Key Model Inputs

Parameter	Model 1	Model 2	Source
Baseline Population Characteristics			
Age	63.7	64.9	TEMPO-1 and TEMPO-3[25,32]
Sex, Male	64.7%	63.3%	
Modified HY Stage at Baseline*	Stage 1: 23.7% Stage 2: 76.3% Stage 3: 0% Stage 4: 0% Stage 5: 0%	Stage 1: 0% Stage 2: 66.6% Stage 3: 33.4% Stage 4: 0% Stage 5: 0%	
Clinical Inputs			
Mean MDS Part II Score by HY Stage	Stage 1: 6.4 Stage 2: 9.8 Stage 3: 17.1 Stage 4: 23.2 Stage 5: 29.7		Authors analysis of PPMI data[62]
Mean MDS Part III Score by HY Stage	Stage 1: 17.9 Stage 2: 32.2 Stage 3: 46.9 Stage 4: 58.9 Stage 5: 75.6		
Mean Daily OFF Time Hours by HY Stage	Stage 1: 1.59 Stage 2: 1.13 Stage 3: 1.75 Stage 4: 1.97 Stage 5: 2.57		
Change in MDS-UPDRS Part II Scores			
Tavapadon vs. Placebo	-1.86 (-2.59, -1.15)	-	NMA
Levodopa vs. Placebo	-2.67 (-6.92, 1.56)	-	NMA
Change in MDS-UPDRS Part III Scores			
Tavapadon vs. Placebo	-7.17 (-8.86, -5. 46)	-	NMA
Levodopa vs. Placebo	-6.31 (-8.49, -4.19)	-	NMA
OFF Time Reduction (Hrs per Day)			
Tavapadon vs. Placebo	-	0.95 (0.34. 1.55)	NMA
Other Dopamine Agonist vs. Placebo	-	1.41 (1.06, 1.75)	NMA
Other Medication Pooled Effect vs. Placebo	-	0.49 (0.37, 0.62)	NMA
Impulse Control Disorder			
Tavapadon Incidence	0.010	0.024	TEMPO-1 and -3
Other Dopamine Agonist Cycle 1 Incidence	-	0.069	
Progression Through HY Stages	[Please see Supplement Table E2.2]		
Cost Inputs			
Tavapadon, Annual	$15,000		IPD Analytics

Parameter	Model 1	Model 2	Source
Levodopa, Annual	$289	-	Redbook
Other Dopamine Agonists, Annual	-	$3,588	Redbook
Monotherapy Market Basket	-	$1,444	Redbook
Costs by HY Stage, Annual	Stage 1: $7,604 Stage 2: $8,021 Stage 3: $35,054 Stage 4: $53,502 Stage 5: $96,063		Johnson 2013[70]
HCP Consultation Cost, Annual	0 h OFF/day: $440 1 h OFF/day: $495 2 h OFF/day: $510 3 h OFF/day: $599 ≥4 h OFF/day: $649		Thach 2021[71]
Hospitalization Cost (incl. ER/ICU), Annual	0 h OFF/day: $428 1 h OFF/day: $932 2 h OFF/day: $1,878 3 h OFF/day: $3,128 ≥4 h OFF/day: $2,714		
Dyskinesia - Incremental Cost per 6-Month Cycle	$5,164		Song 2023[72]
Hypotension – Incremental Cost per 6-Month Cycle	$6,606		
Somnolence - Incremental Cost per 6-Month Cycle	$7,548		
Hallucination - Incremental Cost per 6-Month Cycle	$13,463		
Impulse Control Disorder - Incremental Cost per 6-Month Cycle	$14,505		
Future Unrelated Medical Costs	Varies by age and gender		Jiao & Basu[73]
Utility Inputs			
Utilities by HY Stages and Proportion of OFF Time	[Please see Supplement Table E2.4]		Lowin et al. (2017)[65]
Utility Incremental Change by MDS-UPDRS Reduction	Part 2: -0.04 Part 3: -0.02		NICE (2016)[68]

DA: dopamine agonist; ER: emergency room, h: hours, HY: Hoehn and Yahr; ICU: intensive care unit, MDS-UPDRS: Movement Disorder Society–Unified Parkinson's Disease Rating Scale; NICE: National Institute for Health and Care Excellence; OFF-time: proportion of waking hours spent in the OFF state; PPMI: Parkinson's Precision Medicine Initiative; USD: US dollars

*HY distribution based on the TEMPO trials and half stage (i.e., 1.5) were evenly divided with the two closest stages.

Note: All costs are inflated to 2026 USD. Baseline health-state utilities by HY stage and OFF-time category, and annual HY-stage transition probabilities, are reported in the Supplement. All costs were updated to 2026 USD.

Transition Probabilities

Transition probabilities were identical across both models and across the treatment and comparator arms, reflecting the assumption that none of the evaluated therapies modify disease progression. Treatment effects were therefore applied to symptoms and functional outcomes rather than to the rate of progression. Probabilities were estimated from the PPMI cohort, restricted to patients enrolled for at least two years to better represent patients at the point at which they would typically be diagnosed. A small number of patients in the PPMI data moved to a less severe HY stage between assessments. However, because backward progression was not considered clinically plausible, these patients were instead retained in the proportion remaining in their current stage. Annual HY-stage transition probabilities are reported in the Supplement Table E2.2.

Functional and Motor Fluctuation Status

Within each HY health state, motor and functional status were characterized using the MDS-UPDRS Part II and Part III scores, and motor and non-motor fluctuation (such as anxiety, fatigue, pain, and cognitive slowing) burden was characterized by daily OFF-time. Mean scores by HY stage were estimated from the PPMI cohort and applied identically in both models (Table 4.2). Both models tracked OFF-time and MDS-UPDRS Part II and Part III scores; however, OFF-Time influenced outcomes only in Model 2, where the treatment effect operates through a reduction in daily OFF-time. In Model 1, OFF-time was tracked but was not connected to costs or utilities, as the interventions in that model were not expected to alter it.

Treatment effects were estimated from network meta-analysis as previously described (Section 3.2). For Model 1, the treatment effect was the mean difference in MDS-UPDRS Part II and III scores for tavapadon and levodopa; for Model 2, it was the mean difference in daily OFF-time for tavapadon in combination with levodopa compared to other treatments. The effects were directly incorporated by shifting the relevant within-stage mean in the treatment arm relative to the comparator arm across all HY stages.

Discontinuation

For tavapadon, direct evidence on treatment discontinuation was available only for the first cycle, from the TEMPO trials (pooled TEMPO-1/TEMPO-2 in Model 1; TEMPO-3 in Model 2). No trial data were available to characterize discontinuation beyond the trial period, so longer-term discontinuation was informed by a real-world analysis of the comparator regimens.

Using Merative MarketScan Medicare Supplemental data, a national convenience sample of administrative claims for retirees with employer-sponsored Medicare supplemental coverage, we conducted a retrospective analysis of discontinuation among the comparator regimens. Using a new-user design, we identified initiators of Parkinson's disease pharmacotherapy who had at least 12 months of continuous enrollment with no prior PD drug use before their first fill, and followed them from initiation until discontinuation, disenrollment, death, or the end of the study period. Treatment discontinuation was defined as the absence of a refill within 90 days after exhaustion of the previous prescription's days' supply. We fit parametric survival distributions to the time-to-discontinuation data, with the log-normal providing the best fit, and derived per-cycle (6-month) probabilities from the fitted survivor function through cycle 25, holding the probability constant thereafter.

In Model 1, we used the first-line DA monotherapy discontinuation pattern from MarketScan to help form a proxy for tavapadon monotherapy. In Model 2, we used the second-line DA plus levodopa pattern to inform the comparator arm and, after rate-ratio anchoring, as the proxy for the tavapadon plus levodopa arm. In both models, the first cycle for tavapadon was based on the TEMPO trials. Because no head-to-head data were available, the trial-period discontinuation from each trial was compared with the corresponding MarketScan estimate to derive a rate ratio, which was then applied to the DA patterns to obtain the tavapadon patterns. Full details of this analysis are provided in Supplement Section E2.

In Model 1, no discontinuation was applied to the levodopa comparator arm or to patients after they switched from tavapadon to levodopa, based on clinical expert input that patients would likely continue on levodopa for as long as feasible. In Model 2, once patients on either arm moved to the monotherapy market basket (65% levodopa, 35% DA monotherapy), no further discontinuation was assumed. See Supplement Section E2 and Table E2.1 for details.

The base case used a lifetime horizon. Alternative horizons were examined in scenario analyses following clinical input that many patients are on particular therapies over relatively short horizons.

Mortality

All-cause mortality was modeled using an excess-hazard approach based on standardized mortality ratios (SMRs). Background mortality was drawn from US life tables published by the National Center for Health Statistics, with age- and sex-specific rates applied at each cycle so that background mortality increased as the cohort aged.[74] Stage-specific SMRs were estimated from the PPMI cohort as the ratio of observed deaths within each HY stage to the deaths expected from age- and sex-matched life-table rates over the same person-time at risk, and were applied as a multiplicative scalar to the background rate within each health state. Because the PPMI cohort skews toward earlier-stage disease, observed deaths at advanced HY stages were limited and the corresponding SMRs carried greater uncertainty; alternative SMR values from the published PD mortality literature were explored in sensitivity analyses.

Adverse Events

In each of the models, adverse events can occur in any cycle and the costs and disutilities associated with them are applied for one cycle. The rates are generally independent across cycles. Adverse-event rates for the tavapadon arms were taken from the TEMPO trials (TEMPO-1 and TEMPO-2 for Model 1, TEMPO-3 for Model 2); comparator-arm rates were then derived by applying relative risks from our NMA to these tavapadon rates.[25,26] For somnolence/excessive daytime sleepiness and orthostatic hypotension/dizziness, the relative risk was applied as a constant across all cycles in both models. For hallucinations, this approach was applied only in Model 2. Hallucinations were not included as an adverse event in Model 1 because the available evidence was not sufficiently robust to support a comparison between tavapadon and levodopa. However, dyskinesia and ICDs were treated differently. For dyskinesia, no events were reported among tavapadon-treated patients in TEMPO-1 or TEMPO-2. Therefore, no dyskinesia was assumed for tavapadon in Model 1. For the levodopa arm in Model 1, the rate was taken from the real-world cumulative incidence of Rascol (2000) over five years and held constant thereafter.[75] In Model 2, dyskinesia was based on TEMPO-3 for tavapadon and the NMA for the comparator. In Model 2, the tavapadon rate was based on the TEMPO-3 trial. For Model 1, the incidence of ICDs for tavapadon was derived from TEMPO-1 and TEMPO-2 and kept constant across model cycle. Similarly, for Model 2, the ICD incidence for tavapadon was derived from TEMPO-3 and kept constant across cycles. This approach was informed by manufacturer-provided data. For the comparator treatments, ICD incidence was assumed to increase over time because impulse control problems are associated with cumulative exposure to older dopamine agonists. In Model 2, this increase was modelled using the cumulative hazard pattern for dopamine agonist treatment reported by Corvol et al. (2018). For levodopa in Model 1, the ICD pattern was assumed to be consistent with that observed among patients not receiving dopamine agonists in Corvol et al. (2018).[76] Details of the adverse event rates used are provided in Supplement Section E2.

Adverse event disutilities were derived as follows. For impulse control disorder, we used a study that measured quality of life with the PDQ-8 in patients with and without ICD and used a published crosswalk from PDQ-8 scores to EQ-5D.[77,78] For dyskinesia, we applied a regression estimate of the change in EQ-5D per additional hour of dyskinesia, assuming a mean of two hours among patients who experienced it.[79] For somnolence/excessive daytime sleepiness we used previously published estimates.[80] For hallucinations, no disutility estimate could be identified, so a value of -0.05 was assumed and this was varied in the sensitivity analyses. For orthostatic hypotension/dizziness, we assumed the disutility arose from falls; we therefore estimated the incremental number of falls attributable to hypotension and applied a fall disutility.[81,82]

Health State Utilities

Health-state utilities were informed by published estimates stratified by HY stage and OFF-time severity from Lowin et al. (2017), which provided the baseline utility structure and captured the combined effect of disease stage and motor fluctuation burden on health-related quality of life.[65] Under this structure, a patient's baseline utility depended on both their HY stage and their daily OFF-time, so that, holding HY stage constant, patients with greater baseline OFF-time were assigned lower utilities. In Model 2, this meant that treatment-related reductions in OFF-time produced utility gains directly through the HY and OFF-time matrix of QALYs; in Model 1, where OFF-time was not altered by treatment, OFF-time affect only the baseline utility level and did not differ between arms.

MDS-UPDRS Part II and Part III scores were used to capture treatment related improvements in motor and functional related symptoms that are not otherwise reflected in HY stage or OFF-time. We could not identify any published utility mapping that jointly incorporates HY stage, OFF-time and MDS-UPDRS Part II and III scores as simultaneous predictors of health related quality of life. Because the baseline HY/OFF utility matrix already reflected the average motor and functional severity associated with each disease state, incorporating the level of Part II and Part III scores into the utility calculation would have double-counted that severity. We therefore excluded baseline Part II and III scores from the utility calculation and used these subscales only to value treatment-related change: within each HY-by-OFF-time category, the expected Part II and Part III scores were estimated from the PPMI cohort, and only treatment-related deviations from these within-state means were translated into incremental utility adjustments using the linear EQ-5D mapping recommended by NICE (2016).[68,69] Specifically, each one-point change in Part II away from the within-state mean corresponded to a utility change of 0.04, and each one-point change in Part III to a change of 0.02, with utilities bounded between 0 and 1.[68,69] Incorporating both subscales reflected the complementary information each provides, Part II captures the patient-reported functional impact of motor symptoms, and Part III captures clinician-assessed motor severity, so that a reduction in either subscale translated into a utility gain while preserving the established relationship between disease stage, motor fluctuation burden, and baseline utility.

Drug Utilization

Tavapadon dosing, 5–15 mg once daily, followed the regimen evaluated in the TEMPO trials, with TEMPO-1 informing the early PD cohort and TEMPO-3 informing the motor-fluctuation cohort; treatment duration and discontinuation were derived from observed persistence in the respective trials. Although TEMPO-2 also evaluated tavapadon monotherapy in early PD, it used flexible dosing (5–15 mg titrated to tolerability) rather than the fixed 5 mg and 15 mg doses of TEMPO-1; because the model applies a single dose-invariant treatment effect, the fixed-dose trial provides a more directly modelable regimen, and simulating the TEMPO-2 population produced qualitatively similar conclusions. For Model 1, levodopa utilization was informed by the NMA, with the annual carbidopa/levodopa acquisition cost reflecting one 25 mg/100 mg tablet taken eight times daily. For Model 2, a market-basket approach reflected the mix of dopamine agonists used in practice, with annual acquisition costs based on ropinirole HCl 3 mg three times daily, pramipexole dihydrochloride IR 1 mg three times daily, and rotigotine 2 mg/24-hour transdermal patch once daily.

Cost Inputs

Annual direct medical costs were assigned to each patient based on their current HY stage and daily OFF-time burden. Baseline health-state costs by HY stage were drawn from Johnson et al. (2013), and an incremental cost was added based on the patient's OFF-time category, reflecting the additional resource use associated with motor fluctuations reported in Thach et al. (2021).[70,71] Patients experiencing OFF episodes incurred higher costs, and patients with greater daily OFF-time (≥4 hours per day) incurred higher costs still, consistent with the dose–response relationship between OFF-time and resource use in that study. Additional costs were applied when a patient experienced an adverse event, see Supplement Section E for additional details. Total annual costs were therefore the sum of the HY-stage baseline cost, the OFF-time increment, and any adverse-event costs, updated at each cycle as patients transitioned between health states. All costs were inflated to 2026 US dollars.

Drug Costs

Because tavapadon had not yet received regulatory approval, a placeholder price of $15,000 per year (as reported by IPD Analytics) was used as the intervention acquisition cost in both models. In Model 1, levodopa was costed at the median generic wholesale acquisition cost (WAC) from RED BOOK ($289 per year), consistent with ICER Reference Case guidance for generic agents. In Model 2, the dopamine agonist comparator used a market-basket approach: market-share weights were derived from a 2024 Merative MarketScan Medicare Supplemental analysis restricted to the three most-dispensed agents and normalized to 100% (ropinirole 51.9%, pramipexole 41.6%, rotigotine 6.4%), and annual WAC for each agent was sourced from RED BOOK (with the SSR Health net price applied for rotigotine), yielding a weighted-average annual dopamine agonist cost of $3,588.

Non-Drug Costs

HY-stage non-drug related health-state costs were assigned using stage-specific excess PD-related direct medical costs from Johnson et al. (2013), defined as costs beyond those of an age- and sex-matched patient without PD. For the earliest stages, Johnson et al. estimated costs from a fixed annual bundle of outpatient consultations and physical therapy; for HY 3–5, Johnson et al. drew on a Medicare claims analysis at three disability proxies (newly diagnosed, first use of an ambulatory assistance device, and first institutionalization). The resulting stage costs, inflated to 2026 USD, ranged from $7,604 (HY 1) to $96,063 (HY 5) (Table 4.2). Because these costs were available only by HY stage, no further stratification by MDS-UPDRS Part II or Part III score was applied. Direct medical costs, therefore, varied across arms only through differences in HY-stage occupancy, and not through the within-stage motor and functional improvements captured in the utility calculation.

In Model 2, OFF-time episodes were a major driver of direct medical costs. OFF-time related costs were based on Thach et al. (2021), a US real-world study quantifying PD-related health care costs stratified by average daily OFF hours, and were applied as an increment on top of the HY-stage costs (not as a standalone total) to avoid double-counting the general direct-medical burden already captured by the Johnson stage costs. Each arm was assigned the OFF-time stratified HCP consultation and hospitalization (including ER/ICU) cost level corresponding to its modeled average daily OFF hours (0, 1, 2, 3, or ≥4), so that the between-arm difference captured the incremental medical cost attributable to the between-arm difference in OFF-time. Costs reported in 2020 USD were inflated to 2026 USD using the PCE-H price index (BEA Table 2.3.4, Line 16; multiplier ≈ 1.238).[71,83]

Medical costs of treatment-related adverse events were drawn from Song et al. (2023) and supplemented with hypotension costs from François et al. (2017), applied as incremental costs per six-month cycle and inflated to 2026 USD. Future age- and sex-specific unrelated health care costs were also included over the model lifetime (Jiao and Basu, 2021).[72,73,82]

Societal Costs

A modified societal perspective was presented as a co-base case alongside the health care sector perspective.

In both models, we estimated patient productivity losses first based on lost employment, absenteeism, and presenteeism reported in the 2026 Lewin/Michael J. Fox Foundation (MJFF) report (2024 USD, inflation-adjusted to 2026 USD), which quantifies these components among US patients with Parkinson's disease.[84] These estimates set a baseline for the per-patient level of productivity loss, which we applied to each arm and converted to a per-cycle cost. Because this level is not tied to OFF hours and as such does not vary by treatment, we also include an OFF-hour attributable portion responsive to each arm's OFF time. OFF time-related productivity costs were

estimated using the annual absenteeism and presenteeism associated with OFF time reported by Abeynayake et al. (2020),[85] corresponding to 25.75 and 42.43 days per year, respectively. These estimates were scaled using the mean daily OFF time of 2.9 hours reported for US patients by Thach et al. (2021).[86] to derive productivity loss per OFF hour. Productivity was valued at $33.02 ($48.05 including fringe benefits) per hour to reflect the cost of formal labor. The resulting cost per OFF hour was applied to the daily OFF hours experienced by patients in each treatment arm to estimate a per-cycle cost. As the treatment effect in Model 1 was not linked to OFF hours, no difference in OFF-related productivity loss was assumed between the treatment arms. (See Supplement Section E2, productivity costs subsection for added details.)

Care partner costs comprised two conceptually distinct, non-overlapping quantities. First, the formal (paid) labor a care partner forgoes was valued as lost market earnings. Second, the informal (unpaid) caregiving time provided was valued by the opportunity-cost method at average US wage rates. Care partner formal labor loss was tied to OFF-time at 75 hours of paid work lost per year for each additional hour of daily OFF-time.

Informal caregiving time was captured by both HY stage and OFF-time. Informal care partner hours increased with worsening HY stage based on the real-world estimates of Ciepielewska et al. (2025).[87] An additional OFF-time-attributable increment was derived from Abeynayake and Tanner (2020), who reported approximately 38 unpaid care hours per week for care partners of patients experiencing OFF periods versus approximately 28 hours for those without—an increment of roughly 10 hours per week.[85] Because this was a binary OFF/no-OFF contrast rather than a per-hour gradient, it was converted to a per-OFF-hour rate using a linear, through-the-origin relationship anchored to the mean daily OFF-time among OFF-experiencing patients in PPMI (3.29 hours/day), yielding 10÷3.29=3.04 care partner hours per week per additional daily OFF hour. This rate was applied to the between-arm difference in daily OFF hours so that the incremental informal-care effect was driven entirely by the OFF-time reduction the treatment produced, and did not double-count the OFF-time related caregiving already embedded in the stage-based estimates.

Model Outcomes

Model outcomes included total life years (LYs), quality-adjusted life years (QALYs), equal-value life years (evLYs), total OFF-time, and total costs for each intervention over a lifetime horizon. Costs, LYs, QALYs, evLYs, and OFF-time were discounted at 3% per year; undiscounted results are presented in the Supplement.

Analytic Methods

Cost-effectiveness was estimated using incremental cost-effectiveness ratios, comparing tavapadon with levodopa in Model 1 and with the dopamine agonist market basket in Model 2. Co-base-case

analyses were conducted from a health care sector perspective (direct medical costs only) and from a modified societal perspective that additionally incorporated productivity and other indirect costs.

One-way sensitivity analyses were conducted to identify key drivers of model outcomes, and probabilistic sensitivity analyses were performed by jointly varying all parameters across 10,000 simulations to generate 95% credible ranges. Threshold analyses identified the tavapadon prices corresponding to $50,000, $100,000, $150,000, and $200,000 per QALY and per evLY gained. Scenario analyses, where data permitted, examined the duration of treatment effect required to reach particular cost-effectiveness thresholds, modeled OFF-time and MDS-UPDRS scores as categorical (rather than mean) values within HY stages to capture within-stage heterogeneity, and considered early treatment discontinuation.

4.3. Results

Base-Case Results

Table 4.3 presents the discounted total costs, life years (LYs), quality-adjusted life years (QALYs), equal-value life years (evLYs), and total OFF-time for tavapadon compared with its comparator, for Model 1 (early PD) and Model 2 (PD with motor fluctuations), under both the health care sector and modified societal perspectives.

Under the health care sector perspective, in Model 1 levodopa had total discounted costs of $1,056,000 with 6.716 QALYs, 6.716 evLYs, and 11.13 LYs, compared with $1,083,000, 6.701 QALYs, 6.701 evLYs, and 11.13 LYs for tavapadon; tavapadon was thus both more costly and slightly less effective than levodopa in this model. In Model 2, the dopamine agonist market basket had total discounted costs of $1,153,000 with 5.467 QALYs, 5.467 evLYs, and 9.63 LYs, compared with $1,182,000, 5.477 QALYs, 5.477 evLYs, and 9.63 LYs for tavapadon; tavapadon was thus more costly but slightly more effective than the market basket.

Under the modified societal perspective, total discounted costs were higher in both arms owing to the inclusion of productivity and care partner costs, while health outcomes were unchanged. In Model 1, tavapadon had total discounted costs of $1,698,000 versus $1,671,000 for levodopa, remaining both more costly and less effective than levodopa. In Model 2, tavapadon had total discounted costs of $1,910,000 versus $1,879,000 for the dopamine agonist market basket, remaining more costly but more effective than the comparator.

Because the evaluated therapies were assumed not to modify disease progression or mortality, life years were identical between arms in both models; differences were driven by symptomatic effects on MDS-UPDRS scores (Model 1) and OFF-time (Model 2), by adverse-event profiles, and by drug acquisition costs. In Model 2, tavapadon accrued slightly more total OFF-time than the dopamine agonist market basket (7,100 versus 7,015 discounted hours); the small QALY difference favoring tavapadon therefore reflected differences in adverse-event profiles rather than a reduction in OFF-time.

Table 4.3. Discounted Results for the Base-Case for Tavapadon Compared to Levodopa (Model 1) or Tavapadon Compared to Other Dopamine Agonists (Model 2)

Treatment	Intervention Acquisition Costs*	Intervention-Related Costs†	Total Costs*	OFF Time (Total Hours)‡	QALYs	evLYs	Life Years
Model 1: Health System Perspective							
Levodopa	$3,200	$0	$1,056,000	-	6.716	6.716	11.13
Tavapadon	$37,000	$0	$1,083,000	-	6.701	6.701	11.13
Model 1: Modified Societal Perspective							
Levodopa	$3,200	$0	$1,671,000	-	6.716	6.716	11.13
Tavapadon	$37,000	$0	$1,698,000	-	6.701	6.701	11.13
Model 2: Health System Perspective							
Other Dopamine Agonists	$5,300	$0	$1,153,000	7,015	5.467	5.467	9.63
Tavapadon	$39,700	$0	$1,182,000	7,100	5.477	5.477	9.63
Model 2: Modified Societal Perspective							
Other Dopamine Agonists	$5,300	$0	$1,879,000	7,015	5.467	5.467	9.63
Tavapadon	$39,700	$0	$1,910,000	7,100	5.477	5.477	9.63

evLYs: equal-value life years, QALY: quality-adjusted life year

*Based on placeholder price.

†Intervention-related costs do not include the price of the drug only (and no administrative costs).

‡OFF time was not estimated in Model 1.

Table 4.4. Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY Gained*	Cost per evLY Gained*	Cost per Life Year Gained*
Tavapadon (Model 1, Health System Perspective)	Levodopa	More Costly, Less Effective	More Costly, Less Effective	Not estimable†
Model 1 Modified Societal Perspective	Levodopa	More Costly, Less Effective	More Costly, Less Effective	Not estimable†
Tavapadon (Model 2, Health System Perspective)	Other dopamine agonists	$2.9 million	$2.9 million	Not estimable†
Model 2 Modified Societal Perspective	Other dopamine agonists	$3.1 million	$3.1 million	Not estimable†

evLYs: equal-value life years, QALY: quality-adjusted life year

*Based on placeholder price.

†Not estimable; the evaluated therapies did not affect survival, so there was no incremental life-year difference.

Table 4.4 presents the incremental results which can also be derived from the results in Table 4.3. In Model 1, tavapadon had an incremental cost of $26,400 and 0.015 fewer QALYs than levodopa in both the health system and modified societal perspectives. In Model 2, tavapadon had an incremental cost of $28,700 and 0.010 incremental QALYs versus the dopamine agonist market basket, yielding $2.9 million per QALY gained and per evLY gained; the cost per life year gained was not estimable because the therapies did not affect survival. In Model 2, the incremental cost rose from $28,700 under the health care sector perspective to $30,400 under the modified societal perspective, because tavapadon patients accrued more OFF-time and therefore greater productivity and care partner costs, yielding approximately $3.1 million per QALY gained. Because there were no incremental life years in either model, the cost per evLY gained equaled the cost per QALY gained, and the cost per life year gained was not estimable. All results at the tavapadon placeholder price are subject to revision when a US price is set.

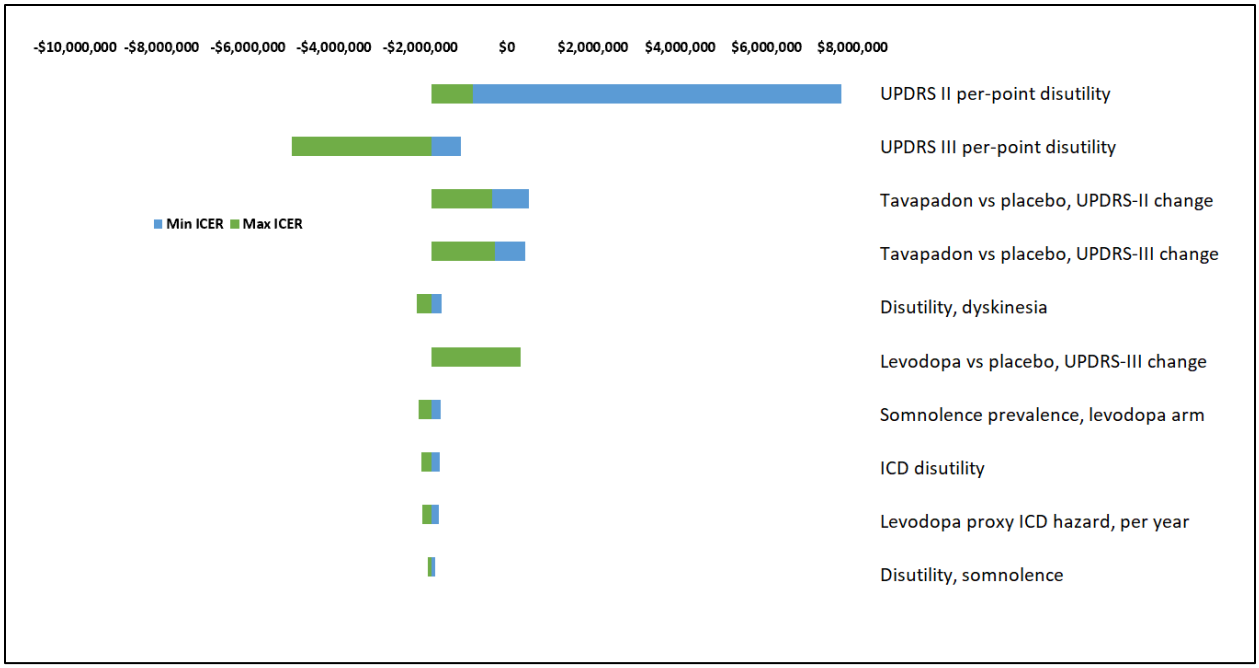
Sensitivity Analyses

To assess the effect of parameter uncertainty, we varied each input across plausible ranges defined by available measures of uncertainty (e.g., standard errors, confidence intervals) or, where these were unavailable, by reasonable ranges.

In Model 1, the incremental cost effectiveness ratio was most sensitive to the UPDRS score disutility parameters mapping motor and functional scores to utility values. The UPDRS Part II per point disutility was the largest driver, with ratios from −$783,000 (i.e., remaining more costly and less effective than levodopa) to $7.7 million per QALY or evLY gained, followed by the UPDRS Part III per point disutility, from −$5 million to −$1.1 million. The relative treatment effects estimated in the network meta-analysis were the next most influential. The tavapadon UPDRS Part II effect produced ratios from −$329,000 to $510,000 which included cost effective values, and the Part III effect from −$282,000 to $424,000. Negative ratios almost all reflected reductions in incremental QALYs with higher costs, indicating values under which tavapadon was both more costly and less effective than levodopa. Results were identical under the health care sector and modified societal perspectives in Model 1 because the therapies did not affect survival and the productivity and care partner costs did not differ between arms.

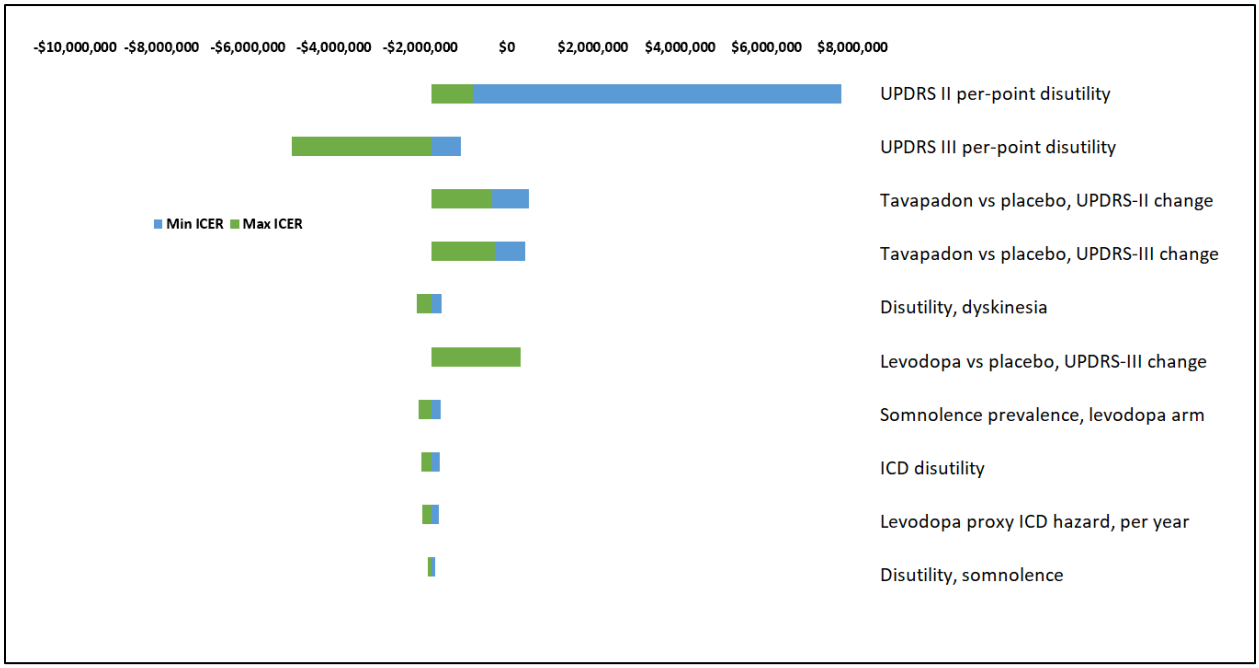
In Model 2, the incremental CE ratio was most sensitive to the impulse control disorder disutility and the dopamine agonist ICD hazard ratio, followed by the magnitude of the OFF-time reduction for tavapadon relative to dopamine agonists—the parameter that, at its most favorable value, most improved tavapadon's relative effectiveness. Somnolence prevalence in each arm and the HY-stage OFF-time disutilities also influenced the ratio. The ranking of influential parameters was similar across the two perspectives. Adverse-event parameters beyond those noted had comparatively small effects.

Figure 4.2. Tornado Diagram: Panel A. Model 1, Health System Perspective



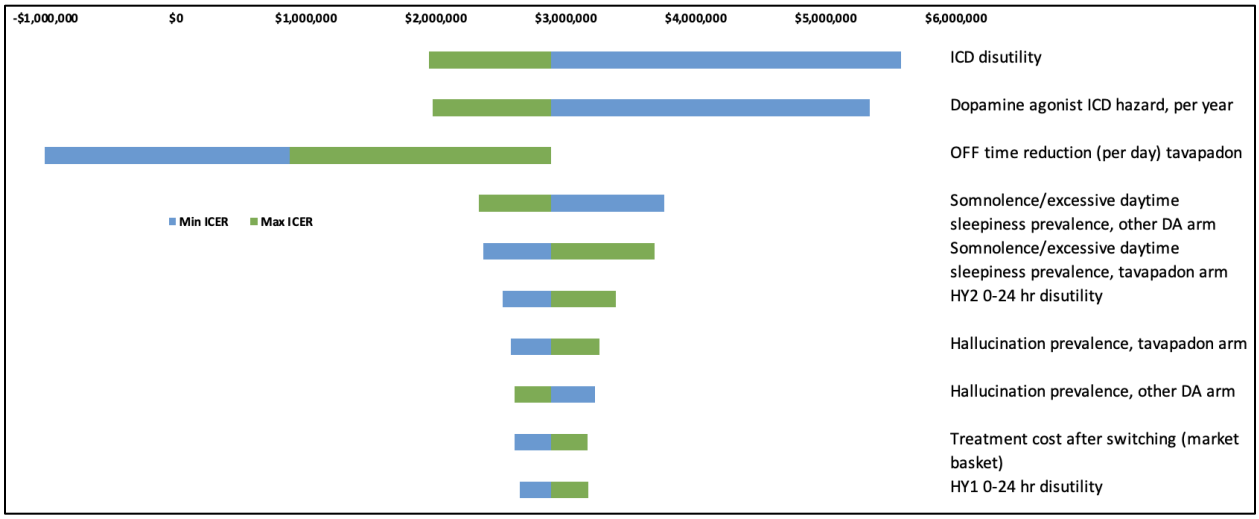
ICD: impulse control disorders, ICER: incremental cost-effectiveness ratio, UPDRS: Unified Parkinson's Disease Rating Scale

Figure 4.3. Tornado Diagram: Panel B. Model 1, Modified Societal Perspective



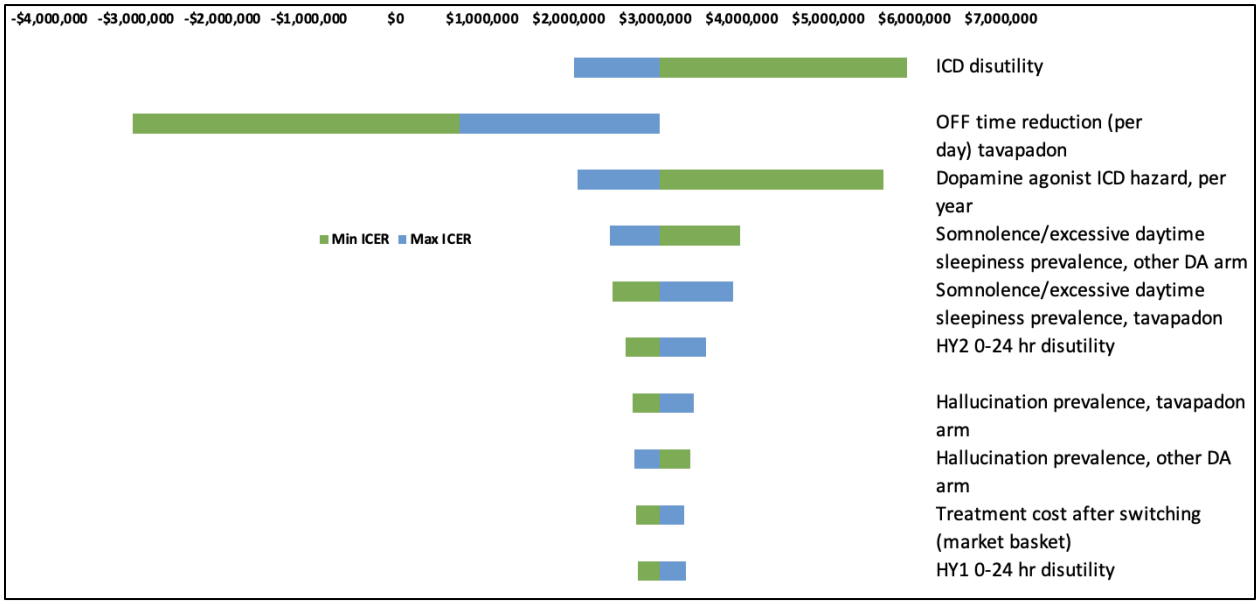
ICD: impulse control disorders, ICER: incremental cost-effectiveness ratio, UPDRS: Unified Parkinson's Disease Rating Scale

Figure 4.4. Tornado Diagram: Panel C. Model 2, Health System Perspective



HY: Hoehn and Yahr, ICD: impulse control disorders, ICER: incremental cost-effectiveness ratio

Figure 4.5. Tornado Diagram: Panel D. Model 2, Modified Societal Perspective



HY: Hoehn and Yahr, ICD: impulse control disorders, ICER: incremental cost-effectiveness ratio

These results (above in Figures 4.2 through 4.5 and below in Table 4.5) are broadly consistent with the base cases for both models. For Model 1, there was greater variance in the incremental ratios overall. In terms of percent of cases cost effective under different threshold values, 0.4% of simulations were cost effective at $50,000 per evLY gained under both perspectives. It rose to 23.2% at $200,000 per evLY gained, meaning even at the highest threshold examined, tavapadon was cost-effective in fewer than one quarter of simulations. For Model 2, the probability remained at or below 0.4% at every threshold under both perspectives. The probability of being cost effective decreases slightly at higher values because in a very few number of simulations tavapadon was less costly and less effective.

Table 4.5. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: Tavapadon versus Levodopa (Model 1); Tavapadon versus Other Dopamine Agonists (Model 2)

	Cost Effective at $50,000 per evLY Gained*	Cost Effective at $100,000 per evLY Gained*	Cost Effective at $150,000 per evLY Gained*	Cost Effective at $200,000 per evLY Gained*
Tavapadon (Model 1), Health System Perspective	0.4%	7.7%	16.6%	23.2%
Tavapadon (Model 1), Modified Societal Perspective	0.4%	7.7%	16.6%	23.2%
Tavapadon (Model 2), Health System Perspective	0.3%	0.3%	0.3%	0.3%
Tavapadon (Model 2), Modified Societal Perspective†	0.4%	0.4%	0.3%	0.3%

evLYs: equal-value life years

*Based on placeholder price.

†The proportion of simulations below the threshold decreases due to a simulation where the treatment was both less effective and less costly.

Scenario Analyses

We conducted seven scenario analyses, each under both the health care sector and modified societal perspectives, to examine the robustness of the base-case results to alternative time horizons, an alternative discontinuation structure, and alternative representations of within-state heterogeneity and future costs (Table 4.6). Tavapadon remained less effective and more costly by levodopa in Model 1 in all scenarios except when the discontinuation rate is modified (see Table 4.6 below). The scenarios have a larger effect in the Model 2 incremental cost-effectiveness ratio, and are discussed below mainly in terms of their effect on that ratio. Further details of the scenario results are shown the Supplement Section E.

Scenario Analysis 1: Shorter Time Horizon (Two Years)

In this scenario, all costs and outcomes were accrued over a two-year horizon rather than over the patient's lifetime. Tavapadon remained more costly and less effective than levodopa in Model 1 under both perspectives. In Model 2, tavapadon was also more costly and less effective (more costly and less effective than the dopamine agonist market basket). The truncated horizon captures relatively more of tavapadon's front-loaded acquisition cost than of its gradually accruing health benefit.

Scenario Analysis 2: Shorter Time Horizon (10 Years)

In this scenario, costs and outcomes were accrued over a 10-year horizon. Tavapadon remained more costly and less effective than levodopa in Model 1. In Model 2, the incremental cost-effectiveness ratio was $2.8 million per QALY gained under the health care sector perspective and $3 million under the modified societal perspective, similar to the base-case ratios of $2.9 million and $3.1 million, reflecting the same cost-versus-benefit timing dynamic operating over an intermediate accrual period. There are 1.5% of patients on tavapadon in the base case of model 2 after year 10 so it is not surprising the numbers are similar. They differ slightly because of differences between tavapadon and the market basket.

Scenario Analysis 3: Discontinuation Rate Is Zero After Cycle 1 for Tavapadon

In this scenario, the discontinuation rate for tavapadon is zero after cycle 1. In Model 1, tavapadon goes from less costly more effective to having a very slight improvement in QALYs resulting from a better AE profile in later cycles. The cost per QALY for tavapadon is roughly $15 million in both perspectives. In Model 2, the incremental cost ratio gets lower again because of AE decline and is $726,000 per QALY in the health system perspective and $594,000 in the societal perspective.

Scenario Analysis 4: Using the Distribution of MDS-UPDRS Part II and Part III Scores and OFF-Time

In the base case, each health state was assigned the mean MDS-UPDRS Part II and Part III scores and mean daily OFF-time for its HY stage. In this scenario, the full within-state distributions were used instead of the stage-level means. The scenario left the results unchanged: Model 1 remained more costly, less effective, and the Model 2 ratio was unchanged.

Two features of the model structure account for this insensitivity. First, in Model 1, OFF-time is not linked to costs or to utilities, so the distribution of OFF-time cannot affect the results in that model. Second, MDS-UPDRS Part II and Part III scores enter the utility calculation only through the treatment-related change from the within-state mean, not through their absolute level; the level of within-state severity is already captured by the Lowin et al. (2017). HY/OFF utility structure, and incorporating the score levels directly would have double-counted that severity (see Section 4.2). Because the treatment effect is applied as a fixed shift relative to the within-state mean, substituting the full distribution for the mean leaves the treatment-related change, and therefore the incremental QALYs, unchanged. In Model 2, OFF-time is linked to utility, so the distribution has a marginal effect on absolute utilities; however, because the treatment-related change in QALYs is again unaffected, the incremental result is effectively unchanged, and tavapadon remained more costly, less effective.

Scenario Analysis 5: Excluding Future Unrelated Health Care Costs

In this scenario, future unrelated health care costs were excluded. This had no effect on the incremental cost-effectiveness ratio in either model, leaving Model 1 more costly, less effective and the Model 2 ratio at $2.9 million (health care sector) and $3.1 million (modified societal) per QALY gained.

The reason is structural. Future unrelated health care costs accrue for each year a patient is alive, so they affect the incremental comparison between two treatments only to the extent that the treatments differ in survival, and therefore in the number of life-years over which such costs are incurred. In both models, the evaluated therapies were assumed not to affect mortality, and life-years were identical between the treatment and comparator arms. The future unrelated costs were therefore incurred in equal amounts in both arms and canceled exactly when the incremental (between-arm) difference was taken, leaving the incremental costs, incremental QALYs, and the resulting ratio unchanged.

Scenario Analysis 6: Excluding Adverse Event in Tavapadon Treated Group After First Cycle

Evidence on tavapadon's adverse event profile is limited to short-term follow-up from the TEMPO-1, TEMPO-2, and TEMPO-3 trials as well as academic-in-confidence manufacturer data, which indicated that adverse event incidence declined during the maintenance phase following titration. Because the base case applied a constant adverse event rate over the full horizon, this scenario examined the effect of tavapadon's potentially more favorable long-term safety by excluding adverse events entirely: from the tavapadon arm in Model 1, and from both arms in Model 2. Tavapadon remained more costly and less effective than levodopa in Model 1 under both perspectives. In Model 2 the ratio was $1 million (health care sector) and $1.1 million (modified societal) per QALY gained.

Scenario Analysis 7: OFF-time Related Disutility Halved

In the base case, the utility decrement per hour of daily OFF-time was taken from Lowin et al. (2017).[65] Given the uncertainty surrounding this parameter, and its conceptual overlap with the severity already captured by the HY-stage utility values, this scenario halved the decrement. The scenario was applied in Model 2 only, as the OFF-time terms in Model 1 carry no treatment-effect adjustment and are identical in the two arms, and therefore do not affect the incremental results. In Model 2, the modeled reduction in daily OFF-time is smaller for tavapadon (0.95 hours per day) than for other dopamine agonists (1.41 hours per day), so the tavapadon arm accrues the larger OFF-time disutility; halving the decrement therefore raised incremental QALYs from 0.010 to 0.016 and lowered the incremental cost-effectiveness ratio to $1.8 million per QALY gained under the health care sector perspective and $1.9 million under the modified societal perspective, compared with base-case ratios of $2.9 million and $3.1 million.

More specific details of each scenario are provided in Supplement Section E5 and Table E5.1.

Table 4.6. Scenario Analysis Results

Scenario	Health Care Sector		Modified Societal	
	Cost/QALY	Cost/evLY	Cost/QALY	Cost/evLY
Model 1				
Base Case	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Shorter Time Horizon (2 Years)	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Shorter Time Horizon (10 Years)	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Zero Discontinuation After Cycle 1 for Tavapadon	$15.2 million	$15.2 million	$15.2 million	$15.2 million
Distribution of Part II/III Scores and OFF-time	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Exclude Future Unrelated Health Care Costs	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
No Adverse Event in Tavapadon Group	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Model 2				
Base Case	$2.9 million	$2.9 million	$3.1 million	$3.1 million
Shorter Time Horizon (2 Years)	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective	More Costly, Less Effective
Shorter Time Horizon (10 Years)	$2.8 million	$2.8 million	$3 million	$3 million
Zero Discontinuation After Cycle 1 in Tavapadon	$726,000	$726,000	$594,000	$594,000
Distribution of Part II/III Scores and OFF-time	$2.9 million	$2.9 million	$3.1 million	$3.1 million
Exclude Future Unrelated Health Care Costs	$2.9 million	$2.9 million	$3.1 million	$3.1 million
No Adverse Event in Tavapadon Group	$1 million	$1 million	$1.1 million	$1.1 million

OFF-time Related Disutility Halved	$1.8 million	$1.8 million	$1.9 million	$1.9 million

Note: Placeholder price of $15,000 based on IPD Analytics predicted price.

Threshold Analyses

Tables 4.7 presents the annual tavapadon prices at which the incremental cost-effectiveness ratio would meet $50,000, $100,000, $150,000, and $200,000 per QALY gained and per evLY gained, under the health care sector perspective. Because the evaluated therapies did not affect survival, there were no incremental life years in either model and equal-value life years equaled QALYs. Hence, the evLY-based threshold prices (Table 4.8) were identical to the QALY-based prices (Table 4.7). In the base case for Model 2 in the societal perspective the incremental costs and QALYs were such that even at a zero price for tavapadon the resulting incremental cost effectiveness ratio was above $200,000.

In Model 1, because tavapadon was more costly and less effective than levodopa, no positive price achieved cost-effectiveness at any threshold. In Model 2, the annual tavapadon prices required to reach these thresholds ranged from $109 (at $50,000 per QALY gained) to $897 (at $200,000 per QALY gained), compared with the placeholder price of $15,000 per year (IPD Analytics). Under the modified societal perspective, no positive price achieved cost-effectiveness at any threshold in Model 2; even at a price of $0, the incremental cost-effectiveness ratio remained above $200,000 per QALY gained, because the non-drug costs incurred in the tavapadon arm exceeded those in the comparator arm by more than the value of the small QALY gain.

Table 4.7. QALY-Based Threshold Analysis Results

	Estimated Price Per Unit*	Annual Price to Achieve $50,000 per QALY Gained	Unit Price to Achieve $100,000 per QALY Gained	Unit Price to Achieve $150,000 per QALY Gained	Unit Price to Achieve $200,000 per QALY Gained
Tavapadon (Model 1), Health System Perspective	$15,000	No positive price is cost-effective			
Tavapadon (Model 1), Modified Societal Perspective	$15,000	No positive price is cost-effective			
Tavapadon (Model 2), Health System Perspective	$15,000	$109	$372	$635	$897
Tavapadon (Model 2), Modified Societal Perspective	$15,000	There is no positive unit price that would achieve a ratio at or less than $200,000 per QALY gained			

QALY: quality-adjusted life year, WAC: wholesale acquisition cost

*Estimated price from IPD Analytics.

Table 4.8. evLY-Based Threshold Analysis Results

	Estimated Price Per Unit*	Annual Price to Achieve $50,000 per evLY Gained	Unit Price to Achieve $100,000 per evLY Gained	Unit Price to Achieve $150,000 per evLY Gained	Unit Price to Achieve $200,000 per evLY Gained
Tavapadon (Model 1), Health System Perspective	$15,000	No positive price is cost-effective			
Tavapadon (Model 1), Modified Societal Perspective	$15,000	No positive price is cost-effective			
Tavapadon (Model 2), Health System Perspective	$15,000	$109	$372	$635	$897
Tavapadon (Model 2), Modified Societal Perspective	$15,000	There is no positive unit price that would achieve a ratio at or less than $200,000 per QALY gained.			

evLYs: equal-value life years, QALY: quality-adjusted life year, WAC: wholesale acquisition cost

Model Validation

See Supplement Section E for details on model validation.

Prior Economic Model

See Supplement Section E for a description of prior economic models.

Uncertainty and Controversies

Several sources of uncertainty should be considered when interpreting these results. Most importantly, tavapadon had not received regulatory approval at the time of this analysis, so a placeholder annual price of $15,000 was used; the cost-effectiveness results and the budget impact estimates will change once a US price is set, and the threshold-price analyses are intended to support interpretation across a range of possible prices.

Additionally, our base case results are highly sensitive to change, given modest increases in lifetime cost with tavapadon and small differences in effectiveness. The latter estimates in particular are based on point estimates from network meta-analyses, which often included wide and overlapping confidence intervals. Small changes in effectiveness could therefore substantially affect our conclusions, particularly in our analyses of the early PD population, as observed in one-way and probabilistic sensitivity analyses.

Although care partner impact is a substantial component of the overall burden of Parkinson's disease, the model did not capture care partner health-related quality of life. We were unable to

identify published estimates linking care-partner utility or disutility to patient disease severity or OFF-time, and therefore could not incorporate a care partner disutility in the base case. Care partner impacts were reflected only through informal care partner time and care partner productivity costs in the modified societal perspective. As a result, the total care partner impact, particularly the quality-of-life impact on care partners, is likely underestimated.

The model structure relied on HY stage to define health states. Although HY stage is the best available marker of progression in real-world data and has been widely used in prior PD economic models, it does not fully capture all dimensions of disease, and within-stage heterogeneity in motor severity and OFF-time was therefore handled through MDS-UPDRS and OFF-time adjustments rather than through additional health states. Transition probabilities, functional and OFF-time profiles by stage, and stage-specific mortality were estimated from the PPMI cohort, which skews toward earlier-stage disease; estimates for advanced HY stages, including stage-specific SMRs and health-state costs, are correspondingly more uncertain, and alternative values were examined in sensitivity analyses.

Treatment effects were derived from an NMA and applied as constant shifts in MDS-UPDRS scores and OFF-time for as long as patients remained on therapy, with no assumed effect on disease progression or mortality; long-term real-world persistence and effectiveness data for tavapadon were not yet available.

MDS-UPDRS scores from the TEMPO trials were converted to original UPDRS units before being applied to the NICE utility mapping, introducing additional structural uncertainty into the utility estimates.

In the modified societal perspective, patient productivity loss and care partner burden were tied to daily OFF-time rather than to MDS-UPDRS Part II or Part III scores, because the available evidence linked productivity and caregiving to OFF-time but not to MDS-UPDRS scores. As a result, treatment-related improvements in MDS-UPDRS scores affected the model only through patient health-related quality of life (QALYs) and did not generate any offsetting reduction in productivity or care partner costs. This has two implications. First, MDS-UPDRS improvements played a more limited role in the societal perspective than OFF-time improvements did, since only the latter reduced indirect costs. Second, the difference in results between Model 1 and Model 2 partly reflects this structural asymmetry: because the tavapadon treatment effect in Model 1 operated through MDS-UPDRS scores while the effect in Model 2 operated through OFF-time, the societal perspective captured indirect-cost offsets from the treatment effect only in Model 2. If, in reality, motor and functional improvements captured by the MDS-UPDRS also reduce patient productivity loss or care partner burden independent of OFF-time, the societal perspective would understate the value of treatment in Model 1, and the estimated cost-effectiveness of tavapadon in early PD would be correspondingly conservative.

4.4 Summary and Comment

Using two de novo semi-Markov models populated with real-world PPMI data and treatment effects from the TEMPO trials, we estimated the cost-effectiveness of tavapadon for early Parkinson's disease (versus levodopa) and for Parkinson's disease with motor fluctuations (versus other dopamine agonists added to levodopa). At the placeholder price of $15,000 per year, and using the evidence available on its effectiveness relative to key comparators, tavapadon was more costly and slightly less effective than levodopa in Model 1. In Model 2, tavapadon was more costly and slightly more effective than the dopamine agonist market basket, yielding an incremental cost-effectiveness ratio of approximately $2.9 million per QALY (and per evLY) gained. These findings were consistent under both the health care sector and modified societal perspectives but varied substantially in sensitivity analyses, especially for the early PD population. Our best estimates find that at its placeholder price, tavapadon is more expensive and slightly less effective than levodopa in early Parkinson's disease, and more expensive but slightly more effective than other dopamine agonists in Parkinson's disease with motor fluctuations, with base-case findings well above commonly cited cost-effectiveness thresholds in both populations. However, in probabilistic sensitivity analyses, there was uncertainty in the direction of the comparison in early Parkinson's disease, where tavapadon was cost-effective in almost one quarter of simulations at $200,000 per QALY gained. For example, varying inputs related to the relative treatment effects on motor and functional scores led to either increases in the incremental cost-effectiveness ratio or decreases to a point where tavapadon may be more effective than levodopa. Because the comparators are predominantly low-cost generic agents and the evaluated therapies were assumed not to modify disease progression, the results were most sensitive to estimates of the magnitude and durability of its symptomatic effect on OFF-time and motor function. These estimates should be interpreted in light of the placeholder price and the uncertainties described above and will be updated as a US price and additional long-term data become available.

5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, care partners, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the intervention in this review.

Table 5.1. Benefits Beyond Health and Special Ethical Priorities

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
There are particular obligations to people with this condition because of disease severity and/or unmet need with currently available therapies.	To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported for the modeled populations below. For early PD, individuals treated with levodopa monotherapy was used as a reference group. For those with motor fluctuations, individuals treated with a combination of dopamine agonists and levodopa were used as a reference group. evLY/QALY shortfalls for early PD patients Absolute shortfall: 9.8 Proportional shortfall: 59.4% evLY/QALY shortfalls for PD patients with motor fluctuations: Absolute shortfall: 11.1 Proportional shortfall: 67.0% The absolute and proportional shortfalls represent the total and proportional health units of remaining quality adjusted life expectancy, respectively; that would be lost due to un- or under-treated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews.
There are particular obligations to people with this condition because it disproportionately affects those from a racial/ethnic group that have not been equitably served by the health care system.	None identified. PD appears to be more common in men and in non-Hispanic White populations, although there may be underdiagnosis in some populations as noted in the background.

Benefits Beyond Health and Special Ethical Priorities	Relevant Information
Apart from issues around disease severity/unmet need and race/ethnicity, there are other particular obligations to people with this condition.	None identified.
The treatments are likely to improve care partners' quality of life and/or ability to pursue their own education, work, and family life.	The available evidence does not yet demonstrate major improvements in patients treated with tavapadon compared with available alternatives, so it is unlikely to produce substantial improvements in care partners quality of life.
If payment/cost were not an issue, the treatments are likely to improve access to treatment because of its method of delivery and/or treatment setting.	This varies by population. In early PD, tavapadon is taken once daily as monotherapy, whereas the main comparator, carbidopa/levodopa, is typically taken several times per day; a once-daily regimen may reduce administration burden in this population. In PD with motor fluctuations, both tavapadon and the comparator dopamine agonists are added to existing levodopa therapy, so patients in both arms retain the levodopa dosing schedule; tavapadon adds a single daily dose, while ropinirole and pramipexole are taken three times daily and rotigotine is applied as a once-daily patch. In both populations, all treatments are self-administered orally or transdermally and require no specialized treatment setting.

ICER did not calculate the Health Improvement Distribution Index (HIDI) for tavapadon. The HIDI is intended to indicate whether greater use of a treatment would be likely to reduce or exacerbate existing health disparities, based on the distribution of the affected condition across racial and ethnic groups. Parkinson's disease is more commonly diagnosed among men and among non-Hispanic White populations, which are subpopulations that generally receive more timely diagnosis and specialty care. Improving treatment in these populations would therefore be unlikely to narrow overall health disparities in the larger US population.

6. Health Benefit Price Benchmark

ICER does not provide a Health Benefit Price Benchmark as part of draft reports because results may change with revision following receipt of public comments. We therefore caution readers against assuming that the values provided in the Threshold Prices section of this draft report will match the Health Benefit Price Benchmark that will be presented in the next version of this Report.

7. Potential Budget Impact

7.1. Overview of Key Assumptions

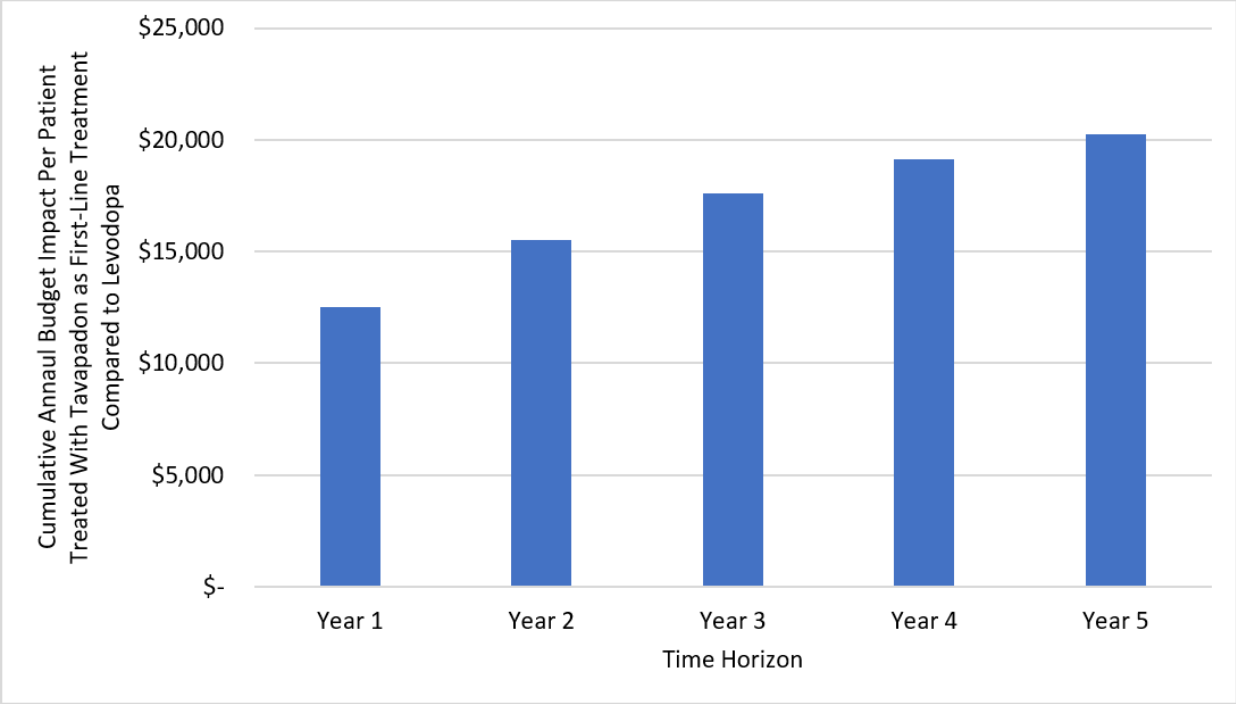
We used results from the cost-effectiveness models to estimate the total potential budgetary impact of tavapadon for the Parkinson's disease population. Potential budget impact is defined as the total differential cost of using tavapadon rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. We used the placeholder price and the threshold prices (at $50,000, $100,000, $150,000, and $200,000 per evLY gained) for tavapadon in these estimates. For 2025–2026, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is approximately $821 million per year for new drugs.

The analysis included patients starting tavapadon as first-line treatment and patients starting tavapadon as add-on therapy to levodopa, corresponding to the two modeled populations. To size the first-line candidate population, we multiplied the US population averaged over the next five years (342,339,134)[88] by the prevalence of Parkinson's disease (approximately 0.34%)[89] and by the proportion of patients not yet treated with any pharmacologic therapy (37.6%),[90] yielding 436,786 patients. To size the add-on candidate population, we multiplied the same population and prevalence by the proportion treated with levodopa (43.7%),[90] yielding 508,141 patients, for a total eligible population of 944,927. For this analysis, we assumed 20% of eligible patients would initiate treatment in each of the five years, or 188,985 patients per year (87,357 first-line and 101,628 add-on).

7.2. Results

Figure 7.1 illustrates the cumulative per-patient potential budget impact of tavapadon as first-line treatment compared with levodopa over the five-year time horizon, assuming 20% uptake each year. At the placeholder price of $15,000 per year, the average annual potential budget impact per patient treated was approximately $12,500 in year one and $20,200 in year five.

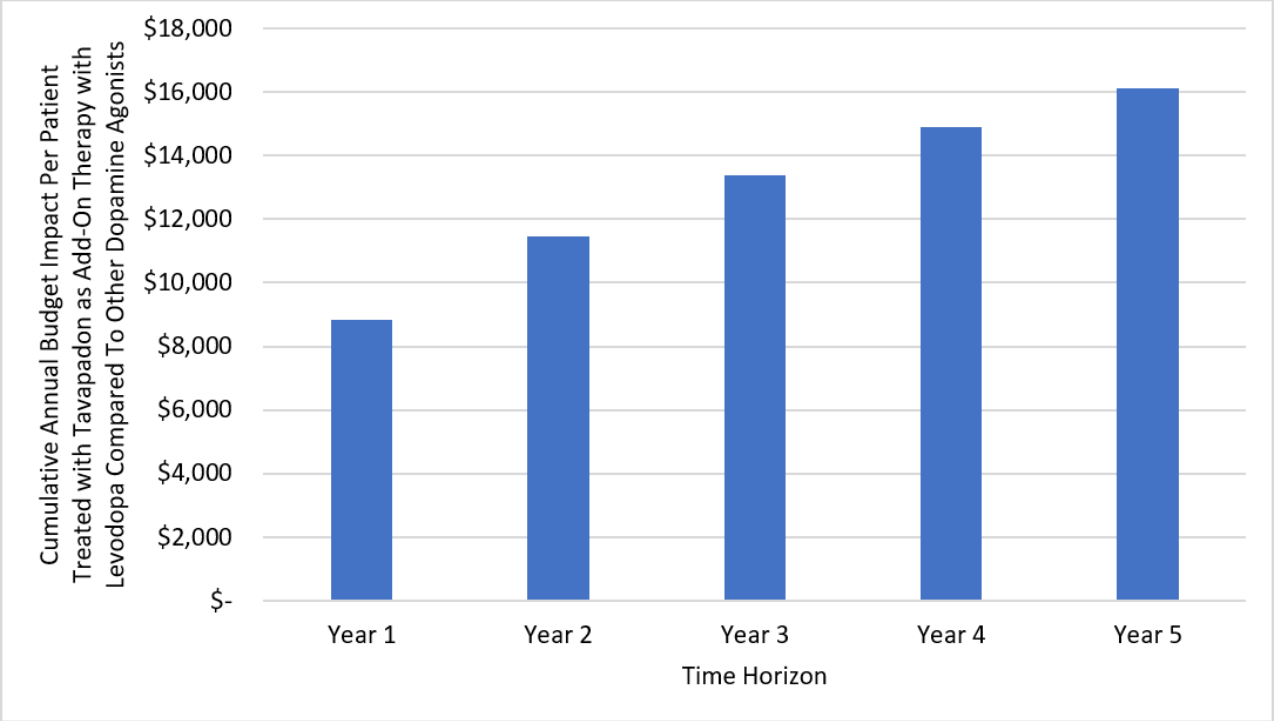
Figure 7.1. Cumulative Annual Budget Impact Per Patient Treated with Tavapadon as First-Line Treatment Compared to Levodopa



At the placeholder price of $15,000 per year, 46% of the first-line candidate population could be treated with tavapadon before reaching the potential budget impact threshold of $821 million. The proportion of the eligible population that could be treated before reaching the potential budget impact threshold was not estimated at threshold prices because no threshold price would make tavapadon as first-line treatment cost-effective at any of the evaluated thresholds.

Figure 7.2 illustrates the cumulative per-patient potential budget impact of tavapadon as add-on treatment with levodopa compared to other dopamine agonists over the five-year time horizon, assuming 20% uptake each year. At the placeholder price of $15,000 per year, the average annual potential budget impact per patient treated was approximately $8,800 in year one and $16,100 in year five.

Figure 7.2. Cumulative Annual Budget Impact Per Patient Treated with Tavapadon as Add-On Therapy with Levodopa Compared To Other Dopamine Agonists



At the placeholder price of $15,000 per year, 50% of the candidate population for add-on treatment could be treated with tavapadon before reaching the potential budget impact threshold of $821 million. At the $50,000, $100,000, $150,000, and $200,000 per evLY threshold prices ($109, $372, $635, and $897 from the health care system perspective), 100% of the population could be treated before reaching the potential budget impact threshold.

References

1. Tanner CM, Ostrem JL. Parkinson's Disease. *N Engl J Med*. Aug 1 2024;391(5):442-452. doi:10.1056/NEJMra2401857
2. The Lewin Group I. *Economic Burden and Future Impact of Parkinson's Disease Final Report*. 2026. https://zenodo.org/records/19257592
3. Kaye AD, Ford BM, Abbott BM, Broocks KM, Novacic S, Shekoohi S. Emerging Clinical Role of Tavapadon, a Novel Dopamine Partial Agonist, in the Treatment of Parkinson's Disease. *Diseases*. Sep 2 2025;13(9)doi:10.3390/diseases13090290
4. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. May 2019;18(5):459-480. doi:10.1016/s1474-4422(18)30499-x
5. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. May 2010;67(5):589-95. doi:10.1001/archneurol.2010.65
6. Zhuo C, Zhu X, Jiang R, et al. Comparison for Efficacy and Tolerability among Ten Drugs for Treatment of Parkinson's Disease: A Network Meta-Analysis. *Sci Rep*. Apr 4 2017;8:45865. doi:10.1038/srep45865
7. Whone AL, Watts RL, Stoessl AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. *Annals of Neurology*. 2003 2003;54(1):93-101. doi:https://doi.org/10.1002/ana.10609
8. Rascol O, Brooks DJ, Brunt ER, Korczyn AD, Poewe WH, Stocchi F. Ropinirole in the treatment of early Parkinson's disease: A 6-month interim report of a 5-year levodopa-controlled study. *Mov Disord*. January 1998 1998;13(1):39-45. doi:https://doi.org/10.1002/mds.870130111
9. Parkinson Study Group. Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease A Randomized Controlled Trial. *Jama*. 2000;284(15):1931-1938. doi:doi:10.1001/jama.284.15.1931
10. Adler CH, Sethi KD, Hauser RA, et al. Ropinirole for the Treatment of Early Parkinson's Disease. *Neurology*. August 01, 1997 1997;49(2):393-399.
11. Singer C, Lamb J, Ellis A, Layton G. A comparison of sumanirole versus placebo or ropinirole for the treatment of patients with early Parkinson's disease. *mov Disord*. 15 March 2007 2007;22(4):476-482. doi:https://doi.org/10.1002/mds.21361
12. Giladi N, Boroojerdi B, Korczyn AD, Burn DJ, Clarke CE, Schapira AHV. Rotigotine transdermal patch in early Parkinson's disease: A randomized, double-blind, controlled study versus placebo and ropinirole. *mov Disord*. 15 December 2007 2007;22(16):2398-2404. doi:https://doi.org/10.1002/mds.21741
13. Watts RL, Jankovic J, Waters C, Rajput A, Boroojerdi B, Rao J. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. *Neurology*. 01/23/2007 2007;69(23):272-276. doi:10.1212/01.wnl.0000252355.79284.22
14. Poewe W, Rascol O, Barone P, et al. Extended-release pramipexole in early Parkinson disease A 33-week randomized controlled trial. *Neurology*. 08/23/2011 2011;77(8):759-766. doi:https://doi.org/10.1212/WNL.0b013e31822affb0

15. Shannon KM, J.P. BJ, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology*. 09/01/1997 1997;49(3):724-728. doi:https://doi.org/10.1212/WNL.49.3.724
16. Barone P, Santangelo G, Morgante L, et al. A randomized clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients. *European Journal of Neurology*. 05/12/2026 2015;22(8):1184-1191. doi:https://doi.org/10.1111/ene.12724
17. Olanow CW, Rascol O, Hauser RA, et al. A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease. *N Engl J Med*. 09/24/2009 2009;361(13):1268-1278. doi:10.1056/NEJMoa0809335
18. Poewe W, Seppi K, Fitzer-Attas C, et al. Efficacy of rasagiline in patients with the parkinsonian variant of multiple system atrophy: a randomised, placebo-controlled trial. *Lancet Neurol*. 02/2015 2015;14(2):145-152. doi:https://doi.org/10.1016/s1474-4422(14)70288-1
19. Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M, Group. CS. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal Levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). *Acta Neurologica Scandinavica*. 04/03/2002 2002;105(4):245-255. doi:https://doi.org/10.1034/j.1600-0404.2002.1o174.x
20. Allain HP, P.; Neukirch, H.C. Symptomatic Effect of Selegiline in De Novo Parkinsonian Patients. *mov Disord*. 1993;8(S1)(1):S36-S40. doi:https://doi.org/10.1002/mds.870080508
21. Palhagen S, Heinonen EH, Hagglund J, et al. Selegiline delays the onset of disability in de novo parkinsonian patients. *Neurology*. 08/01/1998 1998;51(2):520-525. doi:https://doi.org/10.1212/WNL.51.2.520
22. Viallet F, Pitel S, Lancrenon S, Blin O. Evaluation of the safety and tolerability of rasagiline in the treatment of the early stages of Parkinson's disease. *Current Medical Research and Opinion*. 04/12/2012 2012;29(1):23-31. doi:https://doi.org/10.1185/03007995.2012.752351
23. Hanagasi HA, Gurvit H, Unsalan P, et al. The Effects of Rasagiline on Cognitive Deficits in Parkinson's Disease Patients Without Dementia: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. *mov Disord*. 04/15/2011 2011;26(10):1851-1858. doi:10.1002/mds.23738
24. Larsen JP, Boas J, Group N-DS. The effects of early selegiline therapy on long-term levodopa treatment and parkinsonian disability: An interim analysis of a norwegian–danish 5-year study. *mov Disord*. 03/1997 1997;12(2):175-182. doi:https://doi.org/10.1002/mds.870120207
25. Pahwa R, Moro E, Espay AJ, et al. Fixed-Dose Tavapadon for Early Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurol*. May 1 2026;83(5):452-460. doi:10.1001/jamaneurol.2026.0590
26. Fernandez HH, Bhatia P, Cloud L, et al. Safety, tolerability, and efficacy of flexible-dose tavapadon for Parkinson's disease (TEMPO-2): a phase 3, randomised, placebo-controlled, double-blind trial. *Lancet Neurol*. 2026;25(8):721-730. doi:10.1016/s1474-4422(26)00215-2
27. Gray R, Ives N, Rick C, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet*. Sep 27 2014;384(9949):1196-205. doi:10.1016/s0140-6736(14)60683-8

28. Zhang ZX, Shang HF, Hu XY, et al. Rotigotine transdermal patch in Chinese patients with early Parkinson's disease: A randomized, double-blind, placebo-controlled pivotal study. *Parkinsonism Relat Disord*. 07/2016 2016;28:49-55. doi:https://doi.org/10.1016/j.parkreldis.2016.04.022
29. Hattori N, Takeda A, Takeda S, et al. Rasagiline monotherapy in early Parkinson's disease: A phase 3, randomized study in Japan. *Parkinsonism Relat Disord*. 03/2019 2019;60doi:https://doi.org/10.1016/j.parkreldis.2018.08.024
30. Goetz CG, Stebbins GT, Tilley BC. Calibration of unified Parkinson's disease rating scale scores to Movement Disorder Society-unified Parkinson's disease rating scale scores. *Mov Disord*. Sep 1 2012;27(10):1239-42. doi:10.1002/mds.25122
31. Sako W, Kogo Y, Koebis M, et al. Comparative efficacy and safety of adjunctive drugs to levodopa for fluctuating Parkinson's disease - network meta-analysis. *NPJ Parkinsons Dis*. Oct 19 2023;9(1):143. doi:10.1038/s41531-023-00589-8
32. H. FH, H. IS, A. HR, et al. Tavapadon as Adjunctive Treatment for Parkinson Disease: The TEMPO-3 Randomized Clinical Trial. *JAMA Neurol*. May 1 2026;83(5):442-451. doi:10.1001/jamaneurol.2026.0577
33. Gray R, Patel S, Ives N, et al. Long-term Effectiveness of Adjuvant Treatment With Catechol-O-Methyltransferase or Monoamine Oxidase B Inhibitors Compared With Dopamine Agonists Among Patients With Parkinson Disease Uncontrolled by Levodopa Therapy: The PD MED Randomized Clinical Trial. *JAMA Neurol*. Feb 1 2022;79(2):131-140. doi:10.1001/jamaneurol.2021.4736
34. Boiser; RPRDZMATCORSSDICJ, Zadikof C. TEMPO-4: A Phase 3 Open-Label Trial to Investigate the Safety and Efficacy of Longterm Administration of Tavapadon in People With Parkinson’s Disease. 2025; Accessed 07/08/2026.
35. Sánchez-Ferro Á, Matarazzo M, Martínez-Martín P, et al. Minimal Clinically Important Difference for UPDRS-III in Daily Practice. *Mov Disord Clin Pract*. Jul-Aug 2018;5(4):448-450. doi:10.1002/mdc3.12632
36. Hauser RA, Gordon MF, Mizuno Y, et al. Minimal clinically important difference in Parkinson's disease as assessed in pivotal trials of pramipexole extended release. *Parkinsons Dis*. 2014;2014:467131. doi:10.1155/2014/467131
37. Horváth K, Aschermann Z, Kovács M, et al. Minimal clinically important differences for the experiences of daily living parts of movement disorder society-sponsored unified Parkinson's disease rating scale. *Mov Disord*. May 2017;32(5):789-793. doi:10.1002/mds.26960
38. Winter Y, Lubbe D, Oertel W, Dodel R. QL2 Evaluation of Minimal Clinically Important Differences for Health-Related Quality of Life Scales in Parkinson'S Disease. *Value in Health*. 2012;15(7):A279. doi:10.1016/j.jval.2012.08.484
39. CADTH. *COMMON DRUG REVIEW, Clinical Review Report - LEVODOPA/CARBIDOPA (DUODOPA)*. 2018.
40. LeWitt PA, Lyons KE, Pahwa R. Advanced Parkinson disease treated with rotigotine transdermal system PREFER Study. *Neurology*. 04/17/2007 2007;68(16):1262-1267. doi:https://doi.org/10.1212/01.wnl.0000259516.61938.bb
41. Zhang Z, X.; Liu, C, F.; Tao, E, X.; Shao, M.; Liu, Y, M.; Wang, J.; Asgharnejad, M.; Xue, H, B.; Surmann, E.; Bauer, L. Rotigotine transdermal patch in Chinese patients with advanced Parkinson's disease: A randomized, double-blind, placebo-controlled pivotal study.

Parkinsonism Relat Disord. 11/2017 2017;44:6-12. doi:https://doi.org/10.1016/j.parkreldis.2017.08.015
42. Nicholas PA, Borgohain R, Chana P, et al. A Randomized Study of Rotigotine Dose Response on 'Off' Time in Advanced Parkinson's Disease. *J Parkinsons Dis*. 2014;4(3):361-373. doi:https://doi.org/10.3233/JPD-130320
43. Poewe WH, Rascol O, Quinn N, et al. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. *Lancet Neurol*. 06/2007 2007;6(6):513-520. doi:https://doi.org/10.1016/S1474-4422(07)70108-4
44. Ma TZHGLWYZMRaA. Health-Related Quality of Life in Patients With Different Diseases Measured With the EQ-5D-5L: A Systematic Review. *Frontiers in Public Health*. June 21 2021 2021;9doi:https://doi.org/10.3389/fpubh.2021.675523
45. Reichmann H, Boas J, MacMahon D, Myllyla. V, Hakala. A, Reinikainen K. Efficacy of combining levodopa with entacapone on quality of life and activities of daily living in patients experiencing wearing-off type fluctuations. *Acta Neurologica Scandinavica*. 12/09/2004 2005;111(1):21-28. doi:https://doi.org/10.1111/j.1600-0404.2004.00363.x
46. Brooks DJ, Sagar H, Group U-IES. Entacapone is beneficial in both fluctuating and non-fluctuating patients with Parkinson's disease: a randomised, placebo controlled, double blind, six month study. *Journal of Neurology, Neurosurgery, & Psychiatry*. 01/28/2003 2003;74(8):1071-1079. doi:https://doi.org/10.1136/jnnp.74.8.1071
47. Fenelon G, Gimenez-Roldan S, Montastruc JL, et al. Efficacy and tolerability of entacapone in patients with Parkinson's disease treated with levodopa plus a dopamine agonist and experiencing wearing-off motor fluctuations. A randomized, double-blind, multicentre study. *Journal of Neural Transmission*. 03/2003 2003;110:239-251. doi:https://doi.org/10.1007/s00702-002-0799-z
48. Ferreira JJ, Lees A, Rocha J-F, Poewe W, Soares-da-Silva P. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. *Lancet Neurol*. 02/2016 2015;15(2):154-165. doi:https://doi.org/10.1016/S1474-4422(15)00336-1
49. Lees AJ, Ferreira J, Rascol O, et al. Opicapone as Adjunct toLevodopa Therapy inPatients With Parkinson Disease and Motor Fluctuations A Randomized Clinical Trial. *JAMA Neurol*. 02/2017 2017;74(2):197-206. doi:doi:10.1001/jamaneurol.2016.4703
50. Takeda A, Takahashi R, Tsuboi Y, et al. Randomized, Controlled Study of Opicapone in Japanese Parkinson's Patients with Motor Fluctuations. *mov Disord*. 02/2021 2020;36(2):415-423. doi:10.1002/mds.28322
51. Hattori N, Takeda A, Takeda S, et al. Efficacy and safety of adjunctive rasagiline in Japanese Parkinson's disease patients with wearing-off phenomena: A phase 2/3, randomized, double-blind, placebo-controlled, multicenter study. *Parkinsonism Relat Disord*. 2018;53:21-27. doi:https://doi.org/10.1016/j.parkreldis.2018.04.025
52. Rascol O, Brooks DJ, Melamed E. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. *The Lancet*. 03/12/2005 2005;365(9463):947-954. doi:https://doi.org/10.1016/S0140-6736(05)71083-7

53. Parkinson Study Group. A Randomized Placebo-Controlled Trial of Rasagiline in Levodopa-Treated Patients With Parkinson Disease and Motor Fluctuations The PRESTO Study. *JAMA Neurol*. 02/2005 2005;62(2):241-248. doi:doi:10.1001/archneur.62.2.241
54. Zhang ZX, Shao M, Chen SD, et al. Adjunct rasagiline to treat Parkinson's disease with motor fluctuations: a randomized, double-blind study in China. *Translational Neurodegeneration*. 6/30/2018 2018;7doi:https://doi.org/10.1186/s40035-018-0119-7
55. Zhang LN, Zhang ZQ, Chen YM, et al. Efficacy and safety of rasagiline as an adjunct to levodopa treatment in Chinese patients with Parkinson's disease: a randomized, doubleblind, parallel-controlled, multi-centre trial. *Int J Neuropsychopharmacol*. 08/2013 2013;16(7):1529-1537. doi:doi:10.1017/S1461145713000175
56. Mizuno Y, Abe T, Hasegawa K, et al. Ropinirole is effective on motor function when used as an adjunct to levodopa in Parkinson's disease: STRONG study. *Mov Disord*. 10/15/2007 2007;22(13):1860-1865. doi:10.1002/mds.21313
57. Pahwa R, Stacy MA, Factor SA, et al. Ropinirole 24-hour prolonged release Randomized, controlled study in advanced Parkinson disease. *Neurology*. 04/03/2007 2007;68(14):1108-1115. doi:https://doi.org/10.1212/01.wnl.0000258660.74391.c1
58. Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease: Results of a double-blind, placebo-controlled, parallel-group study. *Neurology*. 07/01/1997 1997;49(1):162-168. doi:https://doi.org/10.1212/WNL.49.1.162
59. Lieberman A, Olanow CW, Sethi K, et al. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. *Neurology*. 10/01/1998 1998;51(4):1057-1062. doi:https://doi.org/10.1212/WNL.51.4.1057
60. Mishra B, Sudheer P, Rajan R, et al. Bridging the gap between statistical significance and clinical relevance: A systematic review of minimum clinically important difference (MCID) thresholds of scales reported in movement disorders research. *Heliyon*. Mar 15 2024;10(5):e26479. doi:10.1016/j.heliyon.2024.e26479
61. Horváth K, Aschermann Z, Ács P, et al. Minimal clinically important difference on the Motor Examination part of MDS-UPDRS. *Parkinsonism Relat Disord*. Dec 2015;21(12):1421-6. doi:10.1016/j.parkreldis.2015.10.006
62. PPMI. Parkinson's Precision Medicine Initiative. https://www.ppmi-info.org/access-data-specimens/download-data/
63. Chaudhuri KR, Pickard AS, Alobaidi A, et al. The Cost Effectiveness of Levodopa-Carbidopa Intestinal Gel in the Treatment of Advanced Parkinson's Disease in England. *Pharmacoeconomics*. May 2022;40(5):559-574. doi:10.1007/s40273-022-01132-y
64. Dams J, Balzer-Geldsetzer M, Siebert U, et al. Cost-effectiveness of neurostimulation in Parkinson's disease with early motor complications. *Mov Disord*. Aug 2016;31(8):1183-91. doi:10.1002/mds.26740
65. Lowin J, Sail K, Baj R, et al. The cost-effectiveness of levodopa/carbidopa intestinal gel compared to standard care in advanced Parkinson's disease. *J Med Econ*. Nov 2017;20(11):1207-1215. doi:10.1080/13696998.2017.1379411
66. Eggington S, Valldeoriola F, Chaudhuri KR, Ashkan K, Annoni E, Deuschl G. The cost-effectiveness of deep brain stimulation in combination with best medical therapy, versus best medical therapy alone, in advanced Parkinson's disease. *J Neurol*. Jan 2014;261(1):106-16. doi:10.1007/s00415-013-7148-z

67. Nyholm D, Eggington S, Holm A. Therapies for Advanced Parkinson's Disease in Sweden: A Cost-Effectiveness Analysis Using Real-World Data. *Neurol Ther*. Jun 2025;14(3):801-812. doi:10.1007/s40120-025-00730-0
68. National Institute for Health and Care Excellence. *Parkinson's Disease in Adults (NG71): Appendix F: Full Health Economics Report*. 2017. Accessed June 3, 2026. https://www.nice.org.uk/guidance/ng71/evidence/appendix-f-he-report-pdf-4538466259
69. Cox E, Wade R, Hodgson R, et al. Assessment of existing cost-effectiveness evidence. *Devices for remote continuous monitoring of people with Parkinson's disease: a systematic review and cost-effectiveness analysis*. 2024. *Health Technology Assessment*.
70. Johnson SJ, Diener MD, Kaltenboeck A, Birnbaum HG, Siderowf AD. An economic model of Parkinson's disease: implications for slowing progression in the United States. *Mov Disord*. Mar 2013;28(3):319-26. doi:10.1002/mds.25328
71. Thach A, Jones E, Pappert E, Pike J, Wright J, Gillespie A. Real-world assessment of "OFF" episode-related healthcare resource utilization among patients with Parkinson's disease in the United States. *J Med Econ*. Jan-Dec 2021;24(1):540-549. doi:10.1080/13696998.2021.1913009
72. Song Y, E JY, Guo T, et al. Treatment Patterns and Healthcare Resource Use in Medicare Beneficiaries with Parkinson's Disease. *Clinicoecon Outcomes Res*. 2023;15:631-643. doi:10.2147/ceor.S422023
73. Jiao B, Basu A. Catalog of Age- and Medical Condition-Specific Healthcare Costs in the United States to Inform Future Costs Calculations in Cost-Effectiveness Analysis. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jul 2021;24(7):957-965. doi:10.1016/j.jval.2021.03.006
74. Arias E, Xu J, Kenneth K. United States life tables, 2023. *Natl Vital Stat Rep*. 2025;74(6):1-63. doi:https://dx.doi.org/10.15620/cdc/174591
75. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med*. May 18 2000;342(20):1484-91. doi:10.1056/nejm200005183422004
76. Corvol JC, Artaud F, Cormier-Dequaire F, et al. Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology*. Jul 17 2018;91(3):e189-e201. doi:10.1212/wnl.0000000000005816
77. Leroi I, Ahearn DJ, Andrews M, McDonald KR, Byrne EJ, Burns A. Behavioural disorders, disability and quality of life in Parkinson's disease. *Age Ageing*. Sep 2011;40(5):614-21. doi:10.1093/ageing/afr078
78. Chen G, Garcia-Gordillo MA, Collado-Mateo D, et al. Converting Parkinson-Specific Scores into Health State Utilities to Assess Cost-Utility Analysis. *Patient*. Dec 2018;11(6):665-675. doi:10.1007/s40271-018-0317-5
79. Hjalte F, Gustafsson A, Samuelsson J, Bergquist F, Johansson A, Odin P. Health-Related Quality of Life in Relation to the 5-2-1 Criteria in Parkinson's Disease in Sweden. *Mov Disord Clin Pract*. Oct 2025;12(10):1511-1519. doi:10.1002/mdc3.70120
80. Domingos J, Arija P, Malaty IA, et al. Burden and disutility of sleep disturbance and early morning OFF symptoms in people with advancing Parkinson's disease: a vignette-based approach using the EQ-5D-5L. *J Patient Rep Outcomes*. Apr 14 2026;10(1)doi:10.1186/s41687-026-01053-w

81. Pillay J, Gaudet LA, Saba S, et al. Falls prevention interventions for community-dwelling older adults: systematic review and meta-analysis of benefits, harms, and patient values and preferences. *Syst Rev*. Nov 26 2024;13(1):289. doi:10.1186/s13643-024-02681-3
82. François C, Biaggioni I, Shibao C, et al. Fall-related healthcare use and costs in neurogenic orthostatic hypotension with Parkinson's disease. *J Med Econ*. May 2017;20(5):525-532. doi:10.1080/13696998.2017.1284668
83. U.S. Bureau of Economic Analysis, "Table 2.3.4. Price Indexes for Personal Consumption Expenditures by Major Type of Product". Accessed June 30, 2026.
84. The Lewin Group I. *Economic Burden of Parkinson's and Atypical Parkinsonism in the United States*. 2026.
85. Abeynayake I, Tanner CM. The economic impact of OFF periods in Parkinson disease. *Am J Manag Care*. Oct 2020;26(12 Suppl):S265-s269. doi:10.37765/ajmc.2020.88518
86. Thach A, Jones E, Pappert E, Pike J, Wright J, Gillespie A. Real-world assessment of the impact of "OFF" episodes on health-related quality of life among patients with Parkinson's disease in the United States. *BMC Neurol*. Jan 30 2021;21(1):46. doi:10.1186/s12883-021-02074-2
87. Ciepielewska M, Jones E, Gillespie A, Walker C, LeBrocq L, Weatherby S. Assessing healthcare resource utilization burden and unmet treatment needs in patients with Parkinson's disease: results from a real-world study. *J Comp Eff Res*. Nov 2025;14(11):e240186. doi:10.57264/cer-2024-0186
88. US Census Bureau. 2023 National Population Projections Tables: Main Series. 2023;
89. Marras C, Beck JC, Bower JH, et al. Prevalence of Parkinson's disease across North America. *npj Parkinson's Disease*. 2018/07/10 2018;4(1):21. doi:10.1038/s41531-018-0058-0
90. Kalilani L, Friesen D, Boudiaf N, Asgharnejad M. The characteristics and treatment patterns of patients with Parkinson's disease in the United States and United Kingdom: A retrospective cohort study. *PLoS One*. 2019;14(11):e0225723. doi:10.1371/journal.pone.0225723
91. Foundation Ps. Stages of Parkinson's. https://www.parkinson.org/understanding-parkinsons/what-is-parkinsons/stages
92. Gregory P. What are Impulse Control Disorders? *What are Impulse Control Disorders?* blog. 06/30/2026, 2018. https://www.apdaparkinson.org/what-is-parkinsons/symptoms/impulse-control-disorders/
93. R.A. H, J. F, T.A. Z, et al. A Home Diary to Assess Functional Status in Patients with Parkinson's Disease with Motor Fluctuations and Dyskinesia. *Clinical Neuropharmacology*. 2000;23(2):p 75-81.
94. American Physical Therapy Association. Unified Parkinson's Disease Rating Scale (UPDRS), Movement Disorders Society (MDS) Modified Unified Parkinson's Disease Rating Scale (MDS-UPDRS). 2018. https://www.apta.org/patient-care/evidence-based-practice-resources/test-measures/unified-parkinsons-disease-rating-scale-updrs-movement-disorders-society-mds-modified-unified-parkinsons-disease-rating-scale-mds-updrs
95. Ottersen T, Førde R, Kakad M, et al. A new proposal for priority setting in Norway: Open and fair. *Health Policy*. Mar 2016;120(3):246-51. doi:10.1016/j.healthpol.2016.01.012
96. van de Wetering EJ, Stolk EA, van Exel NJ, Brouwer WB. Balancing equity and efficiency in the Dutch basic benefits package using the principle of proportional shortfall. *Eur J Health Econ*. Feb 2013;14(1):107-15. doi:10.1007/s10198-011-0346-7

97. Stolk EA, van Donselaar G, Brouwer WB, Busschbach JJ. Reconciliation of economic concerns and health policy: illustration of an equity adjustment procedure using proportional shortfall. *Pharmacoeconomics*. 2004;22(17):1097-107. doi:10.2165/00019053-200422170-00001
98. Callaghan BC, De Lott LB, Kerber KA, Burke JF, Skolarus LE. Neurology Choosing Wisely recommendations: 74 and growing. *Neurol Clin Pract*. Oct 2015;5(5):439-447. doi:10.1212/cpj.0000000000000189
99. de Bie RMA, Katzenschlager R, Swinnen B, et al. Update on Treatments for Parkinson's Disease Motor Fluctuations - An International Parkinson and Movement Disorder Society Evidence-Based Medicine Review. *Mov Disord*. May 2025;40(5):776-794. doi:10.1002/mds.30162
100. Pringsheim T, Day GS, Smith DB, et al. Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary: A Report of the AAN Guideline Subcommittee. *Neurology*. Nov 16 2021;97(20):942-957. doi:10.1212/wnl.0000000000012868
101. Excellence NIfHaC. *Parkinson's disease in adults: diagnosis and management*. 2017.
102. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
103. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
104. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
105. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
106. Agboola FW, AC. A Framework for Evaluating the Diversity of Clinical Trials. *Journal of Clinical Epidemiology*. 2024:111299.
107. C. P, A. H, D. M, et al. Care access and utilization among medicare beneficiaries livingwith Parkinson's disease. *NPJ Parkinsons Dis*. July 10 2023 2023;9doi:https://doi.org/10.1038/s41531-023-00523-y
108. Institute for Health Metrics and Evaluation. Data from: Global Burden of Disease Database. 2023.
109. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. Updated January 31, 2020. https://icer.org/evidence-rating-matrix/
110. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care*. Jun 2010;48(6 Suppl):S145-52. doi:10.1097/MLR.0b013e3181d9913b
111. Olanow CW, Hauser RA, Gauger L, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol*. Nov 1995;38(5):771-7. doi:10.1002/ana.410380512
112. Weintraub D, Hauser RA, Elm JJ, Pagan F, Davis MD, Choudhry A. Rasagiline for mild cognitive impairment in Parkinson's disease: A placebo-controlled trial. *Mov Disord*. May 2016;31(5):709-14. doi:10.1002/mds.26617

113. Pahwa R, Lyons KE, Hauser RA, et al. Randomized trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease. *Parkinsonism Relat Disord*. Feb 2014;20(2):142-8. doi:10.1016/j.parkreldis.2013.08.017
114. Hauser RA, Rascol O, Korczyn AD, et al. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. *Mov Disord*. Dec 2007;22(16):2409-17. doi:10.1002/mds.21743
115. Investigators. PSGCC. Long-term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol*. May 2009;66(5):563-70. doi:10.1001/archneur.66.1.nct90001
116. Holloway RG, Shoulson I, Fahn S, et al. Pramipexole vs levodopa as initial treatment for Parkinson disease: a 4-year randomized controlled trial. *Arch Neurol*. Jul 2004;61(7):1044-53. doi:10.1001/archneur.61.7.1044
117. Group. PS. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *Jama*. Apr 3 2002;287(13):1653-61. doi:10.1001/jama.287.13.1653
118. Sethi KD, O'Brien CF, Hammerstad JP, et al. Ropinirole for the treatment of early Parkinson disease: a 12-month experience. Ropinirole Study Group. *Arch Neurol*. Sep 1998;55(9):1211-6. doi:10.1001/archneur.55.9.1211
119. Timmermann L, Asgharnejad M, Boroojerdi B, Dohin E, Woltering F, Elmer LW. Impact of 6-month earlier versus postponed initiation of rotigotine on long-term outcome: post hoc analysis of patients with early Parkinson's disease with mild symptom severity. *Expert Opin Pharmacother*. 2015;16(10):1423-33. doi:10.1517/14656566.2015.1049597
120. Jankovic J, Berkovich E, Eyal E, Tolosa E. Symptomatic efficacy of rasagiline monotherapy in early Parkinson's disease: post-hoc analyses from the ADAGIO trial. *Parkinsonism Relat Disord*. Jun 2014;20(6):640-3. doi:10.1016/j.parkreldis.2014.02.024
121. Smith KM, Eyal E, Weintraub D. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. *JAMA Neurol*. Jan 2015;72(1):88-95. doi:10.1001/jamaneurol.2014.2472
122. Group. PS. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol*. Dec 2003;60(12):1721-8. doi:10.1001/archneur.60.12.1721
123. Mizuno Y, Nomoto M, Kondo T, et al. Transdermal rotigotine in early stage Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *Mov Disord*. Sep 2013;28(10):1447-50. doi:10.1002/mds.25537
124. Poewe W, Juhel N, Haaksma M, et al. Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease† ‡. *Movement Disorders*. 2010/11/15 2010;25(15):2542-2549. doi:10.1002/mds.23317
125. Hubble JP, Koller WC, Cutler NR, et al. Pramipexole in patients with early Parkinson's disease. *Clin Neuropharmacol*. Aug 1995;18(4):338-47. doi:10.1097/00002826-199508000-00006
126. Group. PS. Safety and efficacy of pramipexole in early Parkinson disease. A randomized dose-ranging study. Parkinson Study Group. *Jama*. Jul 9 1997;278(2):125-30. doi:10.1001/jama.1997.03550020057038
127. Kieburtz K. Twice-daily, low-dose pramipexole in early Parkinson's disease: a randomized, placebo-controlled trial. *Mov Disord*. Jan 2011;26(1):37-44. doi:10.1002/mds.23396

128. Navan P, Findley LJ, Jeffs JA, Pearce RK, Bain PG. Randomized, double-blind, 3-month parallel study of the effects of pramipexole, pergolide, and placebo on Parkinsonian tremor. *Mov Disord*. Nov 2003;18(11):1324-31. doi:10.1002/mds.10538
129. Navan P, Findley LJ, Jeffs JA, Pearce RK, Bain PG. Double-blind, single-dose, cross-over study of the effects of pramipexole, pergolide, and placebo on rest tremor and UPDRS part III in Parkinson's disease. *Mov Disord*. Feb 2003;18(2):176-80. doi:10.1002/mds.10320
130. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. Jun 2010;9(6):573-80. doi:10.1016/s1474-4422(10)70106-x
131. Stern MB, Marek KL, Friedman J, et al. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Mov Disord*. Aug 2004;19(8):916-23. doi:10.1002/mds.20145
132. Mally J, Kovacs AB, Stone TW. Delayed development of symptomatic improvement by (--)-deprenyl in Parkinson's disease. *J Neurol Sci*. Dec 1995;134(1-2):143-5. doi:10.1016/0022-510x(95)00240-1
133. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science*. Aug 4 1989;245(4917):519-22. doi:10.1126/science.2502843
134. Koller W. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. Jan 21 1993;328(3):176-83. doi:10.1056/nejm199301213280305
135. Thomas A, Bonanni L, Di Iorio A, et al. End-of-dose deterioration in non ergolinic dopamine agonist monotherapy of Parkinson's disease. *J Neurol*. 12/2006 2006;253:1633-1639. doi:https://doi.org/10.1007/s00415-006-0320-z
136. Hattori N, Mochizuki H, Hasegawa K, et al. Ropinirole Patch Versus Placebo, Ropinirole Extended-Release Tablet in Advanced Parkinson's Disease. *Mov Disord*. Sep 2020;35(9):1565-1573. doi:10.1002/mds.28071
137. Ondo WG, Sethi KD, Kricorian G. Selegiline orally disintegrating tablets in patients with Parkinson disease and "wearing off" symptoms. *Clin Neuropharmacol*. Sep-Oct 2007;30(5):295-300. doi:10.1097/WNF.0b013e3180616570
138. Waters CH, Sethi KD, Hauser RA, Molho E, Bertoni JM. Zydis selegiline reduces off time in Parkinson's disease patients with motor fluctuations: a 3-month, randomized, placebo-controlled study. *Mov Disord*. Apr 2004;19(4):426-32. doi:10.1002/mds.20036
139. Mizuno Y, Nomoto M, Hasegawa K, et al. Rotigotine vs ropinirole in advanced stage Parkinson's disease: a double-blind study. *Parkinsonism Relat Disord*. Dec 2014;20(12):1388-93. doi:10.1016/j.parkreldis.2014.10.005
140. Nomoto M, Mizuno Y, Kondo T, et al. Transdermal rotigotine in advanced Parkinson's disease: a randomized, double-blind, placebo-controlled trial. *J Neurol*. Oct 2014;261(10):1887-93. doi:10.1007/s00415-014-7427-3
141. Rascol O, Lees AJ, Senard JM, Pirtosek Z, Montastruc JL, Fuell D. Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. *Clin Neuropharmacol*. Jun 1996;19(3):234-45. doi:10.1097/00002826-199619030-00005
142. Zesiewicz TA, Chriscoe S, Jimenez T, Upward J, Davy M, VanMeter S. A randomized, fixed-dose, dose-response study of ropinirole prolonged release in advanced Parkinson's disease. *Neurodegener Dis Manag*. Feb 2017;7(1):61-72. doi:10.2217/nmt-2016-0038

143. Zhang Z, Wang J, Zhang X, et al. The efficacy and safety of ropinirole prolonged release tablets as adjunctive therapy in Chinese subjects with advanced Parkinson's disease: a multicenter, double-blind, randomized, placebo-controlled study. *Parkinsonism Relat Disord*. Nov 2013;19(11):1022-6. doi:10.1016/j.parkreldis.2013.07.009
144. Mizuno Y, Kanazawa I, Kuno S, Yanagisawa N, Yamamoto M, Kondo T. Placebo-controlled, double-blind dose-finding study of entacapone in fluctuating parkinsonian patients. *Mov Disord*. Jan 2007;22(1):75-80. doi:10.1002/mds.21218
145. Ferreira JJ, Rocha JF, Falcão A, et al. Effect of opicapone on levodopa pharmacokinetics, catechol-O-methyltransferase activity and motor fluctuations in patients with Parkinson's disease. *Eur J Neurol*. May 2015;22(5):815-25, e56. doi:10.1111/ene.12666
146. Golbe LI, Lieberman AN, Muenter MD, et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. *Clin Neuropharmacol*. Feb 1988;11(1):45-55. doi:10.1097/00002826-198802000-00004
147. Parkinson Study Group. A Controlled Trial of Rasagiline in Early Parkinson Disease: The TEMPO Study. *JAMA Neurol*. 2002;59(12):1937-1943. doi:10.1001/archneur.59.12.1937
148. Allain H, Pollak P, Neukirch HC. Symptomatic effect of selegiline in de novo parkinsonian patients. *Mov Disord*. 1993 1993;8(S1):S36-S-40. doi:https://doi.org/10.1002/mds.870080508
149. The Parkinson's Study Group. Effects of Tocopherol and Deprenyl on the Progression of Disability in Early Parkinson's Disease. *N Engl J Med*. 01/21/1993 1993;328(8):176-183. doi:10.1056/NEJM199301213280305
150. Schapira AH, Barone P, Hauser RA, et al. Extended-release pramipexole in advanced Parkinson disease: a randomized controlled trial. *Neurology*. Aug 23 2011;77(8):767-74. doi:10.1212/WNL.0b013e31822affdb
151. Harvey R, Charokopou M, Arteaga Duarte C, Kiri S. PNS22 Network Meta-Analysis: A Comparison of Bayesian and Frequentist Approaches to Synthesis, and Evaluation of Their Suitability for Decision-Making. *Value in Health*. 2020;23:S647. doi:10.1016/j.jval.2020.08.1466
152. Zhang Q, Chen X, Chen F, Wen S, Zhou C. Dopamine agonists versus levodopa monotherapy in early Parkinson's disease for the potential risks of motor complications: A network meta-analysis. *European Journal of Pharmacology*. 2023/09/05/ 2023;954:175884. doi:https://doi.org/10.1016/j.ejphar.2023.175884
153. Sisodia V, Dubbeld L, De Bie RMA, Duarte GS, Costa J, Dijk JM. Efficacy and safety of adjunctive oral therapy in Parkinson's disease with motor complications: a systematic review and network meta-analysis. *BMJ Neurol Open*. 2024;6(1):e000573. doi:10.1136/bmjno-2023-000573
154. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. Sep 13 2016;316(10):1093-103. doi:10.1001/jama.2016.12195
155. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931-941. doi:10.1016/j.jval.2019.02.009

156. Siebert U, Bornschein B, Walbert T, Dodel RC. Systematic assessment of decision models in Parkinson's disease. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Sep-Oct 2004;7(5):610-26. doi:10.1111/j.1524-4733.2004.75012.x
157. Dams J, Bornschein B, Reese JP, et al. Modelling the cost effectiveness of treatments for Parkinson's disease: a methodological review. *Pharmacoeconomics*. Dec 2011;29(12):1025-49. doi:10.2165/11587110-000000000-00000
158. Dams J, Zapp JJ, König HH. Modelling the Cost Effectiveness of Treatments for Parkinson's Disease: An Updated Methodological Review. *Pharmacoeconomics*. Oct 2023;41(10):1205-1228. doi:10.1007/s40273-023-01289-0
159. Nuijten MJ, van Iperen P, Palmer C, van Hilten BJ, Snyder E. Cost-effectiveness analysis of entacapone in Parkinson's disease: a Markov process analysis. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jul-Aug 2001;4(4):316-28. doi:10.1046/j.1524-4733.2001.44037.x
160. van Boven JF, Novak A, Driessen MT, Boersma C, Boomsma MM, Postma MJ. Economic evaluation of ropinirole prolonged release for treatment of Parkinson's disease in the Netherlands. *Drugs Aging*. Mar 2014;31(3):193-201. doi:10.1007/s40266-013-0150-4
161. Fundament T, Eldridge PR, Green AL, et al. Deep Brain Stimulation for Parkinson's Disease with Early Motor Complications: A UK Cost-Effectiveness Analysis. *PLoS One*. 2016;11(7):e0159340. doi:10.1371/journal.pone.0159340
162. Fann JC, Chang KC, Yen AM, et al. Cost-Effectiveness Analysis of Deep Brain Stimulation for Parkinson Disease in Taiwan. *World Neurosurg*. Jun 2020;138:e459-e468. doi:10.1016/j.wneu.2020.02.150
163. Chandler C, Folse H, Gal P, et al. Modeling long-term health and economic implications of new treatment strategies for Parkinson's disease: an individual patient simulation study. *J Mark Access Health Policy*. Jun 3 2021;9(1):1922163. doi:10.1080/20016689.2021.1922163

Supplemental Materials

A. Background: Supplemental Information

A1. Definitions

Disease Characteristics

Early Stage: We included definitions of early-stage disease based on Hoehn and Yahr stages, number of years since diagnosis, patient age, and/or the UPDRS scores as reflected in clinical trials. We heard from clinical experts that HY stages alone do not reflect the severity of PD disease. As such, we did not restrict inclusion to a single staging criterion, allowing trials of stages I-II or I-III, to maximize the evidence base.

Hoehn and Yahr (HY) Staging: A five-stage scale used to describe the progression of motor symptoms in Parkinson's Disease. In stage 1 patients have mild symptoms such as tremors and movement symptoms that occur but do not impede activities of daily living. In stage 2, motor symptoms such as tremor, rigidity, posture, and walking difficulties start to manifest more. Patients are still able to live independently, but activities of daily living begin to get more difficult. In stage 3 patients start to experience a loss of balance and worsening motor function, with mild to moderate disability. By stage 4, symptoms are severely disabling, requiring assistance with activities of daily living and are unable to live alone. By stage 5, around the clock care is required for patients, who are usually bedridden or wheelchair bound.[91]

Clinical Outcome Measures

EuroQol 5-Dimension (EQ-5D): A standardized five-item tool used to assess health-related quality of life (HRQoL) across various conditions. This scale covers mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Scores range from less than 0 (worse than death) or 1 (excellent health). Visual analogue scale (0-100) captures self-reported health.[44] The MCID for EQ-5D index scores among PD patients is approximately 0.10.[38]

Impulse Control Disorder: A behavioral disturbance closely linked to the use of dopaminergic therapies, in which a person engages in behaviors that result in impaired social or occupational functioning and distress. Common manifestations include pathological gambling, excessive spending, over-eating, and hypersexuality.[92]

Motor Fluctuations: Motor fluctuations are changes in the ability to move and are also referred to as "ON-OFF" times.

Hauser Diary: The Hauser Diary is a self-reported inventory scale that patients use to report four separate states every 30 minutes, which include off-time, on-time with troublesome dyskinesia, or on-time without troublesome dyskinesia.[93]

OFF Times: A state reported in the Hauser Diary, which is marked by stiffness and immobility.[93] Motor fluctuations are changes in the ability to move and are commonly referred to as on times (controlled symptoms) and OFF times (symptoms returned). ON times can be separated into two distinct periods: those with and without troublesome dyskinesia. Longer ON times (hours) and shorter OFF times (hours) indicate better treatment response. The MCIDs for OFF time ranges from 1 to 1.3 hours.[36]

ON Times: A state reported in the Hauser Diary, which indicates good, normal mobility.[93]

ON-Time with Troublesome Dyskinesia: Involuntary twisting and turning movements which differ from the tremor associated with Parkinson's disease.[93]

Parkinson's Disease Questionnaire (PDQ-39): A 39-item questionnaire that assesses health status and quality of life across eight dimensions of daily living, covering relationships, social situations, communication, functioning, and well-being.[87] The MCID for PDQ-39 mobility domain is -3.2.[39]

UPDRS or MDS-UPDRS: The UPDRS is a tool used to measure the severity and progression of Parkinson's disease. This scale is divided into several parts: Part I focuses on thinking, behavior, and mood; Part II focuses on activities of daily living; Part III focuses on motor function rated by a clinician; and Part IV focuses on complications of therapy. Parts I-III use a 0-4 scale, while Part VI uses a yes or no scale. The MDS-UPDRS is a revised version of the UPDRS, which updated all subcategories to be from 0-4, revised the language, adapted to be more sensitive, and aims to differentiate between slight and mild deficits.[94] Clinical trials have predominantly used the original UPDRS scale. Lower UPDRS or MDS-UPDRS scores indicate better treatment. The MCID for UPDRS Part III improvement ranges between -4.8 and -6.2.[35,36] The reported MCID for UPDRS Part II score ranges from -1.8 to -3.05.[36,37] The MCIDs for MDS-UPDRS Part III and Part II scores were -3.25 and -3.05, respectively.[37,61]

Other Relevant Definitions

Absolute and Proportional Shortfalls: Absolute and proportional shortfalls are empirical measurements that capture different aspects of society's instincts for prioritization related to the severity or burden of an illness. The absolute shortfall is defined as the total absolute amount of future health patients with a condition are expected to lose without the treatment that is being assessed.[95] The ethical consequences of using absolute shortfall to prioritize treatments is that conditions that cause early death or that have very serious lifelong effects on quality of life receive the greatest prioritization. Thus, certain kinds of treatments, such as treatments for rapidly fatal

conditions of children, or for lifelong disabling conditions, score highest on the scale of absolute shortfall. The proportional shortfall is measured by calculating the proportion of the total health units of remaining life expectancy that would be lost due to untreated illness.[96,97] The proportional shortfall reflects the ethical instinct to prioritize treatments for patients whose illness would rob them of a large percentage of their expected remaining lifetime. As with absolute shortfall, rapidly fatal conditions of childhood have high proportional shortfalls, but high numbers can also often arise from severe conditions among older adults who may have only a few years left of average life expectancy but would lose much of that to the illness without treatment. Details on how to calculate the absolute and proportional QALY and evLY shortfalls can be found in ICER's reference case. Shortfalls will be highlighted when asking the independent appraisal committees to vote on unmet need despite current treatment options as part of characterizing a treatment's benefits beyond health and special ethical priorities (Section 5).

A2. Potential Cost-Saving Measures in Parkinson's Disease

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, please reference ICER's Value Assessment Framework). These services are ones that would not be directly affected by therapies for Parkinson's disease, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of Parkinson's disease beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with Parkinson's disease that could be reduced, eliminated, or made more efficient. No suggestions were received. We also reviewed 74 Choosing Wisely recommendations in Neurology, but none of them directly applied to the care of patients with Parkinson's disease.[98]

A3. Patient Input on Clinical Trial Design

Manufacturers were asked to submit a written explanation of how they engaged patients in the design of their clinical trials, including the methods used to gather patient experience data and how they determined the outcomes that matter most to patients.

ICER did not receive any feedback on this inquiry.

B. Patient and Other Stakeholder Perspectives: Supplemental Information

B1. Patient Community Input: Methods

Six patients submitted their stories about their experiences with Parkinson's disease. We spoke with representatives from patient organizations. We also held two small-group interviews one with patients with Parkinson's disease and one with care partners of patients with Parkison's disease. Finally, many of these groups provided direct input on the draft scope and the draft report.

B2. Clinical Input: Methods

We spoke with several neurologists who specialize in the care of patients with Parkison's disease and received feedback from them on our draft scope and our draft report.

C. Clinical Guidelines

Bie et al. (2025) - International Parkinson and Movement Disorder Society[99]

The International Parkinson and Movement Disorder Society reviewed therapies for the treatment of motor fluctuations in people with Parkinson's disease (PD) currently treated with levodopa. They found that levodopa extended release, pramipexole immediate release and extended release, ropinirole immediate release, rotigotine, opicapone, safinamide, and bilateral deep brain stimulation were efficacious. In addition, they found that continuous intestinal levodopa infusion, continuous subcutaneous levodopa, continuous subcutaneous apomorphine, ropinirole prolonged release, ropinirole patch, continuous subcutaneous apomorphine, entacapone, rasagiline, istradefylline, amantadine controlled release, zonisamide, bilateral GPi DBS, and pallidotomy were likely efficacious. The dopamine agonists pergolide, bromocriptine, and cabergoline, and the catechol-O-methyltransferase (COMT) inhibitor tolcapone are no longer mentioned, unlike in the previous review. This is either due to insufficient scientific evidence or because they are no longer available for the treatment of PD.

AAN Guideline 2021[100]

The American Academy of Neurology (AAN) recommends levodopa as the preferred initial treatment for motor symptoms in early Parkinson's disease (PD). The AAN advises using the lowest effective dose to manage symptoms while minimizing adverse effects such as dyskinesia. Clinicians can prescribe DAs as the initial dopaminergic therapy in selected patients with early PD aged <60 years who are at higher risk of developing dyskinesia. Clinicians can prescribe monoamine oxidase B (MAO-B) inhibitors as the initial dopaminergic therapy for mild motor symptoms in patients with early PD, but initial therapy with levodopa provides greater motor benefits compared with MAO-B inhibitors.

NICE Guideline 2017[101]

NICE recommends that physicians offer levodopa to people in the early stages of Parkinson's disease whose motor symptoms impact on their quality of life. Physicians can consider a choice of dopamine agonists, levodopa or monoamine oxidase B (MAO-B) inhibitors for people in the early stages of Parkinson's disease whose motor symptoms do not impact on their quality of life.

In addition, they recommend that if someone with Parkinson's disease has developed dyskinesia and/or motor fluctuations, including medicines 'wearing off', seek advice from a health care professional with specialist expertise in Parkinson's disease before modifying therapy. Clinicians should offer a choice of dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors as an adjunct to levodopa for people with Parkinson's disease who have

developed dyskinesia or motor fluctuations despite optimal levodopa therapy, after discussing the person's individual clinical circumstances, the person's individual lifestyle circumstances, preferences, needs and goals, and the potential benefits and harms of the different drug classes.

D. Comparative Clinical Effectiveness: Supplemental Information

D1. Detailed Methods

PICOTS

Population

The populations for this were:

- Population 1: Adults with early-stage PD; (included definitions of early-stage disease based on Hoehn and Yahr stages, number of years since diagnosis, patient age, and/or the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS] scores as reflected in the published literature)
- Population 2: Adults with PD taking levodopa who are experiencing motor fluctuations

Data permitting, evaluated the evidence for treatment effect modification by age (as defined in clinical trials and observational studies) and sex at birth in each of these populations. Data permitting, we evaluated the evidence for treatment effect modification by age (as defined in clinical trials and observational studies) and sex at birth in each of these populations.

Interventions

The full list of interventions was as follows:

- Population 1: Tavapadon
- Population 2: Tavapadon plus levodopa

Comparators

- Population 1:
    - Levodopa
    - Dopamine agonists (pramipexole, ropinirole, and rotigotine)
    - MAO-B inhibitors (rasagiline, selegiline)
- Population 2:
    - Dopamine agonists (pramipexole, ropinirole, and rotigotine) plus levodopa
    - COMT inhibitors (opicapone, entacapone) plus levodopa
    - MAO-B inhibitors (rasagiline, selegiline) plus levodopa

Outcomes

Patient-Important Outcomes

- Changes from baseline in MDS-UPDRS Parts II (motor experiences of daily living) and III scores (motor examinations)
- Changes from baseline in Hauser Diary motor state durations
    - OFF time
    - ON time without troublesome dyskinesia
    - ON time with troublesome dyskinesia
- Health-related quality of life measures
    - Parkinson's Disease Questionnaire (e.g., PDQ-8, PDQ-39)
    - EuroQol-5D (EQ-5D)
    - Short Form-36 (SF-36)
- Activities of daily living
- Care partner burden
- Adverse events including
    - Serious drug-related adverse events
    - Impulse control and related behavioral disorders
    - Dyskinesia
    - Orthostatic hypotension
    - Insomnia
    - Sleep disorder
    - Falls
    - Hallucinations

Other Outcomes

- Discontinuations due to adverse events
- Other disability measures (e.g., self-assessment Parkinson's disease disability scale [SPDDS])
- Fatigue
- Pain
- Cognitive assessments
- Constipation
- MDS-UPDRS Part IV (motor complications)
- Hospitalizations and emergency department (ED) visits

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration.

Settings

All relevant settings were considered, with a focus on the outpatient setting; given the heterogeneous nature of PD and its treatment, however, special attention was paid to ED, hospital, and long-term care settings in the United States.

Study Design

Randomized controlled trials and non-randomized controlled trials with any sample size were included. High-quality comparative observational studies were included.

Table D1.1 PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review.
ABSTRACT		
Abstract	2	See the PRISMA 2020 for Abstracts checklist.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of existing knowledge.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.
METHODS		
Eligibility Criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.
Information Sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.
Search Strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.
Selection Process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.
Data Collection Process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.
Data Items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.
Study Risk of Bias Assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.
Effect Measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.
Synthesis Methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.

Section and Topic	Item #	Checklist Item
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.
Reporting Bias Assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).
Certainty Assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.
RESULTS		
Study Selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.
Study Characteristics	17	Cite each included study and present its characteristics.
Risk of Bias in Studies	18	Present assessments of risk of bias for each included study.
Results of Individual Studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.
Results of Syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.
Reporting Biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.
Certainty of Evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.
DISCUSSION		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.
	23b	Discuss any limitations of the evidence included in the review.
	23c	Discuss any limitations of the review processes used.
	23d	Discuss implications of the results for practice, policy, and future research.
OTHER INFORMATION		

Section and Topic	Item #	Checklist Item
Registration and Protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.
	24c	Describe and explain any amendments to information provided at registration or in the protocol.
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.
Competing Interests	26	Declare any competing interests of review authors.
Availability of Data, Code, and Other Materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.

From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on new therapies for Parkinson's disease followed established best research methods.[102,103] We reported the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[104] The PRISMA guidelines include a checklist of 27 items (see Table D1.1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews. Where feasible and deemed necessary, we also accepted data submitted by manufacturers "in-confidence," in accordance with ICER's published guidelines on acceptance and use of such data).

Table D1.2. Ovid MEDLINE® ALL 1946 to Present, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for Randomized Controlled Trials Only

1	exp Parkinson Disease/
2	("Idiopathic Parkinson Disease"or "Idiopathic Parkinson's Disease"or "Lewy Body Parkinson Disease"or "Lewy Body Parkinson's Disease"or "Paralysis Agitans"or "Parkinson Disease"or "Parkinson's Disease"or "Parkinson Disease, idiopathic"or "Parkinson's Disease, Idiopathic"or "Parkinson's Disease, Lewy Body"or "Primary Parkinsomism"or "Parkinsonism, Primary").ti,ab.
3	1 OR 2
4	("tavapadon").ti,ab
5	("L-Dopa"or "L Dopa"or "Levodopa"or "carbidopa-levodopa"or "levodopa-carbidopa"or "carbidopaadj levodopa"or "Sinemet" OR "Rytary"or "Crexont"or "Stalevo"or "Pramipexole"or "Mirapex"or "Ropinirole"or "Requip"or "rotigotine"or "Neupro"or "selegiline"or "Zelapar"or "rasagiline"or "Azilect"or "Opicapone"or "Ongentsys"or "entacapone"or "Comtan").ti,ab
6	4 OR 5
7	3 AND 6
8	7 NOT (animals not (humans and animals)).sh.
9	8 NOT(addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or dictionary or directory or duplicate publication or editorial or encyclopedia or festschrift or guideline or interactive tutorial or letter or chapter or short survey).pt.

10	control Groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. Or ("clinical trial"or "clinical trial, phase ii"or "clinical trial, phase iii"or "clinical trial, phase iv"or "controlled clinical trial"or "multicenter study"or "randomized controlled trial").pt. or (randomi?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. Or ((single or doubl*) adj2 blind*).ti,ab.
11	9 AND 10
12	11 NOT(exp cohort studies/ or comparative study.pt. or observational study.pt. or exp case-control studies/ or cohort.tw. or (observational adj2 stud*).tw. or prospective.tw. or retrospective.tw. or longitudinal.tw. or compa*.tw. or groups.tw. or case control.tw. or multivariate.tw.)
13	Limit 12 to English language
14	Limit 13 to yr="2016 – 2026"
15	Remove duplicates from 14

Ran 4/16/2026

Table D1.3. Search Strategy of EMBASE for Randomized Controlled Trials Only

1	'Parkinson disease'/exp
2	('idiopathic parkinsonism' OR 'Lewy bodies of Parkinson disease' OR 'Lewy bodies of Parkinson`s disease' OR 'Lewy bodies of Parkinsons disease' OR 'Lewy body Parkinson disease' OR 'Lewy body Parkinson`s disease' OR 'Lewy body Parkinsons disease' OR 'paralysis agitans' OR 'Parkinson dementia complex' OR 'Parkinson`s disease' OR 'Parkinsons disease' OR 'primary parkinsonism' OR 'Parkinson disease'):ti,ab
3	#1 OR #2
4	('tavapadon'):ti,ab
5	('levodopa' OR 'l dopa' OR 'ldopa' OR 'levodopa, carbidopa' OR 'carbidopa, levodopa' OR 'carbidopa NEAR/1 levodopa' OR 'stalevo' OR 'crexont' OR 'rytary' OR 'sinemet' OR 'pramipexole' OR 'ropinirole' OR 'rotigotine' OR 'mirapex' OR 'neupro' OR 'requip' OR 'selegiline' OR 'zelapar'OR 'rasagiline' OR 'azilect'OR 'opicapone' OR 'ongentys'OR 'entacapone' OR 'comtan'):ti,ab
6	#4 OR #5
7	#3 AND #6
8	#7 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'shortsurvey'/it)
9	'clinical':ti,ab AND 'trial':ti,ab OR 'clinical trial'/exp OR 'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR random*:ti,ab OR control*:ti,ab OR 'control group'/exp OR 'drug therapy':lnk
10	#8 AND #9
11	#10 NOT ('observational study'/exp OR 'prospective study'/exp OR 'retrospective study'/exp OR 'longitudinal study'/exp OR 'cohort analysis'/exp OR 'cohort':ti,ab OR 'compa*':ti,ab OR 'groups':ti,ab OR 'case control':ti,ab OR 'multivariate':ti,ab OR retrospective:ti,ab OR prospective:ti,ab OR longitudinal:ti,ab OR ((observational NEAR/2 stud*):ti,ab)
12	#11 AND [english]/lim
13	#12 NOT [medline]/lim
14	#13 AND [2016-2026]/py

Ran 4/16/2026

Table D1.4. Ovid MEDLINE® ALL 1946 to Present for Observational Studies Evaluating Tavapadon

#	Search Terms
1	exp Parkinson Disease/
2	("IdiopathicParkinson Disease" OR “Idiopathic Parkinson’s Disease” OR “Lewy Body Parkinson Disease” OR “Lewy Body Parkinson’s Disease” OR “Paralysis Agitans” OR “Parkinson Disease” OR “Parkinson’s Disease” OR “Parkinson Disease, idiopathic” OR “Parkinson’s Disease, Idiopathic” OR “Parkinson’s Disease, Lewy Body” OR “Primary Parkinsomism” OR “Parkinsonism, Primary”).ti,ab
3	1 OR 2
4	("tavapadon").ti,ab.
5	3 AND 4
6	5 NOT (animals not (humans and animals)).sh.
7	6 NOT (addresses OR autobiography OR bibliography OR biography OR comment OR congresses OR consensus development conference OR dictionary OR directory OR duplicate publication OR editorial OR encyclopedia OR festschrift OR guideline OR interactive tutorial).p
8	limit 7 to English language
9	Remove duplicates from 8

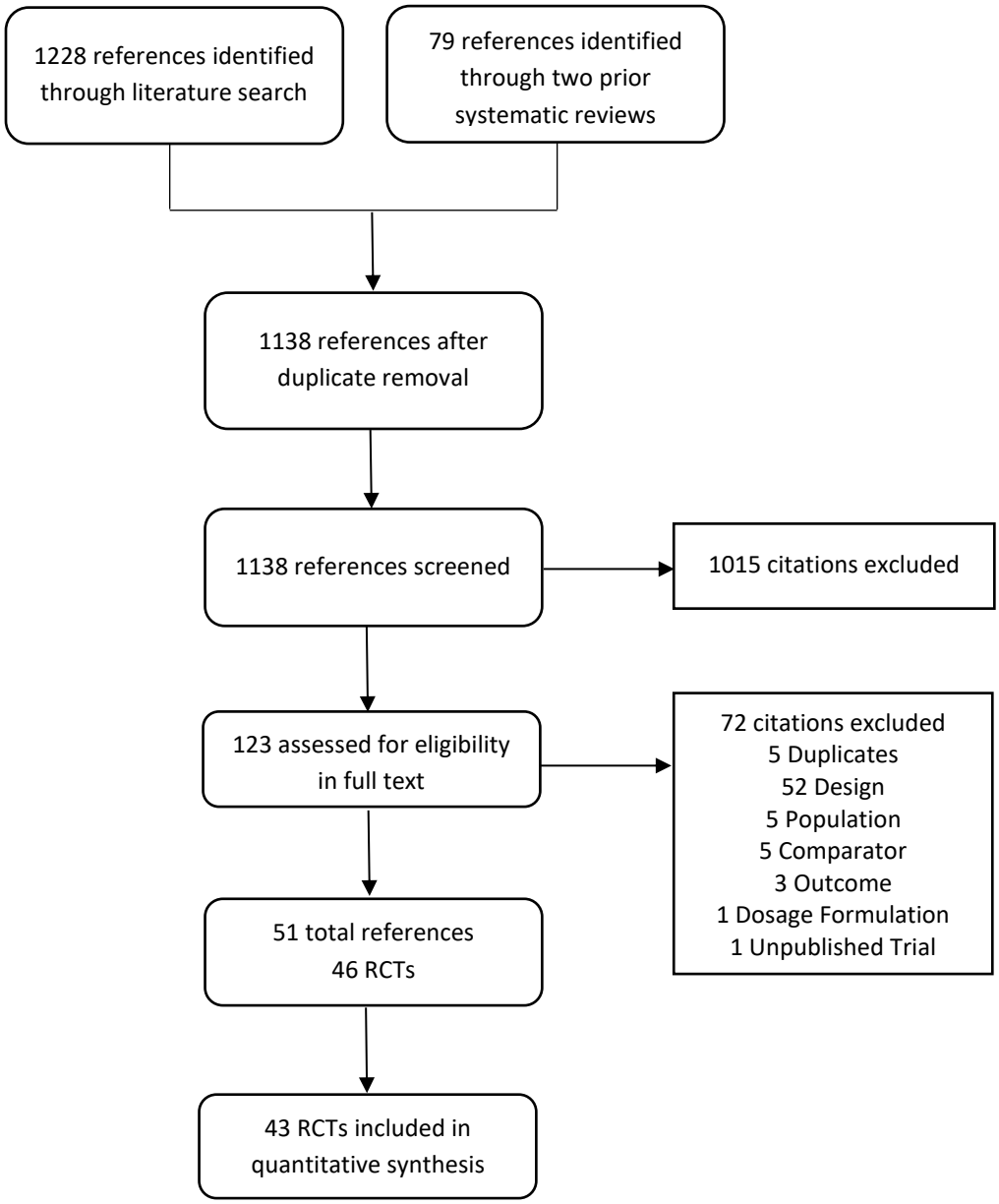
Ran 4/16/2026

Table D1.5. Search Strategy of EMBASE for Observational Studies Evaluating Tavapadon

#	Search Terms
1	'Parkinson disease'/exp
2	('idiopathic parkinsonism' OR 'Lewy bodies of Parkinson disease' OR 'Lewy bodies of Parkinson`s disease' OR 'Lewy bodies of Parkinsons disease' OR 'Lewy body Parkinson disease' OR 'Lewy body Parkinson`s disease' OR 'Lewy body Parkinsons disease' OR 'paralysis agitans' OR 'Parkinson dementia complex' OR 'Parkinson`s disease' OR 'Parkinsons disease' OR 'primary parkinsonism' OR 'Parkinson disease'):ti,ab
3	#1 OR #2
4	('tavapadon’):ti,ab
5	#3 AND #4
6	#5 NOT ('animal experiment'/de OR 'animal model'/de OR 'case report'/de OR 'human cell'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
7	#6 AND [English]/lim
8	#7 NOT [medline]/lim

Ran 4/16/2026

Figure D1.1. PRISMA Flow Chart Showing Results of Literature Search for Parkinson's Disease



Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, Minnesota); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

Data Extraction

Data were extracted into Microsoft Word and Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

Risk of Bias Assessment

We examined the risk of bias for each randomized trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[103,105] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

Low risk of bias*: The study is judged to be at low risk of bias for all domains for this result.*

Some concerns*: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

High risk of bias*: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the following outcomes: UPDRS Part II and III scores and motor state durations (OFF times). See Tables D1.6 and D1.7.

Table D1.6. Risk of Bias Assessment for Early-Stage PD Trials (UPDRS Scores)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Tavapadon						
Pahwa, 2026	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Differential discontinuations due to AEs						
Fernandez, 2026	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Differential discontinuations due to AEs						
Levodopa						
Whone, 2002	Low	Low	High	Low	High	**High**
Note: Differential discontinuations due to AEs; no evidence of using missing data handling						
Rascol, 1998	Low	Low	Low	Low	Low	**Low**
Holloway, 2000	Low	Low	Low	Low	Low	**Low**
Note: Some patients used supplemental levodopa in both arms.						
Dopamine Agonists						
Adler, 1997	Low	Low	High	Low	Low	**High**
Note: Differential discontinuations due to AEs; no evidence of using missing data handling						
Singer, 2007	Low	Low	High	Low	Low	**High**
Note: Almost half of the trial participants discontinued the trial						
Giladi, 2007	Low	Low	Low	Low	Low	**Low**
Zhang, 2016	Low	Low	Low	Low	Low	**Low**
Poewe, 2011	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Differential discontinuations due to AEs						
Shannon, 1997	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Higher discontinuations in both arms						

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
MAO-B Inhibitors						
Barone, 2015	Low	Low	Low	Low	Low	**Low**
Hanagasi, 2011	Low	Low	Some concerns	Low	Some concerns	**High**
Note: Small trial with some patients discontinuing the trial and no use of LOCF; no predefined endpoint						
Siderowf, 2002	Low	Low	Low	Low	Low	**Low**
Hattori, 2019	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Differential discontinuation rates						
Allain, 1993	Low	Low	Low	Low	Low	**Low**
Palhagen, 1998	Low	Low	Low	Low	Low	**High**
Note: Initiated levodopa therapy in the middle of trial design						

LOCF: last observation carried forward, MAO-B: Monoamine oxidase-B.

Table D1.7. Risk of Bias Assessments for Adjunct Therapy PD Trials (Motor State Durations)

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Tavapadon						
Fernandez, 2026	Low	Low	Some concerns	Low	Low	**Some concerns**
Note:						
Dopamine Agonists						
Lewitt, 2006	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Higher discontinuation rates in both arms						
Zhang, 2017	Low	Low	Low	Low	Low	**Low**
Nicholas, 2014	Low	Low	High	Low	Low	**High**
Note: Differential discontinuation rates						
Poewe, 2007	Low	Low	Low	Low	Low	**Low**
Mizuno, 2007	Low	Low	High	Low	Low	**High**
Note: Higher discontinuation rates in both arms and no measure to account for that						
Pahwa, 2007	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Differential discontinuation rates but per protocol analysis showed similar results to ITT						
Lieberman, 1997	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Higher discontinuation rates in both arms						
Schapira, 2011	Low	Low	Low	Low	Low	**Low**
COMT Inhibitors						
Poewe, 2003	Low	Low	High	Low	Low	**High**
Note: Differential discontinuation rates						
Reichmann, 2005	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Higher discontinuation rates in both arms; used ITT-observed cases only						
Brooks, 2002	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Higher discontinuation rates in both arms; used ITT observed cases only						
Lees, 2016	Low	Low	Low	Low	Low	**Low**
Takeda, 2020	Low	Low	Low	Low	Low	**Low**

Studies (Author, Year)	Randomization Process	Deviation from the Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
MAO-B Inhibitors						
Hattori, 2018	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Higher discontinuation rates in both arms						
Rascol, 2005	Low	Low	Some concerns	Low	Low	**Some concerns**
Note: Differential discontinuation rates						
Schwid, 2005	Low	Low	Low	Low	Low	**Low**
Zhang, 2018	Low	Low	Low	Low	Low	**Low**
Zhang, 2013	Low	Low	Low	Low	Low	**Low**

COMT: catechol-O-methyl transferase Inhibitors, ITT: intention-to-treat, MAO-B: Monoamine oxidase-B.

Evaluation of Clinical Trial Diversity

We evaluated the demographic diversity of clinical trials using the ICER-developed Clinical trial Diversity Rating (CDR) Tool.[106] The CDR tool was designed to evaluate the three demographic characteristics described in Table D1.8. Representation for each demographic category was evaluated by quantitatively comparing clinical trial participants with disease-specific prevalence/incidence estimates, using the metric "Participant to Disease-prevalence Representation Ratio" (PDRR). Next, a representation score between 0 to 3 was assigned based on the PDRR estimate (See Table D1.9 for the PDRR cut points that correspond to each representation score). Finally, based on the total score of the demographic characteristics (e.g., race and ethnicity), the categories "Good," "Fair," or "Poor" are used to communicate the overall level of diversity of a clinical trial. The description of the rating categories for each demographic characteristic is provided in Table D1.10.

Table D1.8. Demographic Characteristics and Categories

Demographic Characteristics	Categories
1. Race and Ethnicity*	Racial categories: • White • Black or African American • Asian • American Indian and Alaskan Native • Native Hawaiian and Other Pacific Islanders Ethnic Category: • Hispanic or Latino
2. Sex	• Female • Male
3. Age	• Older adults (≥65 years)

*Multinational trials: For multinational clinical trials, our approach is to evaluate only the subpopulation of patients enrolled from the US on racial and ethnic diversity

Table D1.9. Representation Score

PDRR	Score
0	0
>0 and Less Than 0.5	1
0.5 to 0.8	2
≥0.8	3

PDRR: Participant to Disease-prevalence Representation Ratio

Table D1.10. Rating Categories

Demographic Characteristics	Demographic Categories	Maximum Score	Rating Categories (Total Score)
Race and Ethnicity*	Asian, Black or African American, White, and Hispanic or Latino	12	Good (11-12) Fair (7-10) Poor (≤6)
Sex	Male and Female	6	Good (6) Fair (5) Poor (≤4)
Age	Older adults (≥65 years)	3	Good (3) Fair (2) Poor (≤1)

*American Indian or Alaskan Native & Native Hawaiian or Other Pacific Islander are not factored into the overall racial and diversity rating. However, information on enrollment and PDRR estimates are reported when reliable prevalence estimates are available.

Results

Table D1.11. Diversity Ratings on Race and Ethnicity, Sex, and Age (Older Adults)

Trial	Race and Ethnicity	Sex	Age (Older Adults)
TEMPO-1	Fair	Good	Fair
TEMPO-2	Fair	Good	Fair
TEMPO-3	Fair	Good	Fair

NR: not reported

Table D1.11 presents the clinical trial diversity ratings on race and ethnicity, sex, and age (older adults) for the three Tavapadon trials. Table D1.12 presents the prevalence data, trial data, PDRR, and overall ratings for each demographic category and trial.

Race and Ethnicity: All three tavapadon trials were rated as "fair" for race and ethnicity as they underrepresented Black/African American patients (0.90% of trial participants in TEMPO-1, 0.70% of trial participants in TEMPO-2, and 1.2% of trial participants in TEMPO-3 were Black/African American, vs. 5.90% of patients nationwide with Parkinson's disease) and TEMPO-1 and TEMPO-3 specifically underrepresented Asian patients (0.40% of trial participants in TEMPO-1, and 0.80% of trial participants in TEMPO-3 were Asian vs. 2.30% of patients nationwide with Parkinson's disease).

Sex: All of the Tavapadon trials for which a rating could be assigned were rated as "good" for sex.

Age: TEMPO-1, TEMPO-2 and TEMPO-3 were assigned a "fair" rating for age.

Table D1.12. Race and Ethnicity, Sex, and Age

	Race/Ethnicity							Sex			Age	
	White	Black/ AA	Asian	Hispanic/ Latino	AIAN	NHPI	Total Score	Male	Female	Total Score	≥65 Years	Total Score
Prevalence[107,108]	85.30%	5.90%	2.30%	2.60%	0.30%	NR	-	58.74%	41.26%	--	74.70%	-
TEMPO-1 [25]	97.2%	0.90%	0.40%	6%	0.20%	0.20%	-	64.7%	35.3%	-	52%	-
PDRR	1.14	0.15	0.17	2.31	0.67	NE	-	1.1	0.86	-	0.7	-
Score	3	1	1	3	-	-	8	3	3	6	2	2
Overall Rating	Fair							Good			Fair	
TEMPO-2 [26]	88.2%	0.70%	10.5%	5.3%	0.3%	0%	-	55.6%	44.4%	-	48%	-
PDRR	1.03	0.12	4.57	2.04	1	NE	-	0.95	1.08	-	0.64	-
Score	3	1	3	3	-	-	10	3	3	6	0	2
Overall Rating	Fair							Good			Fair	
TEMPO-3 [32]	96.8%	1.2%	0.8%	5.3%	0.4%	NR	-	63.3%	36.7%	-	56%	-
PDRR	1.13	0.2	0.35	2.04	1.33	NC	-	1.08	0.89	-	0.75	-
Score	3	1	1	3	-	-	8	3	3	6	2	2
Overall Rating	Fair							Good			Fair	

AA: African American, AIAN: American Indian or Alaskan Native, NR: Not Reported, NC: Not Calculated, NE: Not Estimated, NHPI: Native Hawaiian or Pacific Islander, PDRR: Participant to Disease-prevalence Representation Ratio

Note: PDRR ≥0.8 indicates adequate representation

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus.[109,110]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for these treatments, we scanned the ClinicalTrials.gov site to identify studies completed more than two years ago. Search terms include: “Parkinson’s Disease” and “Tavapadon”. We scanned the site to identify studies which would have met our inclusion criteria and for which no findings have been published and did not find any evidence of publication bias.

Data Synthesis and Statistical Analyses

Relevant data on key outcomes were summarized in evidence tables (see main Supplement Section D3) and synthesized both quantitatively and qualitatively in the body of the review. All data analyses were validated by an independent member of the research team. The validator reviewed and confirmed the data analysis methods, data format, and analysis code. The validator re-ran the analysis, validated the results, and confirmed the appropriateness of reported data.

Feasibility of Conducting Network Meta-Analysis (NMA)

We examined the feasibility of conducting an NMA because direct evidence for the comparative efficacy of tavapadon and listed comparators were not available. We examined whether there were notable differences in study populations, study design, intervention type, outcome definition and measurement, and analytic methods, as well as quality of these studies.

For Population 1, a total of 18 trials from a prior NMA and four new trials were deemed sufficiently similar in terms of population, design, intervention type, outcome definitions or measurement, and analytic methods were included in the NMAs.

For Population 2, a total of 21 trials from a prior NMA and one new trial were deemed sufficiently similar in terms of population, design, intervention type, outcome definitions or measurement, and analytic methods were included in the NMAs. Our NMA methods are described below.

NMA Methods

We conducted Bayesian NMAs using random-effects models to estimate a treatment effect for efficacy and safety outcomes including UPDRS Part II scores, UPDRS Part III scores, OFF times, ON times without troublesome dyskinesia, all cause discontinuations, discontinuations due to AEs, serious AEs, dyskinesia, somnolence, hallucinations, and hypotension. Except for the five trials, TEMPO-1, TEMPO-2, TEMO-3, Hattori et al. (2018) and Hattori et al. (2019),[25,29 26,32,51]

all other included trials with early-stage PD population utilized the original UPDRS scale. We converted MDS-UPDRS Part II and Part III scores from these two trials to original UPDRS scores using the conversion method suggested by Goetz et al. (2012) to use as inputs for the NMA analysis.[30]

The input for the NMA evaluating UPDRS Part II and III scores were the change from baseline in mean scores, and the outputs were the relative mean differences with 95% credible intervals using a normal likelihood and identity link. The inputs for the NMA evaluating OFF hours and on hours without troublesome dyskinesia were also the change from baseline in mean hours and the outputs were the relative mean differences with 95% credible intervals using a normal likelihood and identity link. The inputs for the NMAs evaluating all binary outcomes were the number of patients

with an event and the total number of patients. The outputs were the relative risks with 95% credible intervals generated with a binomial likelihood and a log link. Input data for each NMA are provided in Supplement Tables D1.13-D1.17.

We decided a priori that random-effects models would be more appropriate given the heterogeneity in the estimates. We performed both fixed- and random-effects models to confirm this a priori assumption. Model fit in terms of the posterior distribution for the deviance (Dbar), the deviance information criterion (DIC), and heterogeneity (I^2) confirmed the use of the random-effects models.

Table D1.13. Inputs Used in the NMA of UPDRS Scores for Tavapadon Monotherapy

Study	Treatment	Weeks	N	Part III Scores		Part II Scores	
				Mean	SE	Mean	SE
Whone 2003	Levodopa	24	75	-6.2	0.91	NR	NR
Whone 2003	Dopamine Agonist	24	87	-5.6	0.78	NR	NR
Rascol 1998	Levodopa	24	89	-8.4	1.08	NR	NR
Rascol 1998	Dopamine Agonist	24	179	-5.8	0.73	NR	NR
Holloway 2000	Levodopa	26	150	-10.6	1.39	-3.4	1.34
Holloway 2000	Dopamine Agonist	26	151	-7	1.33	-2.5	1.68
Adler 1997	Dopamine Agonist	24	116	-4.5	0.85	NR	NR
Adler 1997	Placebo	24	125	0.2	0.85	NR	NR
Singer 2007	Dopamine Agonist	39	199	-4.34	0.85	-0.85	0.32
Singer 2007	Placebo	39	199	-0.22	0.85	0.67	0.33
Giladi 2007	Dopamine Agonist	37	215	-5.2	0.66	-2.1	0.32
Giladi 2007	Placebo	37	118	-2.1	0.67	-0.1	0.31
Zhang 2016	Dopamine Agonist	24	123	-3.4	0.66	-1.4	0.32
Zhang 2016	Placebo	24	121	-0.3	0.67	0.1	0.31
Poewe 2011	Dopamine Agonist	33	213	-6.1	0.51	-2.1	0.23
Poewe 2011	Placebo	33	103	-1.1	0.71	-0.2	0.33
Shannon 1997	Dopamine Agonist	31	164	-4.7	0.51	-1.8	0.23
Shannon 1997	Placebo	31	171	1.3	0.71	0.4	0.33
Barone 2015	MAO-B Inhibitors	12	58	-0.88	0.56	-1.37	0.35
Barone 2015	Placebo	12	65	0.42	0.51	0.06	0.32
Hanagasi 2011	MAO-B Inhibitors	12	23	-4.35	1.09	-2.17	0.82
Hanagasi 2011	Placebo	12	25	-2.2	0.81	-1.54	0.72
Siderowf 2002	MAO-B Inhibitors	26	134	-2.71	0.59	-1.04	0.29
Siderowf 2002	Placebo	26	138	NA	NA	NA	NA
Hattori 2019	MAO-B Inhibitors	26	118	-3.73	1.09	0.12	0.42
Hattori 2019	Placebo	26	126	-0.4	0.81	2.11	0.37
Allain 1993	MAO-B Inhibitors	12	48	-7	1.60	-3.1	0.55
Allain 1993	Placebo	12	45	-3.7	1.39	-2.3	0.57
Larsen 1997	MAO-B Inhibitors	12	66	-12.8	1.31	NR	NR
Larsen 1997	Placebo	12	76	-10.5	1.06	NR	NR
Palhagen 1998	MAO-B Inhibitors	24	57	-1.5	0.62	0	0.28
Palhagen 1998	Placebo	24	39	2.5	0.70	0.9	0.38
TEMPO-1	Tavapadon	26	116	-7.08	0.62	-1.5	0.32
TEMPO-1	Placebo	26	148	0.75	0.53	0.8	0.28

MAO-B: monoamine oxidase Inhibitor, N: number, NA: not applicable, NR: not reported, SE: standard error

Table D1.14. Inputs Used in the NMA of Motor State Durations for Tavapadon Adjunctive Therapy

Study	Treatment	Weeks	N	OFF Time		Good ON Time	
				Mean	SE	Mean	SE
Lewitt 2006	Dopamine Agonist	24	113	-2.7	0.33	3.5	0.25
Lewitt 2006	Placebo	24	119	-0.9	0.30	1.1	0.35
Zhang 2017	Dopamine Agonist	12	174	-2.36	0.21	2.14	0.23
Zhang 2017	Placebo	12	172	-1.13	0.24	0.89	0.25
Nicholas 2014	Dopamine Agonist	12	94	-2.4	0.27	NR	NR
Nicholas 2014	Placebo	12	105	-1.5	0.30	NR	NR
Poewe 2007	Dopamine Agonist	23	201	-2.8	0.20	2.8	0.25
Poewe 2007	Placebo	23	101	-0.9	0.29	1.4	0.34
Pahwa 2007	Dopamine Agonist	24	201	-2.1	0.64	1.6	0.64
Pahwa 2007	Placebo	24	190	-0.3	0.64	0.1	0.65
Schapira 2011	Dopamine Agonist	18	160	-3.8	0.20	NR	NR
Schapira 2011	Placebo	18	174	-2.6	0.29	NR	NR
Poewe 2003	COMT Inhibitors	24	129	-1.6	0.22	NR	NR
Poewe 2003	Placebo	24	74	-0.9	0.40	NR	NR
Brooks 2002	COMT Inhibitors	24	80	-1.1	0.29	NR	NR
Brooks 2002	Placebo	24	44	-0.3	0.39	NR	NR
Fenelon 2002	COMT Inhibitors	12	99	-0.86	0.29	NR	NR
Fenelon 2002	Placebo	12	63	-0.54	0.39	NR	NR
Ferreira 2016	COMT Inhibitors	14	115	-1.94	0.24	1.82	0.25
Ferreira 2016	Placebo	14	120	-0.94	0.22	0.78	0.24
Lees 2016	COMT Inhibitors	14	147	-1.98	0.23	NR	NR
Lees 2016	Placebo	14	135	-1.08	0.24	NR	NR
Takeda 2020	COMT Inhibitors	14	145	-1.04	0.21	1	0.21
Takeda 2020	Placebo	14	147	-0.42	0.21	0.39	0.21
Hattori 2018	MAO-B Inhibitors	26	129	-1.4	0.22	1.25	0.20
Hattori 2018	Placebo	26	141	-0.5	0.21	0.36	0.19
Rascol 2005	MAO-B Inhibitors	18	222	-1.18	0.15	0.85	0.17
Rascol 2005	COMT Inhibitors	18	218	-1.2	0.15	0.85	0.17
Rascol 2005	Placebo	18	218	-0.4	0.15	0.03	0.17
Schwid 2005	MAO-B Inhibitors	26	149	-1.85	0.20	0.78	0.27
Schwid 2005	Placebo	26	159	-0.91	0.21	Ref	Ref
Zhang 2018	MAO-B Inhibitors	16	158	-1.25	0.16	NR	NR
Zhang 2018	Placebo	16	152	-0.76	0.16	NR	NR
Fernandez 2026	Tavapadon	26	153	-1.88	0.20	1.1	0.28
Fernandez 2026	Placebo	26	201	-0.93	0.18	Ref	Ref

COMT: catechol-O-methyl transferase inhibitors, MAO-B: monoamine oxidase B inhibitors, N: number, NR: not reported, Ref: reference, SE: standard error

Table D1.15. Inputs Used in the NMA of UPDRS Scores for Tavapadon Adjunctive Therapy

Study	Treatment	Weeks	N	UPDRS Part III		UPDRS Part II (On time only)	
				Mean	SE	Mean	SE
Lewitt 2006	Dopamine Agonist	24	113	-6.8	0.80	-3.1	0.47
Lewitt 2006	Placebo	24	119	-3.4	0.76	-0.5	0.36
Zhang 2017	Dopamine Agonist	12	174	-10.4	0.80	-4.2	0.38
Zhang 2017	Placebo	12	172	-3.6	0.76	-1.4	0.41
Nicholas 2014	Dopamine Agonist	12	94	-5.9	0.78	NR	NR
Nicholas 2014	Placebo	12	105	-2.5	0.80	NR	NR
Poewe 2007	Dopamine Agonist	23	201	-10.3	0.61	-4.6	0.31
Poewe 2007	Placebo	23	101	-4.3	0.93	-2.0	0.43
Mizuno 2007	Dopamine Agonist	16	121	-9.5	0.79	NR	NR
Mizuno 2007	Placebo	16	120	-4.5	0.72	NR	NR
Pahwa 2007	Dopamine Agonist	24	201	-6.5	1.81	-3.5	0.78
Pahwa 2007	Placebo	24	190	-1.7	1.83	-0.9	0.79
Lieberman 1997	Dopamine Agonist	32	181	-6.1	0.99	NR	NR
Lieberman 1997	Placebo	32	179	-3.1	1.00	NR	NR
Schapira 2011	Dopamine Agonist	18	160	-9.0	0.99	-2.1	0.46
Schapira 2011	Placebo	18	174	-4.7	1.00	-1.3	0.42
Poewe 2003	COMT Inhibitors	24	129	-3.2	1.19	-1.3	0.62
Poewe 2003	Placebo	24	74	Ref		Ref	
Reichmann 2005	COMT Inhibitors	13	174	-1.9	0.89	-2.3	0.28
Reichmann 2005	Placebo	13	96	Ref		-0.7	0.28
Brooks 2002	COMT Inhibitors	24	80	-4.5	1.33	NR	NR
Brooks 2002	Placebo	24	44	-4.3	1.90	NR	NR
Fenelon 2002	COMT Inhibitors	12	99	NR	NR	-1.0	0.59
Fenelon 2002	Placebo	12	63	NR	NR	-0.3	0.47
Lees 2016	COMT Inhibitors	14	147	-2.0	0.50	-0.5	0.20
Lees 2016	Placebo	14	135	-2.1	0.50	-1.0	0.30
Takeda 2020	COMT Inhibitors	14	145	-3.6	0.40	-0.2	0.30
Takeda 2020	Placebo	14	147	-2.4	0.40	-0.1	0.30
Hattori 2018	MAO-B Inhibitors	26	129	-4.7	0.83	NR	NR

Hattori 2018	Placebo	26	141	-2.9	0.85	NR	NR
Rascol 2005	MAO-B Inhibitors	18	222	-3.4	0.52	NR	NR
Rascol 2005	COMT Inhibitors	18	218	-3.2	0.48	NR	NR
Rascol 2005	Placebo	18	218	-0.5	0.50	NR	NR
Schwid 2005	MAO-B Inhibitors	26	149	-2.9	0.87	0.06	0.40
Schwid 2005	Placebo	26	159	Ref		Ref	
Zhang 2018	MAO-B Inhibitors	16	158	-3.3	0.55	NR	NR
Zhang 2018	Placebo	16	152	-1.8	0.55	NR	NR
Zhang 2013	MAO-B Inhibitors	12	119	-4.5	0.32	NR	NR
Zhang 2013	Placebo	12	125	-2.4	0.32	NR	NR
Fernandez 2026	Tavapadon	26	153	[redacted]			
Fernandez 2026	Placebo	26	201				

COMT: catechol-O-methyl transferase inhibitors, MAO-B: monoamine oxidase B inhibitors, N: number, NR: not reported, Ref: reference, SE: standard error, UPDRS: Unified Parkinson's Disease Rating Scale

Table D1.16. Inputs Used in the NMA of Binomial Outcomes Assessed in the Early-Stage PD Trials

Study	Treatment	Weeks	N	All Cause DCs	DC Due to AEs	Serious AEs	Somnolence	Hypotension
Whone 2003	Levodopa	48	75	20	4	17	33	NR
Whone 2003	Dopamine Agonist	48	87	23	13	18	7	NR
Rascol 1998	Levodopa	24	89	12	12	8	12	5
Rascol 1998	Dopamine Agonist	24	179	19	14	14	22	8
Holloway 2000	Levodopa	102	150	19	NR	NA	26	15
Holloway 2000	Dopamine Agonist	102	151	23	NR	NA	49	9
Adler 1997	Dopamine Agonist	24	116	37	27	NR	42	NR
Adler 1997	Placebo	24	125	20	13	NR	6	NR
Singer 2007	Dopamine Agonist	39	202	95	48	17	63	NR
Singer 2007	Placebo	39	203	108	17	12	17	NR
Giladi 2007	Dopamine Agonist	41	228	54	30	30	51	NR
Giladi 2007	Placebo	41	118	34	6	9	20	NR
Zhang 2016	Dopamine Agonist	24	124	11	6	6	10	1
Zhang 2016	Placebo	24	123	16	7	1	4	0
Watts 2007	Dopamine Agonist	28	181	39	25	NR	60	4
Watts 2007	Placebo	28	95	15	6	NR	19	4
Poewe 2011	Dopamine Agonist	33	223	49	24	16	70	NR
Poewe 2011	Dopamine Agonist	33	213	37	20	11	81	NR
Poewe 2011	Placebo	33	103	12	4	4	15	NR
Shannon 1997	Dopamine Agonist	33	164	28	22	NR	31	16
Shannon 1997	Placebo	33	171	34	24	NR	14	10
Viallet 2013	Dopamine Agonist	15	56	NR	8	1	NR	3
Viallet 2013	MAO-B Inhibitors	15	53	NR	3	1	NR	1
Barone 2015	MAO-B Inhibitors	12	58	9	4	2	NR	NR
Barone 2015	Placebo	12	65	8	0	1	NR	NR
Olanow 2009	MAO-B Inhibitors	36	288	15	9	NR	2	2
Olanow 2009	Placebo	36	595	50	17	NR	9	5
Hanagasi 2011	MAO-B Inhibitors	12	23	NR	0	NR	NR	NR
Hanagasi 2011	Placebo	12	25	NR	0	NR	NR	NR
Hattori 2019	MAO-B Inhibitors	26	118	7	3	4	NR	NR
Hattori 2019	Placebo	26	126	26	8	8	NR	NR
Poewe 2015	MAO-B Inhibitors	48	84	21	14	29	2	8
Poewe 2015	Placebo	48	90	15	7	23	5	3

Study	Treatment	Weeks	N	All Cause DCs	DC Due to AEs	Serious AEs	Somnolence	Hypotension
Siderowf 2002	MAO-B Inhibitors	26	134	8	NR	6	NR	NR
Siderowf 2002	Placebo	26	138	3	NR	4	NR	NR
Allain 1993	MAO-B Inhibitors	12	43	10	1	NR	NR	NR
Allain 1993	Placebo	12	42	4	4	NR	NR	NR
Larsen 1997	MAO-B Inhibitors	12	73	NR	16	NR	NR	NR
Larsen 1997	Placebo	12	81	NR	11	NR	NR	NR
Palhagen 1998	MAO-B Inhibitors	24	81	9	NR	NR	NR	NR
Palhagen 1998	Placebo	24	76	7	NR	NR	NR	NR
TEMPO-1	Tavapadon	31	354	102	64	14	12	16
TEMPO-1	Placebo	31	175	27	6	11	5	4
TEMPO-2	Tavapadon	31	151	57	36	7	6	6
TEMPO-2	Placebo	31	153	23	6	2	5	0

AE: adverse event, COMT: catechol-O-methyl transferase Inhibitors, DC: discontinuation, MAO-B: monoamine oxidase B inhibitors, n: number, NR: not reported, PD: Parkinson's disease

Table D1.17. Inputs Used in the NMA of Binomial Outcomes Assessed in the Adjunct Therapy PD Trials

Study	Treatment	Weeks	N	All DCs	DC due to AEs	Serious AEs	Somnolence	Hypotension	Dyskinesia	Hallucinations
Lewitt 2006	Dopamine Agonist	24	120	37	18	NR	38	2	16	8
Lewitt 2006	Placebo	24	120	26	11	NR	33	8	8	3
Zhang 2017	Dopamine Agonist	12	174	14	8	6	NR	NR	11	NR
Zhang 2017	Placebo	12	172	21	7	6	NR	NR	7	NR
Nicholas 2014	Dopamine Agonist	16	94	14	5	0	9	2	14	10
Nicholas 2014	Placebo	16	108	27	17	5	4	7	3	1
Poewe 2007	Dopamine Agonist	20	405	53	25	34	49	17	55	24
Poewe 2007	Placebo	20	101	26	6	9	8	5	3	1
Lieberman 1998	Dopamine Agonist	24	95	21	15	NR	18	16	32	NR
Lieberman 1998	Placebo	24	54	19	9	NR	6	10	7	NR
Mizuno 2007	Dopamine Agonist	16	121	23	13	6	15	NR	14	12
Mizuno 2007	Placebo	16	122	26	14	3	10	NR	2	2
Pahwa 2007	Dopamine Agonist	24	202	34	13	8	14	11	27	12
Pahwa 2007	Placebo	24	191	57	10	7	7	3	5	2
Lieberman 1997	Dopamine Agonist	32	181	30	24	NR	NR	29	111	NR
Lieberman 1997	Placebo	32	179	39	30	NR	NR	20	73	NR
Schapira 2011	Dopamine Agonist	18	164	16	8	5	18	3	27	9
Schapira 2011	Placebo	18	178	19	7	6	24	2	14	1
Poewe 2003	COMT Inhibitors	24	197	48	41	NR	NR	NR	67	7
Poewe 2003	Placebo	24	104	15	10	NR	NR	NR	27	43
Reichmann 2005	COMT Inhibitors	13	174	27	18	NR	NR	NR	16	NR
Reichmann 2005	Placebo	13	96	18	8	NR	NR	NR	5	NR
Brooks 2002	COMT Inhibitors	24	203	49	38	NR	NR	NR	44	6
Brooks 2002	Placebo	24	97	16	14	NR	NR	NR	10	1
Fenelon 2002	COMT Inhibitors	12	99	21	17	9	NR	NR	31	0
Fenelon 2002	Placebo	12	63	16	7	6	NR	NR	8	4
Ferreira 2016	COMT Inhibitors	14	238	24	13	12	NR	NR	1	6
Ferreira 2016	Placebo	14	121	11	8	6	NR	NR	0	2
Lees 2016	COMT Inhibitors	14	150	26	18	9	NR	NR	36	NR
Lees 2016	Placebo	14	136	14	10	5	NR	NR	11	NR
Takeda 2020	COMT Inhibitors	14	145	18	8	3	NR	NR	18	NR
Takeda 2020	Placebo	14	147	6	3	2	NR	NR	4	NR

Study	Treatment	Weeks	N	All DCs	DC due to AEs	Serious AEs	Somnolence	Hypotension	Dyskinesia	Hallucinations
Hattori 2018	MAO-B Inhibitors	26	129	26	21	10	4	NR	21	5
Hattori 2018	Placebo	26	141	22	9	4	1	NR	10	1
Rascol 2005	COMT Inhibitors	18	227	30	16	12	3	4	14	8
Rascol 2005	MAO-B Inhibitors	18	231	23	7	12	3	5	12	5
Rascol 2005	Placebo	18	229	35	11	17	2	0	9	3
Schwid 2005	MAO-B Inhibitors	26	149	17	NR	18	NR	NR	27	NR
Schwid 2005	Placebo	26	159	19	NR	14	NR	NR	16	NR
Zhang 2018	MAO-B Inhibitors	16	163	12	6	7	1	6	11	2
Zhang 2018	Placebo	16	158	10	5	5	2	0	12	0
Zhang 2013	MAO-B Inhibitors	12	119	11	3	1	0	NR	0	NR
Zhang 2013	Placebo	12	125	14	6	1	1	NR	1	NR
Fernandez 2026	Tavapadon	27	251	93	43	17	13	15	25	14
Fernandez 2026	Placebo	27	254	49	23	14	11	3	4	3

AE: adverse event, COMT: catechol-O-methyl transferase Inhibitors, DC: discontinuation, MAO-B: monoamine oxidase B inhibitors, n: number, NR: not reported, PD: Parkinson's disease

NMA Limitations

There were limitations to our NMAs. First, TEMPO trials defined early-stage PD as HY stage I-II, whereas older trials defined early PD as HY stages I-III. We heard from clinical experts that HY stages alone do not reflect the severity of PD disease. Other factors including number of years since diagnosis, patient age, and/or the UPDRS scores are also important in determining early versus advanced stages of PD. These additional baseline factors were comparable across all the trials included in the early-stage PD population, supporting the inclusion of all trials in the early PD analysis. In addition, only 2-19% participants were identified as stage III in these older trials, suggesting majority of the trial participants were stages I-II and thus comparable to the TEMPO trials population. Second, only seven out of 17 trials used the Hauser diary and the remaining trials used diaries that were similar, but not an exact match. To validate the use of all diary types in the NMA, we conducted a sensitivity analysis including only those seven trials that used the Hauser diary and findings were consistent with the base-case model. Third, only three trials from early-stage PD population and five from levodopa adjunct therapy population reported ICD events. Due to the few trials, we only conducted a fixed- effects NMA for the latter population whereas other NMAs for efficacy and safety outcomes used random-effects approach. Fourth, while we used random-effects models to account for some of the heterogeneity, there were some differences in trial populations in terms of prior conventional therapies used, concomitant medications, disease duration, demographic or clinical risk factors, and follow-up periods that should be acknowledged. Fifth, standard deviation or standard error data were not available for efficacy outcomes in several studies. As such, we imputed the highest standard error data available for each treatment comparisons from other studies as the most conservative approach. Finally, some comparisons in the NMA results of hallucinations and dyskinesia in early-stage PD population were associated with large credible intervals that were impossible to interpret and signaled uncertainty due to limited evidence, variability in the number of events across the trials, and/or poor model convergence. Additional data on these outcomes are required to reliably conduct NMAs on these outcomes.

Additional Clinical Effectiveness Results

Additional Evidence

Population 1: Patients with Early PD

NMA Evidence Base

For Population 1, a total of 46 early-stage PD trials were identified from Zhuo et al. (2016) and 18 of them were included in this review.[6] The reasons for excluding 28 trials were wrong population,[52,53] wrong intervention or comparators of interest,[111,112] allowed dopamine therapy during trial,[112] dosage formulation not of interest,[113] extensions of original trials or post-hoc studies,[75,114-121] less than 12 weeks of maintenance period,[122-133] and other design issues.[134,135] Although we did not require at least 12 weeks of follow-up during the search to gather all conducted trials, we deemed a minimum follow-up period was necessary to compare with 26 weeks data from tavapadon trials and this cut-OFF point was previously used in the guidelines.[99]

PD MED Trial (Early Disease Part)

PD MED was a large, open-label, randomized trial conducted in the United Kingdom and consisted of two parts: early disease and adjuvant treatment. In the early disease randomization part, a total of 1,620 participants were randomly assigned 1:1:1 to receive either levodopa, dopamine agonists, or MAO-B inhibitors. In the PD MED trial early disease part, participants were enrolled if they had untreated PD or those who had been treated for <6 months with dopamine agonists. Participants with dementia were excluded from this trial. A majority of these patients (N=1,058) were randomized among all three treatment options, 348 participants were only randomized between dopamine agonists and levodopa, and 214 participants were only randomized between dopamine agonists and MAO-B inhibitors. Two primary endpoints of this trial were patient rated functional status on the mobility subscale of the 39-item Parkinson's Disease Questionnaire (PDQ-39) and quality-adjusted life-years (QALYs) derived from the EuroQol EQ-5D.[27]

Additional Trials from New Search

Zhang et al. (2016) was a Phase III trial comparing a dopamine agonist (rotigotine transdermal patch ≤8 mg/day) with placebo in a total of 247 patients with early-stage PD.[28] Finally, Hattori et al. (2019) was also a Phase III trial involving two weeks of placebo run-in, followed by randomization of 244 early-stage PD patients to either an MAO-B inhibitor (rasagiline 1 mg/day) or placebo for 26 weeks.[29]

Population 2: Patients on Levodopa Experiencing Motor Fluctuations

NMA Evidence Base

For Population 2, a total of 33 PD trials were identified from Sako et al. (2023) and 21 of them were included in this review.[31] The reasons for excluding 12 trials were unpublished trial (NCT01268891), lower baseline OFF hours,[136] dose changed during the maintenance period,[137,138] and less than 12 weeks of maintenance period.[139-146]

PD MED trial (Adjuvant Treatment Part)

In the PD MED trial adjuvant treatment part, a total of 236 participants were randomized among all three treatment options, 134 participants were only randomized between MAO-B inhibitors and COMT inhibitors, and 130 participants were only randomized between dopamine agonists and COMTs.[33]

Additional Clinical Benefits

Population 1: Patients with Early PD

UPDRS Scores

We conducted two sensitivity analyses for UPDRS Part III and Part II scores excluding trials rated as "high" risk of bias. In both cases, findings were generally similar to the base-case models. See Supplement Tables D1.18-D1.19.

Table D1.18. NMA Results for UPDRS Part III Scores Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives Excluding High RoB Trials

Tavapadon				
0.14 (-3.48, 3.77)	Levodopa			
-2.82 (-5.29, -0.37)	**-2.97 (-5.64, -0.28)**	Dopamine Agonists		
-4.76 (-7.20, -2.15)	**-4.90 (-8.23, -1.44)**	-1.94 (-3.95, 0.24)	MAOBs	
-7.17 (-9.15, -5.15)	**-7.32 (-10.33, -4.26)**	**-4.35 (-5.77, -2.89)**	**-2.41 (-4.0, -0.95)**	Placebo

MAOBs: monoamine oxidase-B inhibitors, RoB: risk of bias

Each box represents the estimated relative mean difference and 95% credible interval. Values less than 0 indicate greater benefit. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect SUCRA.

Table D1.19. NMA Results for UPDRS Part II Scores Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives Excluding High RoB Trials

Tavapadon				
0.90 (-3.41, 5.40)	Levodopa			
0.05 (-0.93, 1.02)	-0.86 (-5.20, 3.35)	Dopamine Agonists		
-0.59 (-1.56, 0.43)	-1.49 (-5.92, 2.79)	-0.63 (-1.43, 0.21)	MAOBs	
-1.87 (-2.66, -1.06)	-2.77 (-7.16, 1.47)	**-1.91 (-2.46, -1.35)**	**-1.27 (-1.89, -0.71)**	Placebo

MAOBs: monoamine oxidase-B inhibitors, RoB: risk of bias

Each box represents the estimated relative mean difference and 95% credible interval. Values less than 0 indicate greater benefit. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect SUCRA.

Health-Related Quality of Life (HRQoL)

Improvements on the PDQ-39 total scores were also greater at week 33 for two different formulations of a particular dopamine agonists (mean difference -2.3 to 5 vs. placebo) in the Poewe et al. (2011) study, but one comparison failed to reach statistical significance.[14] Treatment with an MAO-B inhibitor demonstrated a reduction in both PDQ-39 total scores and mobility scores compared to treatment with placebo (mean difference -5.2 and -3.5, respectively), but only difference in mobility scores achieved statistical significance.[16] However, in another recent study by Hattori et al. (2019), there was no difference in PDQ-39 mobility scores between an MAO-B and placebo.[29]

Population 2: Patients on Levodopa Experiencing Motor Fluctuations

Motor State Durations

We conducted a sensitivity analysis for OFF time hours excluding trials rated as "high" risk of bias. The NMA showed similar findings to the base-case models. See Supplement Table D1.20.

Table D1.20. NMA Results for Daily OFF Times (Hours) Comparing Tavapadon with Other Therapeutic Alternatives as Adjunct to Levodopa Excluding High RoB Trials

Tav + Lev				
-0.55 (-1.26, 0.18)	DA + Lev			
-0.73 (-1.21, -0.26)	-0.18 (-0.86, 0.49)	COMTs + Lev		
-0.76 (-1.23, -0.28)	-0.21 (-0.88, 0.47)	-0.02 (-0.38, 0.34)	MAOBs + Lev	
-1.50 (-1.89, -1.12)	**-0.95 (-1.56, -0.35)**	**-0.77 (-1.05, -0.49)**	**-0.75 (-1.04, -0.47)**	Pbo + Lev

COMTs: Catechol-O-methyltransferase inhibitors, DAs: dopamine agonists, Lev: levodopa, MAOBs: monoamine oxidase-B inhibitors, Pbo: placebo, RoB: risk of bias, Tav: tavapadon

Each box represents the estimated relative mean difference and 95% credible interval. A negative mean difference is favorable. Estimates in bold signify that the 95% credible interval does not contain 0. The treatment order does not reflect SUCRA. Treatment order does not reflect SUCRA.

UPDRS Scores

These NMA results (see Tables D1.21 and D1.22) are qualitatively described in the main section of the report.

Table D1.21. NMA Results for UPDRS Part III Scores Comparing Tavapadon Adjunctive Therapy with Other Therapeutic Alternatives

Tav + Lev				
2.59 (-0.25, 5.38)	**DA + Lev**			
-0.57 (-3.33, 2.21)	**-3.16 (-4.49, -1.75)**	**COMTs + Lev**		
0.05 (-2.70, 2.85)	**-2.53 (-3.89, -1.12)**	0.63 (-0.61, 1.82)	**MAO-Bs + Lev**	
-2.08 (-4.69, 0.55)	**-4.66 (-5.68, -3.63)**	**-1.50 (-2.45, -0.62)**	**-2.13 (-3.07, -1.21)**	**Pbo + Lev**

COMTs: Catechol-O-methyltransferase inhibitors, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, DAs: dopamine agonists, Tav: tavapadon

Each box represents the estimated relative mean difference and 95% credible interval. Values less than 0 indicate greater benefit. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect SUCRA.

Table D1.22. NMA Results for UPDRS Part II Scores Comparing Tavapadon Adjunctive Therapy with Other Therapeutic Alternatives

Tav + Lev				
0.96 (-1.54, 3.48)	**DA + Lev**			
-0.72 (-3.18, 1.78)	**-1.69 (-3.10, -0.24)**	**COMTs + Lev**		
-1.37 (-4.45, 1.75)	-2.33 (-4.66, 0.01)	-0.64 (-2.97, 1.66)	**MAO-Bs + Lev**	
-1.30 (-3.59, 0.98)	**-2.27 (-3.31, -1.23)**	-0.58 (-1.59, 0.37)	0.06 (-2.05, 2.15)	**Pbo + Lev**

COMTs: Catechol-O-methyltransferase inhibitors, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, DAs: dopamine agonists, Tav: tavapadon

Each box represents the estimated relative mean difference and 95% credible interval. Values less than 0 indicate greater benefit. Estimates in bold signify that the 95% credible interval does not contain 0. Treatment order does not reflect SUCRA.

Health-Related Quality of Life (HRQoL)

In the TEMPO-3 trial, although no data were presented, investigators reported no differences in changes from baseline in PDQ-39 total scores or mobility scores between tavapadon and placebo.[32] Nine trials reported data on PDQ-39 scores between the comparators of interest and placebo.[43-45,48-51,54,57] In all cases, treatments with comparators of interest (either dopamine agonists or COMT inhibitors or MAO-B inhibitors demonstrated numerical improvements in either total scores or mobility scores compared to placebo. However, differences between treatments reached statistical significance in only three trials evaluating dopamine agonists and one trial evaluating an MAO-B inhibitor. See Table D1.23.

Table D1.23. Parkinson's Disease Questionnaire (PDQ-39) Scores in the Adjunct Therapy PD Trials

Study	Arms	N	PDQ-39 Total Score		PDQ Mobility Score	
			Change from Baseline (SE)	Treatment Difference (95% CI); p-value	Change from Baseline (SE)	Treatment Difference (95% CI); p-value
Poewe et al. (2007)	**Dopamine Agonist 1**	201	-5.1 (10.1)	-3.8 (NR); p=0.001	-10.0 (16.8)	-8.0 (NR); p<0.0001
	Dopamine Agonist 2	204	-4.7 (9.2)	-3.4 (NR); p=0.003	-8.8 (15.1)	-6.8 (NR); p<0.0001
	Placebo	100	-1.3 (9.4)	Ref	-2.0 (15.9)	Ref
Pahwa et al. (2007)	**Dopamine Agonist**	201	NR		-4.9 (3.36)*	-6.8 (95% CI: -10.07, -3.53); p < 0.001
	Placebo	190			1.9 (3.42)*	Ref
Schapira et al. (2011)	**Dopamine Agonist 1**	165	-13.1 (NR)	-6.9 (NR); p=0.003	NR	
	Dopamine Agonist 2	149	-9.1 (NR)	-2.9 (NR); p=0.23		
	Placebo	164	-6.2 (NR)	Ref		
Study	**Arms**	**N**	**Change from Baseline (SE)**	**Treatment Difference (95% CI); p-value**	**Change from Baseline (SE)**	**Treatment Difference (95% CI); p-value**
Reichmann et al. (2005)*	**COMT Inhibitor**	174	-0.3 (6.9)	-0.60 (95% CI: -2.50, 1.31); NR	NR	
	Placebo	96	0.6 (6.8)	Ref		
Ferreira et al. (2016)	**COMT Inhibitor 1**	115	-2.8 (0.9)	-0.2 (NR); p=0.90	NR	
	COMT Inhibitor 2	120	-4.0 (0.9)	-1.4 (NR); p=0.28		
	Placebo	120	-2.6 (0.9)	Ref		
Lees et al. (2017)	**COMT Inhibitor**	147	-4.4 (1.0)	0.4 (NR); p=0.78	NR	
	Placebo	135	-4.8 (1.0)	Ref		
Takeda et al. (2020)	**COMT Inhibitor**	145	-2.0 (0.7)	0 (NR); p=0.99	NR	
	Placebo	147	-2.0 (0.6)	Ref		
Hattori et al. (2018)	**MAO-B Inhibitor**		NR		-2.80 (1.61)	-6.15 (95% CI: -10.45, -1.81); p=0.006
	Placebo				3.36 (1.52)	Ref
Zhang et al. (2018)	**MAO-B Inhibitor**	163	NR		-4.1 (1.2)	-2.5 (95% CI: -5.59, 0.53); p=0.104
	Placebo	158			-1.6 (1.2)	Ref

CI: confidence interval, COMT: catechol-O-methyltransferase inhibitors, n: number, MAO-B: monoamine oxidase B inhibitors, NR: not reported, PDQ: Parkinson's disease questionnaire, Ref: reference, SE: standard error

*Reported summary index score.

Additional Harms

Population 1: Patients with Early PD

NMA Evidence

Thirteen trials reported data on serious AEs. The NMA showed no significant differences in serious adverse events between tavapadon and any of its therapeutic alternatives as well as in comparisons of any of these to placebo. See Table D1.24.

Table D1.24. NMA Results for Serious AEs Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives

Tavapadon				
0.61 (0.19, 2.18)	Levodopa			
0.64 (0.24, 1.84)	1.05 (0.52, 2.08)	DAs		
0.80 (0.31, 2.41)	1.32 (0.48, 3.70)	1.25 (0.60, 2.70)	MAO-Bs	
0.90 (0.41, 2.26)	1.49 (0.62, 3.57)	1.41 (0.83, 2.50)	1.14 (0.63, 1.96)	Placebo

DAs: dopamine agonists, MAO-Bs: monoamine oxidase-B inhibitors

Each box represents the estimated relative risk and 95% credible interval. Any credible interval that includes 1 indicates no statistically significant differences. Treatment order does not reflect SUCRA.

Fourteen trials reported data on somnolence. The NMA showed no significant differences in risk of somnolence between tavapadon and any of its therapeutic alternatives. Dopamine agonists had significantly higher risks of somnolence compared to the placebo group (RR 2.2) and MAO-B inhibitors (RR 6.3). See Table D1.25.

Table D1.25. NMA Results for Somnolence Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives

Tavapadon				
0.69 (0.13, 3.70)	Levodopa			
0.35 (0.08, 1.41)	0.51 (0.20, 1.27)	DAs		
2.22 (0.31, 16.67)	3.23 (0.51, 25.00)	**6.25 (1.28, 33.33)**	MAO-Bs	
0.76 (0.21, 2.71)	1.10 (0.37, 3.33)	**2.17 (1.20, 4.00)**	0.35 (0.07, 1.52)	Placebo

DAs: dopamine agonists, MAO-Bs: monoamine oxidase-B inhibitors

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Treatment order does not reflect SUCRA.

Ten trials reported data on orthostatic hypotension. The NMA showed no significant differences in risk of orthostatic hypotension between tavapadon and any of its therapeutic alternatives as well as in comparisons of any of these to placebo. See Table D1.26.

Table D1.26. NMA Results for Hypotension Comparing Tavapadon Monotherapy with Other Therapeutic Alternatives

Tavapadon				
2.27 (0.33, 20.00)	Levodopa			
3.03 (0.61, 16.67)	1.35 (0.43, 4.00)	DAs		
2.86 (0.53, 20.00)	1.25 (0.22, 7.14)	0.93 (0.26, 3.57)	MAO-Bs	
3.33 (0.89, 14.29)	1.49 (0.31, 6.25)	1.10 (0.39, 2.78)	1.19 (0.35, 3.45)	Placebo

DAs: dopamine agonists, MAO-Bs: monoamine oxidase-B inhibitors

Each box represents the estimated relative risk and 95% credible interval. Any credible interval that includes 1 indicates no statistically significant differences. Treatment order does not reflect SUCRA.

Additional Direct Evidence from TEMPO Trials

We present direct evidence on outcomes that could not be evaluated through an NMA. There was no data reported on dyskinesia in the TEMPO-1 trial. TEMPO-2 trial found no cases of dyskinesia in either group. A total of 11 trial participants receiving tavapadon 15 mg experienced hallucinations whereas none in tavapadon 5 mg or placebo group. Six trial participants treated with tavapadon flexible doses experienced hallucinations compared to none in the placebo group in the TEMPO-2 trial. Of note, none of these trials provided any definition related to hallucinations.

PD MED Trial (Early Disease Part)

At seven-years follow-up, the estimated all-cause discontinuation probabilities reached 7%, 50%, and 72% for levodopa, dopamine agonists, and MAO-B inhibitors, respectively. The estimated discontinuations due to AEs were 2% for levodopa, 28% for dopamine agonists, and 23% for MAO-B inhibitors. Eight participants treated with dopamine agonists reported to have experienced ICD events and discontinued the treatment compared to one in the MAO-B inhibitors and none in the levodopa group. A total of 16 serious AEs were recorded during this trial: three for levodopa, nine for dopamine agonists, and four for MAO-B inhibitors. Finally, there were no differences in seven-year risks of dementia or developing motor fluctuations or mortality between levodopa and combined groups (i.e., either a dopamine agonist or an MAO-B inhibitor) or between the dopamine agonists and MAO-B inhibitors individually.[27]

Population 2: Patients on Levodopa Experiencing Motor Fluctuations

NMA Evidence

Sixteen trials reported data on serious AEs. The NMA showed no significant differences in serious adverse events between tavapadon and any of its therapeutic alternatives as well as in comparisons of any of these to placebo. See Table D1.27.

Table D1.27. NMA Results for Serious AEs Comparing Tavapadon Adjunct Therapy with Other Therapeutic Alternatives

Tav + Lev				
1.39 (0.53, 3.70)	DAs + Lev			
1.23 (0.46, 3.23)	0.89 (0.45, 1.71)	COMTs + Lev		
1.04 (0.40, 2.74)	0.75 (0.39, 1.42)	0.84 (0.46, 1.52)	MAO-Bs + Lev	
1.16 (0.50, 2.70)	0.83 (0.52, 1.31)	0.94 (0.59, 1.52)	1.11 (0.71, 1.75)	Pbo + Lev

COMTs: Catechol-O-methyltransferase inhibitors, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, DAs: dopamine agonists, Tav: tavapadon

Each box represents the estimated relative risk and 95% credible interval. Any credible interval that includes 1 indicates no statistically significant differences. Treatment order does not reflect SUCRA.

Twelve trials reported data on somnolence. The NMA showed no significant differences in risk of somnolence between tavapadon and any of its therapeutic alternatives as well as in comparisons of any of these to placebo. See Table D1.28.

Table D1.28. NMA Results for Somnolence Comparing Tavapadon Adjunct Therapy with Other Therapeutic Alternatives

Tav + Lev				
0.97 (0.34, 2.76)	DAs + Lev			
1.27 (0.20, 10.00)	1.30 (0.27, 7.69)	COMTs + Lev		
1.39 (0.34, 5.88)	1.43 (0.49, 4.35)	1.10 (0.19, 5.56)	MAO-Bs + Lev	
1.10 (0.41, 2.94)	1.14 (0.81, 1.61)	0.88 (0.15, 4.10)	0.80 (0.28, 2.18)	Pbo + Lev

COMTs: Catechol-O-methyltransferase inhibitors, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, DAs: dopamine agonists, Tav: tavapadon

Each box represents the estimated relative risk and 95% credible interval. Any credible interval that includes 1 indicates no statistically significant differences. Treatment order does not reflect SUCRA.

Ten trials reported data on orthostatic hypotension. The NMA showed no significant differences in risk of orthostatic hypotension between tavapadon and any of its therapeutic alternatives. Dopamine agonists had a significantly lower risks of orthostatic hypotension (RR 0.13) compared to the MAO-B inhibitors. See Table D1.29.

Table D1.29. NMA Results for Hypotension Comparing Tavapadon Adjunct Therapy with Other Therapeutic Alternatives

Tav + Lev				
4.76 (0.69, 50)	DAs + Lev			
0.78 (0.03, 16.78)	0.16 (0.01, 1.75)	COMTs + Lev		
0.60 (0.03, 8.77)	**0.13 (0.01, 0.83)**	0.78 (0.10, 5.55)	MAO-Bs + Lev	
4.17 (0.63, 33.33)	0.86 (0.39, 1.64)	5.26 (0.52, 100)	**6.67 (1.14, 50.0)**	Pbo + Lev

COMTs: Catechol-O-methyltransferase inhibitors, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, DAs: dopamine agonists, Tav: tavapadon
Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Treatment order does not reflect SUCRA.

Fifteen trials reported data on hallucinations. The NMA showed no significant differences in risk of hallucinations between tavapadon and any of its therapeutic alternatives. Dopamine agonists had higher risks of hallucinations compared to the COMT inhibitors (RR 3.4) as well as to the placebo (RR 3.3). See Table D1.30.

Table D1.30. NMA Results for Hallucinations Comparing Tavapadon Adjunct Therapy with Other Therapeutic Alternatives

Tav + Lev				
1.14 (0.26, 5.88)	DAs + Lev			
4.0 (0.87, 25.0)	**3.45 (1.43, 9.09)**	COMTs + Lev		
3.13 (0.54, 20.0)	2.63 (0.84, 8.33)	0.76 (0.24, 2.14)	MAO-Bs + Lev	
3.85 (0.97,16.67)	**3.33 (1.92, 5.88)**	0.95 (0.45, 1.93)	1.25 (0.48, 3.45)	Pbo + Lev

COMTs: Catechol-O-methyltransferase inhibitors, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, DAs: dopamine agonists, Tav: tavapadon
Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Treatment order does not reflect SUCRA.

A total of 22 trials reported data on dyskinesia.[19,32,40-59] Tavapadon had almost five times higher risk of dyskinesia than those treated with placebo (RR 5.3) and four times higher risk of dyskinesia than those treated with MAO-B inhibitors (RR 3.8). There was no significant difference between tavapadon and dopamine agonists as an adjunct therapy. See Table D1.31.

Table D1.31. NMA Results for Dyskinesia Comparing Tavapadon Adjunct Therapy with Other Therapeutic Alternatives

Tav + Lev				
2.38 (0.75, 8.33)	DAs + Lev			
2.86 (0.91, 11.11)	1.19 (0.77, 1.18)	COMTs + Lev		
3.85 (1.89, 14.29)	1.59 (0.95, 3.03)	1.35 (0.81, 2.33)	MAO-Bs + Lev	
5.26 (1.82, 20.0)	**2.22 (1.67, 3.23)**	**1.89 (1.35, 2.63)**	1.41 (0.88, 2.17)	Pbo + Lev

COMTs: Catechol-O-methyltransferase inhibitors, Lev: levodopa, MAO-Bs: monoamine oxidase-B inhibitors, Pbo: placebo, DAs: dopamine agonists, Tav: tavapadon

Each box represents the estimated relative risk and 95% credible interval. Estimates in bold signify that the 95% credible interval does not contain 1. Treatment order does not reflect SUCRA.

PD MED Trial (Adjuvant Treatment Part)

At five-years follow-up, the estimated all-cause discontinuation probabilities reached 55%, 56%, and 58% for dopamine agonists, COMT inhibitors, and MAO-B inhibitors as adjunct therapies to levodopa, respectively. The estimated discontinuations due to AEs were 46% for dopamine agonists, 34% for COMT inhibitors, and 40% for MAO-B inhibitors as adjunct therapies to levodopa. Four participants treated with dopamine agonists reported to have experienced ICD events and discontinued the treatment compared to none in the MAO-B inhibitors or COMT inhibitors group as adjunct therapies to levodopa. Nine serious AEs were reported but treatments received by these nine participants were not disclosed. Finally, there were no differences in 10-year risks of dementia or mortality between dopamine agonists and combined groups (i.e., either an MAO-B inhibitor or a COMT inhibitor) or between the MAO-B inhibitors and COMT inhibitors individually.[33]

D2. Evidence Tables

Table D2.1. Overview of the Early-Stage Parkinson's Disease Trials

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Levodopa Trials						
Whone et al. (2003)[7]	Randomized, double-blind, flexible titration, multinational study N=186	-Ropinirole maximum dose 24 mg per day (n=93) -Levodopa maximum dose 1000 mg per day (n=93)	**Inclusion:** Patients who were in HY stages 1-2.5, had less than 2 years of disease duration. **Exclusion:** Pronounced head tremors, postural dizziness, or severe psychiatric or systemic illness.	4 weeks	Week 4 until Year 2	Mean percent reduction in side-to-side averaged putamen F-dopa uptake. Outcome of interest for this review is change from baseline in UPDRS Part III score at Year 2.
Rascol et al. (1998)[8]	Randomized, double-blind, multicenter study N=268	-Ropinirole maximum dose of 24 mg per day. Mean dose of 9.7 mg per day. Titrated until patient has clinical response (n=179) -Levodopa maximum dose of 1,200 mg per day. Mean dose of 464 mg per day. Titrated weekly until optimum dose (n=89)	**Inclusion**: Patients who were in HY Stages 1-3, requiring dopaminergic therapy. **Exclusion**: Severe psychiatric or systemic illness, drug or alcohol dependence, severe dementia, or postural hypotension.	13 weeks	6-month interim analysis of a 5-year long study.	Change from baseline in UPDRS Part III Scores at Month 6.

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Holloway et al. (2000)[9]	Randomized, double-blind, multicenter, controlled trial N=301	-Pramipexole, 0.75, 1.5, or 3 mg per day. Minimum of 1.5 mg, but could escalate (n=151) -Carbidopa/ Levodopa 37.5/150 or 75/300 mg per day.(n=150)	**Inclusion**: Patients were in HY stages 1-3, <7 years disease duration requiring dopaminergic therapy. **Exclusion**: History of dopaminergic complications, atypical parkinsonism symptoms, or severe comorbidities.	10 weeks	21 months	Time to the first instance of dyskinesia, wearing off, or motor fluctuations. Outcome of interest for this review is change in UPDRS scores by Month 21.
Dopamine Agonist Trials						
Adler et al. (1997)[10]	Prospective, randomized, double-blind, flexible-dose study N=241	-Ropinirole, 0.75 to 24 mg per day. Minimum dose after titration was 4.5 mg per day (n=116) -Placebo (n=125)	**Inclusion:** Patients who were in HY stages 1-3 requiring dopaminergic therapy. **Exclusion:** Treatment with anti-hypertensives or ropinirole, severe systemic illness, psychosis, dementia, history of severe dizziness or fainting. Diagnosis of hypertension, or recent history of alcohol or substance dependence.	4 weeks	8 weeks	Change from baseline in UPDRS Part III at Week 12.

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Singer et al. (2007)[11]	Flexible-dose, randomized, double-blind trial N=614	-Ropinirole 0.75 to 24 mg per day (n=205) -Sumanirole 1 to 16 mg per day (n=204) -Placebo (n=205)	**Inclusion:** Patients who were in HY stages 1-3 requiring dopaminergic therapy but not levodopa. **Exclusion:** Any dose of dopamine agonists within 30 days prior, and levodopa use for more than a year cumulatively within the prior 2 years.	13 weeks	26 weeks	Change from baseline in combined UPDRS Parts II+III, as well as Part II and Part III alone at Week 40
Giladi et al. (2007)[12]	Randomized, double-blind, flexible-dose, controlled trial N=561	-Ropinirole, 0.75, 1.5, 3, 6, or 15 mg per day (n=228) -Rotigotine, 2, 4, 6, or 8 mg per day (n=215) -Placebo (n=118)	**Inclusion:** Patients who were in HY stages 1-3 with UPDRS Part III score of at least 10. **Exclusion:** MMSE score <25, with clinically significant psychiatric or cognitive condition. Did not take dopaminergic therapy within 28 days of baseline visit, or had taken levodopa or dopamine agonists for more than 6 months. Cardiac dysfunction was another exclusion criteria.	13 weeks to achieve maximum dose of ropinirole. 4- week titration phase for the maximum dose of rotigotine. Rotigotine maintained 13 week sham titration period.	24 weeks	Change from baseline in UPDRS Parts II+III combined scores, and Parts II and III subscale scores at Week 37. Safety follow-up at Week 41.

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Zhang et al. (2016)[28] NCT01646268	Phase III, randomized, double-blind, flexible-dose, controlled trial N=247	-Rotigotine titrated to optimum dose, covering 2, 4, 6, or 8 mg per day (n=124) -Placebo patch (n=123)	**Inclusion**: Patients who were in HY stages 1-3, disease duration less than 5 years, MMSE ≥ 25, UPDRS Part III ≥ 10. **Exclusion**: A diagnosis of dementia, active psychosis, hallucinations, depression, impulse control disorders, epilepsy, or treatment with levodopa or dopamine agonist therapy within 28 days before baseline or more than 6 months of therapy.	4 weeks	24 weeks	Change from baseline in UPDRS Parts II+III combined, and Parts II and III subscores at Week 24 of the maintenance phase

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Watts et al. (2007)[13]	Phase III, randomized, double-blind, flexible-dose, controlled trial N=277	-Rotigotine, titrated to maximally tolerated level, at 2, 4, or 6 mg per day (n=181). -Placebo matching patch (n=96).	**Inclusion:** Patients who were HY stages 1-3, with less than5 years of disease duration, and UPDRS Part III score≥10, and an MMSE score ≥25. **Exclusion:** Did not have any dopaminergic therapy within 28 days before baseline visit. Did not have dopaminergic therapy for more than 6 months. No hepatic, renal, or cardiac dysfunction. No epilepsy, history of seizures, strokes, or a TIA within the past year.	3 weeks	24 weeks	Change from baseline in UPDRS Parts II and III subscores at end of maintenance
Poewe et al. (2011)[14] NCT00479401	Randomized, double-blind, flexible-dose, placebo-controlled trial N=539	-Pramipexole Extended Release, flexible titration to 0.375, 0.75, 1.5, 2.25, 3, 3.75, or 4.5 mg per day (n=223) -Pramipexole Immediate Release 0.375, 0.75, 1.5, 2.25, 3, 3.75, or 4.5 per day (n=213) -Matching Placebo (n=103)	**Inclusion**: Patients were in HY stages 1-3, < 5 years disease duration, requiring dopaminergic therapy. **Exclusion:** MMSE score <24, psychiatric disorders impairing trial participation, hypotension, or creatine clearance <50 mL/min	7 weeks	26 weeks	Change from baseline in UPDRS Parts II and III combined scores, and Parts I, II, and III subscores at Week 33

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Shannon et al. (1997)[15]	Randomized, double-blind, placebo-controlled trial N=335	-Pramipexole titrated to maximum tolerated dose, ranging between 0.375 to 4.5 mg per day (n=164) -Placebo (n=171)	**Inclusion**: Patients were in HY stages 1-3 not taking levodopa at study enrollment. Up to 6 months levodopa treatment allowed. **Exclusion**: Atypical or secondary parkinsonism, dementia, psychosis, hypertension, or unstable medical illness.	7 weeks	24 weeks	Change from baseline in UPDRS Parts II and III subscores at Week 31
Viallet et al. (2013)[22]	Randomized, head-to-head, double-blind trial N=109	-Rasagiline 1 mg (n=53) -Pramipexole 1.5 mg per day (n=56)	**Inclusion:** Patients were in HY stages 1-3, with less than 12 weeks treatment with levodopa. **Exclusion:** Pregnant or breastfeeding women, patients with liver disease, or significant comorbidities.	3 weeks	12 weeks	Serious adverse events and clinically important adverse events by Week 15
Monoamine Oxidase Inhibitor Trials						
Barone et al. (2015)[16]	Randomized, double-blind, multi-center, placebo-controlled trial N=123	-Rasagiline 1 mg per day (n=58) -Placebo (n=65)	**Inclusion:** Patients were in HY stages 1-3, a Beck Depression Inventory score ≥15, and stable dopaminergic treatment. **Exclusion:** MMSE scores <26, major depressive disorder, or psychotic symptoms.	12 weeks		Change from baseline in Beck Depression Inventory was primary outcome for this study at Week 12. Secondary outcomes include UPDRS Parts I-IV at Week 12.

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Olanow et al. (2009)[17] NCT00256204	Delayed start, placebo-controlled, randomized, double-blind trial N=1176	-Rasagiline 1 mg (n=288) -Rasagiline 2 mg (n=300) -Placebo (delayed start rasagiline group) (n=588)	**Inclusion: Patients were in** HY stages less than 3 not taking anti-parkinsonism treatment. **Exclusion**: Anti-parkinsonism treatment duration > 3 weeks or taking rasagiline within 120 days before study. PD duration >18 months. HY stage 3 and above.	The first phase of this trial lasted 36 weeks. The second phase of this trial lasted until week 72.		Change from baseline in total UPDRS scores at Week 36 and Week 72. Change from baseline in Parts II and III subscores at Week 36 and 72. Week 36 data was used in this review.
Hanegasi et al. (2011)[23] NCT00696215	Exploratory, randomized, double-blind, placebo-controlled trial N=55	-Rasagiline 1 mg per day (n=23) -Placebo (n=25)	**Inclusion:** Patients were in HY stages 1-3. **Exclusion:** Patients were excluded if they had a diagnosis of Parkinson's dementia, untreated systemic disorders, or were taking psychoactive drugs.	12 weeks		Change from baseline in cognitive testing scores, and depression scores, anxiety, and UPDRS Part III at Week 12
Hattori et al. (2019)[29] NCT02337725	Phase III, randomized, double-blind, placebo-controlled trial N=253	-Rasagiline 1 mg per day (n=118) -Placebo (n=126)	**Inclusion:** Patients were in HY stages 1-3 and had an MDS-UPDRS Part II + Part III total score ≥14. **Exclusion:** Use of investigational drug within 90 days of trial, had an MMSE score less than or equal to 24. Did not use certain anti-parkinsonism medication for specified periods of time.	26 weeks		Change from baseline in MDS-UPDRS Parts II+III, and Parts I, II, III subscores at Week 26

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Poewe et al. (2015)[18] NCT00977665	Randomized, double-blind, placebo-controlled trial N=174	-Rasagiline 1 mg per day (n=84) -Placebo (n=90)	**Inclusion:** Patients were included if they had possible or probable parkinsonian variant multiple system atrophy, according to published clinical criteria. **Exclusion**: Orthostatic symptoms, speech impairment, swallowing impairment, ambulation impairment, frequent falling, or taking disallowed drugs.	48 weeks		Change from baseline in Unified Multiple System Atrophy Rating Scale at Week 48 (Outcome not of interest)
Siderowf et al. (2002)[147]	Randomized, double-blind, placebo-controlled trial N=404	-Rasagiline 1 mg per day (n=134) -Rasagiline 2 mg per day (n=132) -Placebo (n=138)	**Inclusion:** HY stage <3. **Exclusion:** unstable medical problems, atypical parkinsonism, psychiatric disorders, or an MMSE score <23.	1 week	25 weeks	Change from baseline in total UPDRS scores, and Parts II and III subscores at Week 26
Allain et al. (1993)[148]	Randomized, double blind placebo-controlled trial N=93	-Selegiline 10 mg per day (n=48) -Placebo (n=45)	**Inclusion:** Patients were in HY stages below 2.5. **Exclusion:** Depression, psychosis, dementia, progressive supranuclear palsy, or Shy-Drager Syndrome.	3 months		Change from baseline in HY, Hamilton Depression Rating Scale, UPDRS total, and mental state, daily living, and motor examination subscores at Month 3

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Larsen et al. (1997)[24]	Interim analysis of a randomized, double-blind parallel-group trial N=154	-Selegiline 10 mg (n=73) -Placebo (n=81)	**Inclusion:** Patients were in HY stages <3, and were de novo or received levodopa <6 months. **Exclusion:** Diagnosis of secondary parkinsonism, dementia, psychosis, or unstable or serious comorbidities.	5-year long study. Interim analysis gathered when at least 80% of patients have been followed up for 3 years.		Change from baseline in UPDRS Parts I-IV subscales and total by Year 5.
Palhagen et al. (1998)[21]	Randomized, double-blind, placebo-controlled trial N=157	-Selegiline 10 mg (n=81) -Placebo (n=76)	**Inclusion:** Patients were included with previously untreated idiopathic PD. **Exclusion:** Secondary parkinsonism, severe comorbidities, who were over 75 years of age, or with a history of drug or alcohol dependency.	7 years		Time to initiation of levodopa therapy. UPDRS scale scores by evaluated at regular intervals by Year 7
Koller et al. (1993)[149]	Randomized-controlled trial N=800	-Selegiline 10 mg and Tocopherol 2000 IU per day (n=197) -Selegiline 10 mg and placebo (n=202) -Tocopherol 2000 IU and placebo (n=202) -Placebo (n=199)	**Inclusion:** Patients were in HY stages <2, with a disease duration <5 years.	24 months		Functional disability sufficient to initiate levodopa therapy, with a maximum of 24 months of follow-up

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome, Follow-Up Time)
Tavapadon Trials						
Pahwa et al. (2026)[25] **TEMPO-1** **NCT04201093**	Phase III, randomized, double-blind placebo-controlled trial N=529	-Tavapadon 5 mg (n=177) -Tavapadon 15 mg (n=177) -Placebo (n=175)	**Inclusion:** Patients were in HY stages 1-2, with a disease duration < 3 years, <3 months of levodopa. **Exclusion:** Essential tremor, atypical or secondary parkinsonism syndromes, or any clinically significant medical or psychiatric conditions.	4 weeks	27 weeks	Change from baseline in MDS-UPDRS Parts I, II, III, and Parts II and III combined. Week 31
Fernandez et al. (2026)[26 1018] **TEMPO-2** **NCT04223193**	Phase III, randomized double blind placebo controlled flexible dose trial N=304	-Tavapadon 5 to 15 mg daily (n=151) -Placebo (n=153)	**Inclusion:** Patients were in HY stages 1-2, with disease duration <3 years. **Exclusion:** Clinical features consistent with essential tremor, atypical or secondary parkinsonism, or ICD.	Unknown	27 weeks	Change from baseline in MDS-UPDRS scores at Week 27

F-dopa: fluorodopa, HY stage: Hoehn and Yahr Stage, ICD: Impulse Control Disorder, IU: International Units, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale, mg: milligram, MMSE: Mini-Mental State Examination, PD: Parkinson's Disease, UPDRS: Unified Parkinson's Disease Rating Scale

Table D2.2. Overview of the Adjunctive Therapies to Levodopa Trials for Parkinsons Disease

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Dopamine Agonists Adjunctive to Levodopa Trials						
LeWitt et al. (2006)[40]	Randomized-controlled, double-blind trial N=351	-Rotigotine 8 mg (n=119) -Rotigotine 12 mg (n=111) -Placebo (n=120)	**Inclusion:** Patients were in HY stages 2-4 with inadequate response to levodopa. **Exclusion:** Dementia.	5 weeks	24 weeks	Change in absolute time in OFF state by Week 25 after maintenance as measured by home diaries
Zhang et al. (2017)[41] **NCT01646255**	Phase III, randomized-controlled, double-blind trial N=346	-Rotigotine 4, 6, or 8 mg per day. Rotigotine titrated to optimal dose in trial, with maximum possible dose of 16 mg per day. (n=172) -Placebo (n=174)	**Inclusion:** Patients were in HY stages 2-4 with inadequate response to levodopa. **Exclusion:** Dementia, inability to differentiate between ON-OFF states, or severe psychiatric symptoms.	7 weeks	12 weeks	Change in absolute OFF time by Week 12 of Maintenance Phase
Nicholas et al. (2014) [42] **NCT00522379**	Phase III, randomized-controlled, double-blind trial N=514	-Rotigotine 2 mg (n=101) -Rotigotine 4 mg (n=107) -Rotigotine 6 mg (n=104) -Rotigotine 8 mg (n=94) -Placebo (n=108)	**Inclusion:** Patients were in HY stages 2-4 with inadequate response to levodopa. **Exclusion:** Inability to differentiate between ON-OFF states.	4 weeks	12 weeks	Change in OFF time from baseline until Week 12 of Maintenance Phase

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Lieberman et al. (1997)[58]	Double-blind, placebo-controlled trial, followed by an open-label extension period N=360	-Pramipexole, 0.375 to 4.5 mg per day, titrated to maximum tolerated dose. (n=181) -Placebo (n=179)	**Inclusion:** Patients were in HY stages 2-4 with inadequate response to levodopa. **Exclusion:** Atypical parkinsonism, cognitive impairment, or severe comorbidities.	7 weeks	24 weeks	Change from baseline in on and OFF ratings for UPDRS Part II and Part III. Changes in on/OFF time by Week 32
Poewe et al. (2007)[43] **NCT00244387**	Randomized-controlled, double-blind trial N=506	-Pramipexole, 0.375 to 4.5 mg, titrated to optimal dose (n=201) -Rotigotine, 4 to 16 mg per day, titrated to optimal dose (n=204) -Placebo (n=101)	**Inclusion:** Patients were in HY stages below 2 in on state and below 4 in state. >2.5 hours in OFF state/day experiencing motor fluctuations. **Exclusion:** Atypical parkinsonism, psychosis or hallucinations, or MMSE scores <25.	7 weeks	16 weeks	Change from baseline in total OFF time by Week 16 of maintenance period

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Lieberman et al. (1998)[59]	Randomized-controlled, double-blind trial N=149	-Ropinirole 3 mg per day after dose titration, potential increase to 24 mg per day (n=95) -Placebo (n=54)	**Inclusion**: Patients were in HY stages 2-4 in OFF state and experiencing predictable motor fluctuations. **Exclusion**: Unpredictable on-OFF phenomena, or clinically significant medical or laboratory dysfunction.	2 weeks	6 months	Change from baseline in number of patients who achieved a 20% or over reduction in levodopa use and 20% or more reduction in OFF time. Other measures include change from baseline in OFF state at Month 6
Mizuno et al. (2007)[56]	Randomized-controlled, double-blind trial N=243	-Ropinirole 0.75 to 15 mg (n=121) -Placebo (n=122)	**Inclusion:** Patients were in HY stages 2-4, UPDRS Part III sum score of 10 at screening (ON state), who were experiencing motor fluctuations or whom levodopa could not be increased to an optimal level. **Exclusion**: Diagnosis of psychiatric disorders, hypotension, epilepsy, or cardiac disorders.	4 weeks	12 weeks	Change from baseline in UPDRS Part II and III, percentage in time OFF

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Pahwa et al. (2007)[57]	Randomized-controlled, double-blind trial N=393	-Ropinirole 2, 4, 6, 8, 12, 16, 20, or 24 mg (n=202) -Placebo (n=191)	**Inclusion**: Patients were in HY stages 2-4 experiencing suboptimal levodopa therapeutic response. **Exclusion**: Incapacitating peak dose phenomenon, significant clinical, psychiatric, or neurological disorders, or dementia, or drug or alcohol dependency, or hypotension.	3 weeks	21 weeks	Change in OFF time by Week 24
Schapira et al. (2011)[150]	Randomized-controlled, double-blind trial N=517	-Pramipexole ER titrated to optimized dose at 0.375, 0.75, 1.5, 2.25, 3.0, 3.75, or 4.5 mg once daily (n=164) -Pramipexole IR titrated to optimized dose at 0.125, 0.25, 0.50, 0.75, 1.0, 1.25, or 1.5 mg 3 times daily (n=175) -Placebo (n=178)	**Inclusion**: Patients were at HY stages 2-4 experiencing motor fluctuations and taking levodopa. **Exclusion**: MMSE scores <24, atypical parkinsonism, history of deep brain stimulation, psychiatric or non-PD medical disorders capable of impeding trial participation, or hypotension.	7 weeks	11 weeks	Change from baseline at Week 18 in UPDRS Parts II and III. Additionally, changes in daily OFF time as measured by daily diaries.
COMT Inhibitors Adjunctive to Levodopa Trials						

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Poewe et al. (2002)[19]	Randomized-controlled, double-blind trial N=301	-Entacapone 200 mg (n=197) -Placebo (n=104)	**Inclusion**: Levodopa responsive patients with idiopathic PD who needed an enhancement and/or smoothening of levodopa effects were included in this trial. **Exclusion:** Treatment with neuroleptics, neuroleptic antiemetics, catechol-structured drugs, monoamine oxidase (MAO)-A inhibitors or non-selective MAO inhibitors. Severe psychiatric or physical illness.	24 weeks		Change from baseline in total UPDRS scores. Change from baseline in on and OFF time at Week 24
Reichmann et al. (2005)[45]	Phase IV, randomized-controlled, double-blind trial N=270	-Entacapone 200 mg (n=174) -Placebo (n=96)	**Inclusion**: HY stages 1.5-4 experiencing mean 3 hours OFF time taking levodopa **Exclusion**: Symptomatic or secondary parkinsonism, dementia, other major psychiatric, systemic or metabolic disorders	13 weeks		Change in UPDRS Parts I-IV, and change in OFF time in patient diaries by Week 13
Brooks et al. (2003)[46]	Randomized-controlled, double-blind trial N=300	-Entacapone 200 mg (n=203) -Placebo (n=97)	**Inclusion:** Patients were included who were with or without fluctuations treated with levodopa. **Exclusion**: Atypical parkinsonism, dementia, or severe psychiatric or systemic disease.	6 months		Proportion in daily on time by Month 6

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Fenelon et al. (2003)[47]	Randomized-controlled, double-blind trial N=162	-Entacapone 200 mg (n=99) -Placebo (n=63)	**Inclusion**: Patients were in HY 2-4 stage, responsive to levodopa therapy experiencing wearing off. **Exclusion**: Severe peak-dose dyskinesia, severe psychiatric illness, dementia, psychosis, or any other major comorbidity impeding study participation.	3 months		Improvement in on and OFF time by Month 3
Ferreira et al. (2016)[48] **NCT01568073**	Randomized, placebo and active control, double-blind trial N=600	-Entacapone 200 mg (n=122) -Opicapone 5 mg (n=122) -Opicapone 25 mg (n-119) -Opicapone 50 mg (n=116) -Placebo (n=121)	**Inclusion**: Patients were in between Hoehn and Yahr stages 1–3 (during the on state), and had at least 1 year of clinical improvement with levodopa treatment. **Exclusion**: Prior use of entacapone, dyskinesia disability score > 3 on item 33 of UPDRS, or severe or unpredictable periods in the OFF state. Unstable cardiovascular, psychiatric, or other serious illness.	14-15 weeks		Change from baseline in OFF time in self-reported daily diaries by 14-15 weeks

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Lees et al. (2017)[49] NCT01227655	Randomized-controlled, double-blind trial N=427	-Opicapone 25 mg (n=129) -Opicapone 50 mg (n=154) -Placebo (n=144)	**Inclusion**: Patients were between HY 1-3,with 1 year levodopa improvement. **Exclusion**: Dyskinesia disability score >3 on item 33 UPDRS, severe or unpredictable off-periods.	14-15 weeks		Change from baseline in OFF time, with and without dyskinesia at 14-15 weeks
Takeda et al. (2020)[50]	Randomized-controlled, double-blind trial N=437	-Opicapone 25 mg (n=145) -Opicapone 50 mg (n=145) -Placebo (n=147)	**Inclusion**: Patients were between HY stages 1-3, with 1 year levodopa improvement. **Exclusion**: Non-idiopathic PD, dyskinesia disability score >3 item 33 UPDRS, severe and/or unpredictable off periods, treatment with prohibited medications.	14-15 weeks		Change from baseline in OFF time at 14-15 weeks
MAO-B Inhibitors Adjunctive to Levodopa Trials						
Hattori et al. (2018)[51]	Randomized-controlled, double-blind trial N=404	-Rasagiline 0.5 mg (n=134) -Rasagiline 1 mg (n=129) -Placebo (n=141)	**Inclusion**: Patients were between HY stages 2–4 in the OFF state, and mean OFF time of ≥2.5 hours per day. **Exclusion**: Severe dyskinesia or unstable systemic disease, MMSE score ≤24 at the start of the run-in period, and neurosurgery for PD.	26 weeks		Change from baseline in mean OFF time at Week 26 of the treatment period.

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Rascol et al. (2005)[52]	Randomized controlled, double-blind trial N=687	-Rasagiline 1 mg (n=231) -Entacapone 200 mg (n=227) -Placebo (n=229)	**Inclusion**: Patients had an HY score <5 in OFF state, with 1 h every day in the off-state, taking levodopa. **Exclusion**: Antidepressant use, cognitive impairment, or severe vascular or psychiatric disease.	18 weeks		Change from baseline in mean total daily OFF time at week 18
Schwid et al. (2005)[53]	Randomized-control double-blind trial N=472	-Rasagiline 0.5 mg (n=165) -Rasagiline 1 mg (n=149) -Placebo (n=159)	**Inclusion**: Patients were in HY stages below 5 in OFF state, with a stable levodopa dose. And more than 2.5 hours of off-time daily. **Exclusion**: Atypical or secondary parkinsonism, cognitive impairment, depression, unstable medical or neurological disorders.	26 weeks		Change from baseline in total daily OFF time during 26 weeks of treatment
Zhang et al. (2018) NCT01479530 [54]	Randomized-controlled, double-blind trial N=324	-Rasagiline 1 mg (n=165) -Placebo (n=159)	**Inclusion**: Patients were in HY stages <3 in on state, with an optimized levodopa dose, and more than 1 hour/day OFF time. **Exclusion**: Cognitive impairment, melanoma, disabling dyskinesias, or adverse reactions to tyramine-containing foods.	16 weeks		Change from baseline in mean daily OFF time at Week 16

Study	Design	Arms and Dosages	Inclusion/Exclusion Criteria	Titration	Maintenance	Primary Outcome (Outcome and Follow-Up Time)
Zhang et al. (2013)[55]	Randomized-controlled, double-blind trial N=244	-Rasagiline 1 mg (n=119) -Placebo (n=125)	**Inclusion**: Patients had a HY below 5 in OFF state, and were receiving levodopa therapy. **Exclusion**: Diagnosis of Parkinson's syndrome or Parkinson's plus syndrome, cognitive or psychiatric dysfunction	12 weeks		Change from baseline in mean on and OFF times at Week 12
Tavapadon Adjunctive to Levodopa Trial						
Fernandez et al. (2026)[32] **TEMPO-3** **NCT04542499**	Phase III, Randomized-controlled, double-blind trial N=507	-Tavapadon 5 to 15 mg flexible dose (n=255) -Placebo (n=252)	**Inclusion:** Patients were between HY stages of 2-3 in on state, with 2.5 hours of daily off-time, and taking at least 400 mg levodopa/day. **Exclusion**: Diagnosis of atypical or secondary parkinsonism, MoCA score <26, a history of impulse control disorder, history of psychosis or hallucinations for 12 months or less	8 weeks	12 weeks	Change from baseline to week 26 in total daily on time without troublesome dyskinesia in the Hauser Diary.

COMT Inhibitors: Catechol-O-methyl transferase inhibitor, HY stage: Hoehn and Yahr Stage, MAO-B: Monoamine oxidase-B inhibitors, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale, Mg: milligram, MMSE: Mini-Mental State Examination, MoCA: Montreal Cognitive Assessment, PD: Parkinson's Disease, TIA: transient ischemic attack, UPDRS: Unified Parkinson's Disease Rating Scale

Table D2.3. Overview of the Baseline Characteristics for Early Parkinson's Disease Therapy Trials

Trial	Arm	N	Age, Mean (SD)	Female, n, (%)	HY Stage (%)			Mean UPDRS Score (SD)		Duration, Years (SD)
					1	2	3	Part II	Part III	
Whone et al. (2003)[7]	Ropinirole 0.75 mg to 24 mg	87	61 (8.6)	31 (35.6)	19 (21.8)	39 (44.8)	NR	NR	19.2 (8.74)	1.3
	Levodopa 50 mg to 1000 mg	75	59.9 (9.23)	22 (29.3)	22 (12.8)	34 (45.3)	NR	NR	17.7 (8.2)	1.4
Rascol et al. (1998)[8]	Ropinirole 0.75 mg to 24 mg	179	63 (9)	66 (36.9)	23 (12.8)	66 (36.9)	17 (9.5)	NR	21.5 (10.5)	2.5
	Levodopa 50 mg to 1200 mg	89	63 (9)	38 (42.7)	20 (22.5)	33 (37.1)	9 (10.1)	NR	21.7 (11.3)	2.4
Holloway et al. (2000)[9]	Pramipexole 0.75 to 3 mg	151	61.5 (10.1)	55 (36.4)	27 (17.9)	75 (49.7)	5 (3.3)	9.1 (4.1)	22.3 (9.2)	1.5 (1.4)
	Carbidopa/levodopa 37.5/150 mg or 75/300 mg	150	60.9 (10.5)	51 (34)	33 (22)	78 (52)	9 (6.0)	8.3 (4.0)	22 (9.6)	1.8 (1.7)
Adler et al. (1997)[10]	Ropinirole 0.75 mg to 4.5 mg	116	62 (10.6)	46 (39.7)	32 (27.6)	70 (60.3)	14 (12.1)	NR	17.9 (8.8)	24.6 months (20.5)
	Placebo	125	63.8 (10.6)	45 (36)	37 (29.6)	73 (58.4)	15 (12)	NR	17.6 (8.1)	22.7 months (19.3)
Singer et al. (2007)[11]	Ropinirole up to 24 mg	202	65.4 (0.8)	74 (36.6)	NR*			8.1 (0.3)	19.5 (0.6)	1.23 (0.10)
	Placebo	203	64.8 (0.7)	80 (39.4)	NR *			8.5 (0.3)	20.4 (0.7)	1.38 (0.13)
Giladi et al. (2007)[12]	Rotigotine 2 mg, 4 mg, 6 mg, or 8 mg	215	61.1	97 (45)	52 (24)	133 (62)	28 (13)	9.3	23.8	1.4
	Ropinirole 0.75 mg, 1.5 mg, 3 mg, 6 mg or 15 mg	228	61.6	97 (40)	62 (27)	121 (53)	48 (21)	9.1	23.2	1.3
	Matching placebo	118	60.4	50 (42)	30 (25)	70 (59)	18 (15)	8.7	22.6	1.2
Zhang et al. (2016)[28]	Rotigotine 2 mg, 4 mg, 6 mg, or 8 mg	124	59.1 (10.3)	50 (40.3)	37 (29.8)	70 (56.5)	17 (13.7)	9.2 (4.7)	22.8 (10.2)	0.94 (1.17)
	Matching placebo	123	59.7 (10.1)	47 (37.2)	44 (35.8)	72 (58.5)	7 (5.7)	9.3 (4.0)	23.3 (9.4)	1.08 (1.27)

Trial	Arm	N	Age, Mean (SD)	Female, n, (%)	HY Stage (%)			Mean UPDRS Score (SD)		Duration, Years (SD)
					1	2	3	Part II	Part III	
Watts et al. (2007)[13]	Rotigotine 2 mg, 4 mg, or 6 mg	181	62.0 (10.3)	58 (32)	49 (27)	97 (54)	34 (19)	NR	NR	1.3 (1.3)
	Matching placebo	96	64.5 (10.7)	38 (40)	18 (19)	60 (63)	18 (19)	NR	NR	1.4 (1.3)
Poewe et al. (2011)[14]	Pramipexole extended release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, or 4.5 mg	223	61.3 (9.8)	96 (43)	75 (33.6)	148 (66.4)	NR	7.9 (4.3)	21.9 (9.9)	1.0 (1.2)
	Pramipexole immediate release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, or 4.5 mg	213	61.7 (9.6)	92 (43.2)	63 (29.6)	150 (70.4)	NR	7.8 (3.7)	21.1 (9.3)	1.1 (1.4)
	Matching placebo	103	62.0 (9.6)	52 (50.5)	30 (29.1)	73 (70.9)	NR	7.6 (4.4)	21.4 (11.7)	0.9 (1.0)
Shannon et al. (1997)[15]	Pramipexole 0.375 mg to 4.5 mg	164	62.7	132 (39.4)	NR	NR	NR	8.2	18.8	1.8
	Placebo	171			NR	NR	NR	8.3	18.8	
Viallet et al. (2013)[22]	Rasagiline 1 mg	53	63.2 (7.3)	16 (30.2)	NR			NR	NR	2.5 months (3.8)
	Pramipexole 0.375 mg to 1.5 mg	56	62.1 (6.2)	25 (44.6)				NR	NR	4.3 months (7.3)
Barone et al. (2015)[16]	Rasagiline 1 mg	58	66 (8.74)	31 (53.4)	9 (15.5)	29 (50.0)	3 (5.2)	NR	NR	3.7 (3.17)
	Placebo	65	66.1 (8.35)	27 (41.5)	9 (13.8)	34 (52.3)	5 (7.7)	NR	NR	4.8 (3.78)
Olanow et al. (2009)[17]	Rasagiline 1 mg	288	62.4 (9.7)	113 (39.2)	NR*			5.1 (2.8)	14.5 (6.3)	4.6 (4.7) months
	Placebo	595	62.1 (9.7)	224 (38)	NR*			5.2 (3)	13.9 (6.3)	4.4 (4.6) months

Trial	Arm	N	Age, Mean (SD)	Female, n, (%)	HY Stage (%)			Mean UPDRS Score (SD)		Duration, Years (SD)
					1	2	3	Part II	Part III	
Hanegasi et al. (2011)[23]	Rasagiline 1 mg	23	65.2 (9.5)	6 (26.1)	NR*			NR	23.09 (9.96)	4.09 (2.54)
	Placebo	25	67.6 (10.1)	9 (36)	NR*			NR	18.84 (8.62)	3.96 (2.26)
Hattori et al. (2019)[29]	Rasagiline 1 mg	118	67.4 (8.96)	65 (55.1)	NR*			7.2 (5.47) MDS-UPDRS	27.2 (13.8) MDS-UPDRS	1.97 (1.97)
	Placebo	126	65.4 (8.81)	72 (57.1)	NR*			7.0 (4.64) MDS-UPDRS	26.8 (11.59) MDS-UPDRS	1.56 (1.24)
Poewe et al. (2015)[18]	Rasagiline 1 mg	84	64.9 (8.5)	35 (42)	NR	NR	NR	NR	NR	0.7 (0.9)
	Placebo	90	65.1 (8.6)	39 (43)	NR	NR	NR	NR	NR	0.7 (0.8)
Siderowf et al (2002)[147]	Rasagiline1 mg	134	61.6 (10.3)	44 (32.8)	NR*			5.9 (3.4)	17.9 (8.9)	0.92 (1.24)
	Placebo	138	60.5 (10.8)	45 (32.6)	NR*			6.2 (3.5)	17.6 (8.8)	0.94 (1.1)
Allain et al. (1993)[148]	Selegiline 5 mg	48	64.5 (8.5)	23 (47.9)	NR*			8.1 (4.3)	22.5 (10.5)	NR
	Placebo	45	65.4 (10.1)	(44.4)	NR*			8.4 (4.0)	20.2 (9.0)	NR
Larsen et al. (1997)[24]	Selegiline 10 mg	73	64.3 (9.3)	30 (41.1)	NR*			9.8 (4.4)	24.9 (11.6)	2.1 (1.4)
	Matching placebo	81	64.3 (8.7)	37 (45.7)	NR*			9.2 (3.8)	22.8 (10.2)	2.0 (1.2)
Palhagen et al. (1998)[21]	Selegiline 10 mg	81	63.3 (9.1)	32 (39.5)	45 (55.6)	34 (42.0)	2 (2.4)	NR	16.7 (8.8)	1.9 (1.6)
	Placebo	76	64.2 (6.6)	32 (42.1)	49 (64.5)	24 (31.6)	3 (3.9)	NR	14.2 (8.6)	1.9 (1.3)

Trial	Arm	N	Age, Mean (SD)	Female, n, (%)	HY Stage (%)			Mean UPDRS Score (SD)		Duration, Years (SD)
					1	2	3	Part II	Part III	
Koller et al. (1993)[149]	Selegiline 5 mg	202	NR	NR	NR	NR	NR	NR	NR	NR
	Placebo	199	NR	NR	NR	NR	NR	NR	NR	NR
Pahwa et al. (2026)[25]	Tavapadon 5 mg	177	63.7 (9.8)	66 (37.3)	33 (18.6)	115 (65.0)	NR	7.1 (4.0)	24.1 (8.6)	0.75 (0.84)
	Tavapadon15 mg	177	63.8 (9.4)	58 (32.8)	36 (20.3)	127 (71.8)	NR	7.7 (4.2)	24.3 (9.1)	0.76 (0.80)
	Placebo	175	63.5 (9.6)	66 (36.0)	23 (13.1)	129 (73.7)	NR	7.4 (3.8)	24.7 (8.1)	0.69 (0.77)
Fernandez 2026[26]	Tavapadon 5-15 mg	151	63.1 (9)	67 (44.4)	38 (25.2)	89 (58.9)	NR	7.4 (4.3)	23.6 (8·8)	0.88 (0.78)
	Placebo	153	62.6 (9.4)	68 (44.4)	35 (22.9)	96 (62.7)	NR	6.9 (3.9)	23.1 (8.9)	0.85 (0.81)

HY Stage: Hoehn and Yahr Stage, MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale, mg: milligrams, N: number, NR: not reported, SD: Standard Deviation, UPDRS: Unified Parkinson's Disease Rating Scale

*Mean Hoehn-Yahr Stage available.

Table D2.4. Overview of the Baseline Characteristics for Adjunctive Therapy for Parkinson's Disease Therapy Trials

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
LeWitt et al. (2006)[40]	Rotigotine 8 mg	118	66.5 (10.0)	40 (33.9)	NR	NR	NR	6.7 (2.5)	7.7 (4.3)	13.3 (6.7)	27.2 (13.9)	760 (601)
	Placebo	120	66.3 (9.6)	46 (38.3)	NR	NR	NR	6.4 (2.6)	7.7 (4.0)	13.0 (6.9)	26.7 (14.5)	753 (470)

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
Zhang et al. (2016)[41]	Rotigotine 4 mg, 6 mg, or 8 mg	174	61.7 (8.8)	81 (46.6)	62 (35.6)-ON 93 (53.4)-OFF	5 (2.9) -ON 45 (25.9) -OFF	8.9 (2.7)	6.9 (2.7)	6.4 (2.6)	14.2 (5.8)	NR	593.9 (295.16)
	Matching placebo	172	62.8 (9.1)	62 (36)	69 (40.1)-ON 74 (43) -OFF	5 (2.9) -ON 61 (35.5)-OFF	8.8 (2.4)	6.8 (2.4)	6.8 (3.5)	14.3 (6.1)	NR	652.4 (330.8)
Nicholas et al. (2014)[42]	Rotigotine 8 mg	94	63.2 (11.6)	38 (40)	28 (30) -ON 54 (57) -OFF	1 (1) -ON 16 (17) -OFF	NR	6.4 (2.3)	7.5 (4.8)	11.7 (6.2)	23.9 (9.8)	643.0 (365.8)
	Rotigotine 6 mg	104	64.6 (10.4)	31 (30)	38 (37) -ON 57 (55) -OFF	3 (3) -ON 9 (9) -OFF	NR	6.4 (2.7)	7.8 (3.9)	12.6(6.4)	24.7 (13.1)	619 (376.4)
	Rotigotine 4 mg	107	64.6 (9.0)	28 (26)	32 (30) -ON 67 (63) -OFF	2(2) -ON 9(8) -OFF	NR	6.3 (2.3)	7.3 (3.9)	11.8 (6)	23.1 (11.3)	627.7(359.4)

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
	Rotigotine 2 mg	101	64.4 (10.5)	24 (24)	37 (37) -ON 58 (57) -OFF	3(3) -ON 18(18) -OFF	NR	6.4 (2.96)	7.5 (3.9)	12.1 (6.4)	25.3 (12.4)	643.3 (344.5)
	Placebo	108	64.8 (10.2)	34 (31)	29 (27) -ON 60 (56) -OFF	9 (8) -ON 21 (19) -OFF	NR	6.4 (2.6)	7.2 (3.8)	12.8 (6.4)	26.1 (12.5)	642.8 (420.3)
Lieberman et al. (1997)[58]	Pramipexole 0.375 mg to 4.5 mg	181	63.4	62 (34)	NR	NR	NR	NR	9.4	7.3/ 17.4 on/ OFF time	22.8	843.37 (578.86)
	Placebo	179	63.3	63 (35)	NR	NR	NR	NR	9	7.7/ 17.4 on/ OFF time	23.3	819.19 (466.08)
Poewe et al. (2007)[43]	Pramipexole 0.375 mg to 4.5 mg	200	63.2 (9.7)	88 (44)	NR	NR	NR	6.0 (2.5) OFF time	8.4 (4.7)	12.1 (6.0)	26.4 (11.6)	813 (459)
	Rotigotine 4 mg to 16 mg	201	64.3 (9.0)	69 (33%)	NR	NB	NR	6.2 (2.5) OFF time	8.9 (4.2)	12.3 (5.8)	26.3 (11.4)	795 (380)
	Placebo	100	65 (10.0)	29 (29)	NR	NR	NR	6.6 (2.8)	8.5 (5.0)	12.8 (6.2)	26.8 (11.4)	814 (398)

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
								OFF time				
Lieberman et al. (1998)[59]	Ropinirole 0.75 mg to 9 mg	95	NR	NR	38 (40)	18 (19)	NR	39.3 (23.3)	8.6 (4.7)	NR	NR	759 (422)
	Placebo	54	NR	NR	23 (42.6)	10 (18.5)	NR	43.4 (23.3)	9.4 (6.3)	NR	NR	843 (517)
Mizuno et al. (2007)[56]	Ropinirole 0.75 mg to 15 mg.	121	64.9 (9.53)	68 (56.2)	74 (61.2)	6 (5)	NR	NR	66.4 (44.86) months	NR	NR	NR
	Placebo	120	64.7 (9.31)	66 (55)	75 (62.5)	6 (5)	NR	NR	66.2 (49.25) months	NR	NR	NR
Pahwa et al. (2007)[57]	Ropinirole 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, 20 mg, or 24 mg	201	66.3 (9.2)	84 (42)	NR	NR	9.0 (2.8)	7.0 (2.8)	8.6 (4.8)	13.9 (6.2)	29.8 (12.9)	824 (424.4)
	Placebo	190	66.0 (9.7)	61 (32)	NR	NR	9.1 (2.7)	7.0 (2.6)	8.6 (5.2)	14.2 (6.8)	30.7 (14.4)	776 (357.3)
Schapira et al. (2011)[150]	Pramipexole extended release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg	164	61.6 (9.7)	72 (43.9)	NR	NR	NR	NR	6.1 (4.0)	12.7 (6.5)	29.0 (12.9)	568.0
	Pramipexole immediate release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0	175	62.0 (10.3)	77 (44)	NR	NR	NR	NR	6.6 (4.4)	12.3 (5.7)	28.3 (13.3)	609.7

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
	mg, 3.75 mg, or 4.5 mg divided into three daily doses.											
	Matching placebo pills	178	60.9 (9.7)	84 (47.2)	NR	NR	NR	NR	5.9 (3.8)	11.9 (6.1)	27.7 (13.6)	569.3
Poewe et al. (2003)[19]	Entacapone 200 mg.	197	60.7 (9.6)	118 (60)	NR	NR	10.0 (2.6)	6.2 (2.7)	8.3 (4.5)	NR	NR	570 (273)
	Placebo	104	61.1 (9.9)	54 (52)	NR	NR	9.7 (2.8)	6.7 (3.0)	9.5 (4.9)	NR	NR	572 (329)
Reichmann et al. (2005)[45]	Entacapone 200 mg	197	67 (8)	100 (46)	NR	NR	NR	NR	7.5 (4.7)	23.5 (10)	37.6 (13.2)	566 (243)
	Placebo	96	66 (9)	39 (41)	NR	NR	NR	NR	7.1 (4.0)	24.7 (12.3)	38.6 (17)	533 (231)
Brooks et al. (2002)[46]	Entacapone 200 mg	203	66.7 (9.15)	71 (35)	NR	NR	9.5 (2.5)*	7.0 (2.6)	7.8 (5.38)	11.7 (5.8)	23.9 (5.76)	NR
	Placebo	97	66.1 (8.78)	29 (30)	NR	NR	10.1 (2.8)	6.9 (2.9)	7.7 (5.3)	11.97 (6.27)	21.04 (12.01)	NR
Fenelon et al. (2003)[47]	Entacapone 200 mg	99	63.5 (9.96)	36 (33)	NR	NR	9.24	NR	NR	NR	NR	NR
	Placebo	63	65 (6.61)	25 (40)	NR	NR	9.155	NR	NR	NR	NR	NR
Ferreira et al. (2016)[48]	Entacapone 200 mg	122	63.7 (8.8)	46 (38)	NR	NR	9.6 (2.2)	6.5 (2.2)	7.1 (4.1)	NR	25.8 (13.8)	645 (323)
	Opicapone 50 mg	115	63.5 (9.2)	46 (40)	NR	NR	9.9 (2.1)	6.2 (1.8)	7.0 (3.8)	NR	28.4 (13.7)	695 (338)
	Placebo	121	64.3 (9.3)	50 (41)	NR	NR	10.0 (2.0)	6.2 (1.8)	7.7 (4.2)	NR	27.6 (11.7)	675 (302)

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
Lees et al. (2017)[49]	Opicapone 50 mg	147	65.5 (8.4)	58 (39.5)	NR	NR	NR	6.3 (2.2)	8.2 (4.5)	NR	22.5 (12.3)	700 (312)
	Placebo	135	61.5 (8.9)	64 (47.4)	NR	NR	NR	6.1 (2.3)	7.7 (3.7)	NR	22.5 (12.0)	714 (338)
Takeda et al. (2020)[50]	Opicapone 50 mg	145	67.4 (7.8)	85 (58.6)	NR	NR	10.5 (2.3)	6.0 (2.3)	7.7 (4.9)	NR	NR	445.3 (175.8)
	Placebo	147	68.5 (8.6)	64 (61.9)	NR	NR	9.9 (2.7)	6.3 (2.6)	7.5 (3.8)	NR	NR	422.3 (170.1)
Hattori et al. (2018)[51]	Rasagiline 1 mg	129	65.8 (8.5)	83 (64.3)	NR	NR	NR	6.1 (2.4)	9.5 (5)	14.1 (7.2) MDS-UPDRS	27.5 (13.1) MDS-UPDRS	420.7 (166.42)
	Rasagiline 0.5 mg	134	66.1 (8.74)	76 (56.7)	NR	NR	NR	6.3 (2.6)	8.5(4.8)	13.7(6.7) MDS-UPDRS	28.7(13.3) MDS-UPDRS	407.8(134.15)
	Placebo	141	66.3 (7.6)	88 (62.4)	NR	NR	NR	6.05 (2.3)	8.90 (4.5)	13.0 (7.3) MDS-UPDRS	26.8 (14) MDS-UPDRS	399.3 (141.03)
Rascol et al. (2005)[52]	Rasagiline 1 mg	231	63.9 (9)	77 (33)	NR	NR	NR	5.6 (2.4)	8.7 (4.9)	NR	NR	722 (334)
	Entacapone 200 mg	227	63 (9.4)	88(39)	NR	NR	NR	5.6 (2.6)	9.2 (4.7)	NR	NR	706 (321)

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
	Placebo	229	64.8 (8.8)	97 (42)	NR	NR	NR	5.6 (2.4)	8.8 (4.8)	NR	NR	697 (295)
Schwid et al. (2005)[53]	Rasagiline 1 mg	149	62.9 (8.9)	50 (33.6)	NR	NR	NR	6.3 (2.6)	8.8 (5.4)	5.8 (5.0) ON, 15.6 (6.8) OFF	20.8 (11.0) ON state	815 (471)
	Rasagiline 0.5 mg	164	62.6(9.5)	62 (37.8)	NR	NR	NR	6.0(2.0)	9.3(5.6)	5.6(4.8) ON, 15.7(6.6) OF	21.4(12.0) ON state	750(379)
	Placebo	159	64.5 (9.9)	55 (34.6)	NR	NR	NR	6 (2.2)	9.7 (4.9)	6.1 (5.1) ON, 15.5 (5.7) OFF	20.7 (10.3) ON state	821 (485)
Zhang et al. (2018)[54]	Rasagiline 1 mg	163	62.7 (8.9)	60 (37)	NR	NR	9.4 (2.4)	6.1 (2.6)	7.4 (4.8)	15.6 (7.2) OFF state, 6.8 (4.6) ON state	23.8 (10.5)	501 (222)
	Placebo	158	61.7 (9.9)	49 (31)	NR	NR	9.3 (2.5)	6.1 (2.7)	7.1 (4.3)	16.5 (7.5) OFF state, 7.3 (5.1) ON state	25.6 (10.5)	550 (224)

Trial	Arm	N	Age Mean (SD)	Female, n, (%)	HY Stage, N (%)		Diary On/OFF Time (%)		Duration Years (SD)	UPDRS (SD)		Mean Levodopa Dose, mg (SD)
					3	4	ON	OFF		Part II	Part III	
Zhang et al. (2013)[55]	Rasagiline 1 mg	119	61.6 (8.5)	55 (46.2)	NR	NR	9.6 (2.7)	6.3 (2.4)	5.6 (2.1)	15.35 (5.3)	20.30 (6.13)	515.2 mg
	Placebo	125	61.6 (9.5)	58 (46.4)	NR	NR	9.5 (2.6)	6.2 (2.5)	5.4 (2.2)	15.3 (5.6)	20.67 (6.8)	521 mg
TEMPO-3[32]	Tavapadon 5 mg to 15 mg	252	65.6 (8.4)	101 (40.1)	54 (21.4)	NR	10.4	5.6 (2.2)	6.9 (4.5)	13.3 (6.5) MDS	32.6 (14.3) MDS	811.9 (451.4)
	Placebo	255	64.1 (8.5)	85 (33.3)	59 (23.1)	NR	10.6	5.4 (2.5)	6.4 (4.6)	12.5 (7.1) MDS	32.4 (14.3) MDS	817.6 (644.0)

HY Stage: Hoehn and Yahr Stage, MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale, mg: milligrams, N: number, SD: standard deviation, UPDRS: Unified Parkinson's Disease Rating Scale,

*Value is for fluctuating patients.

Table D2.5. Change From Baseline in the UPDRS Parts II and III Scores for Early Parkinson's Disease Therapy

Study	Arms	Week	N	UPDRS Part II Scores			UPDRS Part III Scores		
				Treatment Difference	SE	CI	Treatment Difference	SE	CI
Whone et al. (2003)[7]	Levodopa 50 mg to 1000 mg	24	75	UPDRS Part II Data Unavailable			-0.6	0.91	NR
	Ropinirole 0.75 mg to 24 mg	24	87				NA	NA	NA
Rascol et al. (1998)[8]	Levodopa 50 to 1200 mg	24	89	UPDRS Part II Data Unavailable			-4.8	NR	NR
	Ropinirole0.75 mg to 24 mg	24	179				NA	NA	NA
Holloway et al. (2000)[9]	Carbidopa/Levodopa 37.5/150 mg or 75/300 mg	26	150	-0.9	1.3	NR	3.6	NR	NR
	Pramipexole 0.75 mg to 3 mg	26	151	NA	1.7	NR	NA	NA	NA
Adler et al. (1997)[10]	Ropinirole 0.75 mg to 4.5 mg	24	116	UPDRS Part II Data Unavailable			-4.7	NR	NR
	Placebo	24	125				NA	NA	NA
Singer et al. (2007)[11]	Ropinirole up to 24 mg	39	199	-1.52	NR	NR	-4.12	NR	NR
	Placebo	39	199	NA	NR	NR	NA	NA	NA
Giladi et al. (2007)[12]	Ropinirole 0.75 mg, 1.5 mg, 3 mg, 6 mg, or 15 mg	37	228	NR			NR		
	Rotigotine 2 mg, 4 mg, 6 mg, or 8 mg	37	215	-2	NR	NR	-3.1	NR	NR
	Placebo	37	118	NA			NA	NA	NA
Watts et al. (2007)[13]	Rotigotine 2 mg, 4 mg, or 6 mg	24	181	UPDRS Data Unavailable					
	Placebo	24	96						
Zhang et al. (2016)[28]	Rotigotine 2 mg, 4 mg, 6 mg, or 8 mg	24	123	-1.53	0.4	(-2.29, -0.77)	-3.27	0.92	(-5.07, -1.48)
	Placebo	24	121	NA	NA	NA	NA	NA	NA

Study	Arms	Week	N	UPDRS Part II Scores			UPDRS Part III Scores		
				Treatment Difference	SE	CI	Treatment Difference	SE	CI
Poewe et al. (2011)[14]	Pramipexole extended release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 2.75 mg, or 4.5 mg	33	213	-1.9	NR	NR	5	NR	NR
	Pramipexole immediate release 0.375, 0.75 mg, 3 mg, 3.75 mg, or 4.5 mg	33	207	-2.2	NR	NR	5.3	NR	NR
	Placebo	33	103	NA	NR	NR	NA	NA	NA
Shannon et al. (1997)[15]	Pramipexole 0.375 mg, to 4.5 mg	31	164	-2.2	NR	NR	-6	NR	NR
	Placebo	31	171	NA	NR	NR	NA	NR	NR
Viallet et al. (2013)[22]	Pramipexole 0.375 mg to 1.5 mg	15	53	UPDRS Data Unavailable					
	Rasagiline 1 mg	15	56						
Barone et al. (2015)[16]	Rasagiline 1 mg	12	58	-1.43	NR	NR	-1.3	NR	NR
	Placebo	12	65	NA	NA	NA	NA	NA	NA
Olanow et al. (2009)[17]	Rasagiline 1 mg	36	288	UPDRS Data Unavailable					
	Placebo	36	595						
Hanagasi et al. (2011)[23]	Rasagiline 1 mg	12	23	-0.53	1.09	NR	-2.15	1.34	NR
	Placebo	12	25	NA	NA	NA	NA	NA	NA
Poewe et al. (2015)[18]	Rasagiline 1 mg	48	84	UPDRS Data Unavailable					
	Placebo	48	90						
Siderowf et al. (2002)[147]	Rasagiline 1 mg	26	134	-1.04	0.29	(-1.60, -0.48)	-2.71	0.59	(-3.86, -1.55)
	Placebo	26	138	NA	NR	NR	NA	NR	NR

Study	Arms	Week	N	UPDRS Part II Scores			UPDRS Part III Scores		
				Treatment Difference	SE	CI	Treatment Difference	SE	CI
Hattori et al. (2019)[29]	Rasagiline 1 mg	26	118	-2.19	0.49	(-3.14, -1.24)	-3.98	0.93	(-3.86, -1.55)
	Placebo	26	126	NA	NA	NA	NA	NR	NR
Allain et al. (1993)[148]	Selegiline 5 mg	12	48	-0.8	NR	NR	-3.3	NR	NR
	Placebo	12	45	NA	NA	NA	NA	NA	NA
Larsen et al. (1997)[24]	Selegiline 10 mg	12	73	UPDRS Part II Data Unavailable			-2.3	NR	NR
	Placebo	12	81				NA	NA	NA
Palhagen et al. (1998)[21]	Selegiline 10 mg	24	81	0.9	NR	NR	-4	NR	NR
	Placebo	24	76	NA	NA	NA	NA	NA	NA
Koller et al. (1993)[149]	Selegiline 5 mg	14 months	202	UPDRS Data Unavailable					
	Placebo	14 months	199						
TEMPO-1[25]	Tavapadon 5 mg	26	132	-2.5	0.43	(-3.3, -1.7)	-9	0.89	(-10.8, -7.3)
	Tavapadon 15 mg	26	116	-2.6	0.43	(-3.4, -1.7)	-9.4	0.92	(-11.2, -7.6)
	Placebo	26	148	NA	NA	NA	NA	NA	NA
TEMPO-2[26]	Tavapadon 5 mg to 15 mg	26	99	-1.5	0.46	(-2.4, -0.6)	-7.6	1.05	(-9.7, -5.6)
	Placebo	26	134	NA	NA	NA	NA	NA	NA

CI: confidence interval, N: number, SE: standard error, UPDRS: Unified Parkinson's Disease Rating Scale

Table D2.6. Change From Baseline in the Daily Off-Time, and Daily Good-On Time for Adjunctive Parkinson's Disease Therapy

Study	Arms	Week	N	Daily OFF Time			Good Daily ON-Time		
				Treatment Difference	SE	CI	Treatment Difference	SE	CI
LeWitt et al. (2006)[40]	Rotigotine 8 mg	24	113	-1.8	NR	(-2.6, -1)	2.4	NR	NR
	Placebo		119	NA	NA	NA	NA	NA	NA
Zhang et al. (2017)[41]	Rotigotine 4, 6, or 8 mg	12	174	-1.2	NR	(-1.83, -0.57)	1.26	NR	(0.6, 1.91)
	Placebo		172	NA	NA	NA	NA	NA	NA
Nicholas et al. (2014)[42]	Rotigotine 8 mg		94	-0.9	NR	(-1.59, -0.11)	ON-Time Data Unavailable		
	Rotigotine 6 mg		101	-0.6	NR	(-1.41, 0.03)			
	Rotigotine 4 mg		103	-0.6	NR	(-1.35, 0.06)			
	Rotigotine 2 mg		99	-0.4	NR	-1.22, 0.23)			
	Placebo		105	NA	NR	NA			
Poewe et al. (2007)[43]	Pramipexole 0.475 mg to 4.5 mg	23	201	-1.94	NR	(-2.63, -1.25)	1.3	NR	NR
	Rotigotine 4 mg to 16 mg		204	-1.58	NR	(-2.27, -0.90)	1.4	NR	NR
	Placebo		101	NA	NR	NA	NA	NR	NR
Lieberman et al. (1998)[59]	Ropinirole 0.75 mg to 9 mg	24	95	Percent Reduction Reported			ON-Time Data Unavailable		
	Placebo		54						
Mizuno et al. (2007)[56]	Ropinirole 0.75 mg to 15 mg	16	121	-1.2	NR	NR	ON-Time Data Unavailable		
	Placebo		120	NA	NA	NA			
Pahwa et al. (2007)[57]	Ropinirole 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, 20 mg, or 24 mg	24	201	-1.7	NR	(-2.34, -1.09)	1.5	NR	(0.85, 2.13)
	Placebo		190	NA	NA	NA	NA	NA	NA

Study	Arms	Week	N	Daily OFF Time			Good Daily ON-Time		
				Treatment Difference	SE	CI	Treatment Difference	SE	CI
Lieberman et al. (1997)[58]	Pramipexole 0.375 mg to 4.5 mg	32	181	Percent Reduction Reported			ON-Time Data Unavailable		
	Placebo		179						
Schapira et al. (2011)[150]	Pramipexole immediate release 0.475 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, or 4.5 mg total daily dose	18	171	-2.1	NR	NR	ON-Time Data Unavailable		
	Pramipexole extended release .475 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, or 4.5 mg		160	-1.2	NR	NR			
	Placebo		174	NA	NA	NA			
Poewe et al. (2003)[19]	Entacapone 200 mg	24	129	-0.7	NR	(-1.64, -0.12)	ON-Time Data Unavailable		
	Placebo		74	NA	NA	NA			
Reichmann et al. (2005)[45]	Entacapone 200 mg	13	174	-0.1	NR	NR	ON-Time Data Unavailable		
	Placebo		96	NA	NA	NA			
Brooks et al. (2002)[46]	Entacapone 200 mg	24	80	-0.8	NR	NR	ON-Time Data Unavailable		
	Placebo		44	NA	NA	NA			
Fenelon et al. (2003)[47]	Entacapone 200 mg	12	99	-0.32	NR	NR	ON-Time Data Unavailable		
	Placebo		63	NA	NA	NA			
Ferreira et al. (2016)[48]	Opicapone 50 mg	14-15	115	-1.01	NR	(-1.62, -0.41)	1.04	NR	(0.4, 1.69)
	Entacapone		120	-0.67	NR	(-1.27, -0.072)	0.79	NR	(0.16, 1.43)
	Placebo		120	NA	NA	NA	NA	NA	NA

Study	Arms	Week	N	Daily OFF Time			Good Daily ON-Time		
				Treatment Difference	SE	CI	Treatment Difference	SE	CI
Lees et al. (2017)[49]	Opicapone 50 mg	14-15	147	-0.91	SD: 0.32	(-1.6, -0.21)	ON-Time Data Unavailable		
	Placebo		135	NA	NA	NA			
Takeda et al. (2020)[50]	Opicapone 50 mg	14-15	145	-0.62	0.3	(-1.22, -0.03)	0.61	NR	NR
	Placebo		147	NA	NA	NA	NA	NA	NA
Hattori et al. (2018)[51]	Rasagiline 1 mg	26	129	-0.9	NR	(-1.489, -0.301)	0.9	NR	(0.36, 1.435)
	Rasagiline 0.5 mg		143	-0.49	NR	(-1.080, 0.1)	0.55	NR	(0.014, 1.081)
	Placebo		141	NA	NA	NA	NA	NA	NA
Rascol et al. (2005)[52]	Rasagiline 1 mg	18	222	-0.78	0.2015	(-1.18, -0.39)	0.82	NR	(0.36, 1.27)
	Entacapone 200 mg		218	-0.8	0.2015	(-1.2, -0.41)	0.82	NR	(0.36. 1.27)
	Placebo		218	NA	NA	NA	NA	NR	NA
Schwid et al. (2005)[53]	Rasagiline 1 mg	26	149	-0.94	NR	(-1.36, -0.51)	0.78	0.27	(0.26, 1.31)
	Rasagiline 0.5 mg		164	-0.49	NR	(-0.91, -0.08)	0.51	NR	(0, 1.03)
	Placebo		159	NA	NR	NA	NA	NA	NA
Zhang et al. (2018)[54]	Rasagiline 1 mg	16	158	-0.5	NR	(-0.92, -0.07)	ON-Time Unavailable		
	Placebo		152	NA	NA	NA			
Zhang et al. (2013)[55]	Rasagiline 1 mg	12	119	1.058	NR	(0.681, 1.435)	ON-Time Unavailable		
	Placebo		125	NA	NR	NA			
TEMPO-3[32]	Tavapadon 5 to 15 mg	26	153	-0.94	NR	(-1.48, -0.41)	1.1	0.28	(0.6, 1.7)
	Placebo		201	NA	NR	NA	NA	NA	NA

CI: confidence interval, N: number, SE: standard error, UPDRS: Unified Parkinson's Disease Rating Scale

Table D2.7. Overview of Health Related Quality of Life Endpoints for Early Parkinson's Disease Trials

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
Whone et al. (2003)[7]	Ropinirole 0.75 mg to 24 mg	87	NR	NR	NR	NR
	Levodopa 50 mg to 1000 mg	75	NR	NR	NR	NR
Rascol et al. (1998)[8]	Ropinirole 0.75 mg to 24 mg	179	NR	NR	NR	NR
	Levodopa 50 mg to 1200 mg	89	NR	NR	NR	NR
Holloway et al. (2000)[9]	Pramipexole 0.75 mg to 3 mg	151	NR	NR	NR	NR
	Carbidopa/levodopa 37.5/150 mg or 75/300 mg	150	NR	NR	NR	NR
Adler et al. (1997)[10]	Ropinirole 0.75 mg to 4.5 mg	116	NR	NR	NR	NR
	Placebo	125	NR	NR	NR	N
Singer et al. (2007)[11]	Ropinirole up to 24 mg	202	NR	NR	NR	NR
	Placebo	203	NR	NR	NR	NR
Giladi et al. (2007)[12]	Rotigotine 0.75 mg, 1.5 mg, 3 mg, 6 mg, or 15 mg	215	NR	NR	NR	NR
	Ropinirole 2 mg, 4 mg, 6 mg, or 8 mg	228	NR	NR	NR	NR
	Placebo	118	NR	NR	NR	NR
Zhang et al. (2017)[28]	Rotigotine 2 mg, 4 mg, 6 mg, or 8 mg	124	NR	NR	NR	NR
	PLACEBO	123	NR	NR	NR	NR
Watts et al. (2007)[13]	Rotigotine 2 mg, 4 mg, or 6 mg	181	NR	NR	NR	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
	Placebo	95	NR	NR	NR	NR
Thomas et al. (2006)[135]	Ropinirole 15 mg	27	NR	NR	NR	NR
	Pramipexole 2.1 mg	25	NR	NR	NR	NR
Poewe et al. (2011)[14]	Pramipexole immediate release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, or 4.5 mg	213	NR	-6.5 (95% CI: 8.6 to 4.5) (p value vs. placebo 0.004) total score adjusted mean change. Treatment difference mean vs. placebo = -5	5.9 (95% CI: 3.2 to 8.7) (p value vs. placebo=0.11) Visual Analogue Scale score adjusted mean change, treatment difference vs. placebo = 3.8	NR
	Pramipexole extended release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, or 4.5 mg	223	NR	-3.8 (95% CI: 5.9 to 1.8) (p value vs. placebo 0.18) adjusted mean change. Treatment difference mean vs. placebo = -2.3	4.2 (95% CI: 1.5 to 7.0) (p value vs. placebo 0.38) Visual Analogue Scale score adjusted mean change. Treatment difference vs. placebo = 2.1	NR
	Placebo	103	NR	-1.5 (95% CI: -4.4 to 1.5) Adjusted mean change	2.1 (95% CI: 1.8 to 6.1) Visual Analogue Scale score adjusted mean change	NR
Shannon et al. (1997)[15]	Pramipexole 0.375 mg to 4.5 mg	164	NR	NR	NR	NR
	Placebo	171	NR	NR	NR	NR
Viallet et al. (2013)[22]	Rasagiline 1 mg	53	5.5	NR	NR	NR
	Pramipexole 0.375 mg to 1.5 mg	56	5.2	NR	NR	NR
Barone et al. (2015)[16]	Rasagiline 1 mg	58	NR	-6.24 (SD=2.69)	NR	NR
	Placebo	65	NR	-1.03 (SD=2.33)	NR	NR
Olanow et al. (2009)[17]	Rasagiline 1 mg	288	NR	NR	NR	NR
	Placebo	595	NR	NR	NR	NR
Hanagasi et al. (2011)[23]	Rasagiline 1 mg	23	NR	NR	NR	NR
	Placebo	25	NR	NR	NR	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
Hattori et al. (2019)[29]	Rasagiline 1 mg	118	NR	1.24 (SE=0.72) summary index score change from baseline. Treatment difference versus placebo = -1.6 (95% CI: -3.59 to 0.38)	NR	NR
	Placebo	126	NR	2.84 (SE=0.70) summary index score change from baseline.	NR	NR
Poewe et al. (2015)[18]	Rasagiline 1 mg	84	NR	NR	NR	NR
	Placebo	90	NR	NR	NR	NR
Siderowf et al. (2002)[147]	Rasagiline 1 mg	134	NR	NR	NR	NR
	Placebo	138	NR	NR	NR	NR
Allain et al. (1993)[148]	Selegiline 5 mg	48	NR	NR	NR	NR
	Placebo	45	NR	NR	NR	NR
Larsen et al. (1997)[24]	Selegiline 10 mg	73	NR	NR	NR	NR
	Placebo	81	NR	NR	NR	NR
Palhagen et al. (1998)[21]	Selegiline 10 mg	81	NR	NR	NR	NR
	Placebo	76	NR	NR	NR	NR
Koller et al. (1993)[149]	Selegiline 5 mg	202	NR	NR	NR	NR
	Placebo	199	NR	NR	NR	NR
TEMPO-1[25]	Tavapadon 5 mg	177	NR	-0.92 (95% CI: -2.25 to -0.42) total score change from baseline. Treatment difference vs. placebo = -1.00 (95% CI: -2.78 to 0.77)	0.016 (95% CI: -0.001 to -0.03) change from baseline in Index score. Treatment difference vs. placebo=0.04 (95% CI: 0.02 to 0.06)	NR
	Tavapadon 15 mg	177	NR	0.22 (95% CI: -1.18 to 1.62) total score change from baseline.	0.006 (95% CI: -0.01 to 0.02) change from baseline in Index score. Treatment	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
				Treatment difference= 0.13 (95% CI: -1.70 to 1.96)	difference vs. placebo=0.02 (95% CI: 0.01 to 0.05)	
	Placebo	175	NR	0.09 (95% CI: -1.18 to 1.36) total score change from baseline.	-0.02 (95% CI: -0.04 to -0.01) change from baseline in index score.	NR
TEMPO-2[26]	Tavapadon 5 to 15 mg	151	NR	-0.68 (95% CI: -2.31 to 0.95) change from baseline summary index. Treatment difference vs. placebo = -0.89 (95% CI: -3.01 to 1.22)	0.02 (95% CI: -0.004, 0.04) change from baseline in index score. Treatment difference vs. placebo = 0.02 (95% CI: -0.01 to 0.05)	NR
	Placebo	153	NR	0.21 (95% CI: -1.23, 1.66) change from baseline in summary index	-0·002 (95% CI: -0.02, 0.02) change from baseline in summary index	NR

CI: confidence interval, , EQ-5D: EuroQoL 5D measure, N:number, NR: not reported, PDQ-8: Parkinson's Disease Questionnaire 8. PDQ-39: Parkinson's Disease Questonnaire-3 , SE: standard error SD: standard deviation,SF-36: Short-Form Health Survey,

Table D2.8. Overview of Health Related Quality of Life Endpoints for Adjunctive Therapy Parkinson's Disease Trials

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
LeWitt et al. (2006)[40]	Rotigotine 8 mg	118	NR	NR	NR	NR
	Placebo	120	NR	NR	NR	NR
Zhang et al. (2017)[41]	Rotigotine 4, 6, or 8 mg	174	-2.2 (5.4) change from baseline in total score	NR	NR	NR
	Placebo	172	-0.4 (4.7) change from baseline in total score	NR	NR	NR
Nicholas et al. (2014)[42]	Rotigotine 8 mg	94	NR	NR	NR	NR
	Rotigotine 6 mg	104	NR	NR	NR	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
	Rotigotine 4 mg	107	NR	NR	NR	NR
	Rotigotine 2 mg	101	NR	NR	NR	NR
	Placebo	108	NR	NR	NR	NR
Lieberman et al. (1997)[58]	Pramipexole 0.375 mg to 4.5 mg	181	NR	NR	NR	NR
	Placebo	179	NR	NR	NR	NR
Poewe et al. (2007)[43]	Pramipexole 0.375 mg to 4.5 mg	200	NR	–5.1 (SE: 10.1) change from baseline in the total score. Treatment difference = -3.8 -10.0 (SE:16.8). Change from baseline in mobility score treatment difference = -8.0	NR	NR
	Rotigotine 4 mg to 16 mg	201	NR	-4.7 (SE:9.2) change from baseline in the total score. Treatment difference=-3.4 -8.8 (SE:15.1). Change from baseline in mobility score treatment difference = -6.8		
	Placebo	100	NR	-1.3 (SE=9.4) change from baseline in the total score. -2 (SE=15.9) change from baseline in mobility score.	NR	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
Lieberman et al. (1998)[59]	Ropinirole 0.75 mg to 9 mg	95	NR	NR	NR	NR
	Placebo	54	NR	NR	NR	NR
Mizuno et al. (2007)[144]	Ropinirole 0.75 mg to 15 mg	121	NR	NR	NR	NR
	Placebo	201	NR	NR	NR	NR
Pahwa et al. (2007)[57]	Ropinirole 2 mg, 4 mg, 6 mg, 8 mg, 16 mg, 20 mg, or 24 mg	201	NR	-4.9 (SE=3.36) change from baseline in mobility scores.	NR	NR
	Placebo	190	NR	1.9 (SE=3.42) change from baseline in mobility scores.	NR	NR
Schapira et al. (2011)[150]	Pramipexole extended release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg	164	NR	-9.1 change from baseline in total score. Treatment difference = -2.9	NR	NR
	Pramipexole immediate release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg	175	NR	-13.1 change from baseline in total score. Treatment difference = -6.9	NR	NR
	Placebo	178	NR	-6.2 change from baseline in total score	NR	NR
Poewe et al. (2003)[19]	Entacapone 200 mg	197	NR	NR	NR	NR
	Placebo	104	NR	NR	NR	NR
Reichmann et al. (2005)[45]	Entacapone 200 mg	174	NR	-0.3 (SE=6.9) change from baseline in total score. Treatment difference =	NR	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
				-0.60 (95% CI: -2.50, 1.31)		
	Placebo	96	NR	0.6 (6.8) change from baseline in total score	NR	NR
Brooks et al. (2003)[46]	Entacapone 200 mg	204	NR	NR	NR	NR
	Placebo	97	NR	NR	NR	NR
Fenelon et al. (2003)[47]	Entacapone 200 mg	99	NR	NR	NR	Mental score -0.5 (10.2) physical score 2.5 (7.7) change from baseline
	Placebo	63	NR	NR	NR	Mental score -1.1 (10.9), physical score 0.4 (9.3) change from baseline
Ferreira et al. (2016)[48]	Entacapone 200 mg	122	NR	-4·0 (0·9) change from baseline in total score. Treatment difference = -1.4	NR	NR
	Opicapone 50 mg	115	NR	-2.8 (0.9) change from baseline in total score. Treatment difference = 0.4	NR	NR
	Placebo	121	NR	-2.6 (0.9) LSM change from baseline	NR	NR
Lees et al. (2017)[49]	Opicapone 50 mg	147	NR	-4.4 (1.0) change from baseline in total scores.	NR	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
				Treatment difference = 0.4		
	Placebo	135	NR	-4.8 (1.0) change from baseline in total scores.	NR	NR
Takeda et al. (2020)[50]	Opicapone 50 mg	145	NR	-2.0 (0.7) change from baseline in total scores	NR	NR
	Placebo	147	NR	-2.0 (0.6) change from baseline) in total scores	47 NR	NR NR
Hattori et al. (2018)[51]	Rasagiline 1 mg	129	NR	-2.8 (SE=1.61) change from baseline in mobility score. Treatment difference = -6.15 (95% CI: -10.45 to -1.81)	NR	NR
	Placebo	141	NR	3.36 (SE=1.52) change from baseline in mobility score.	NR	NR
	Rasagiline 1 mg	231	NR	NR	NR	NR

Study	Arms	N	PDQ-8	PDQ-39	EQ-5D	SF-36
Rascol et al. (2005)[52]	Entacapone 200 mg	227	NR	NR	NR	NR
	Placebo	229	NR	NR	NR	NR
Schwid et al. (2005)[53]	Rasagiline 1 mg	149	NR	NR	NR	NR
	Rasagiline 0.5 mg	164	NR	NR	NR	NR
	Placebo	159	NR	NR	NR	NR
Zhang et al. (2017)[41]	Rasagiline 1 mg	163	NR	-4.1 (SE=1.2) change from baseline in mobility score. Treatment difference -2.5 (95% CI: -5.59 to 0.53)	Utility index 0.05 (0.02), Health state 5.09 (1.20), mean change, (SE)	NR
	Placebo	158	NR	-1.6 (SE=1.2) change from baseline in mobility score.	Utility index 0.00 (0.02), Health state 0.77 (1.18) mean change, (SE)	NR
Zhang et al. (2013)[55]	Rasagiline 1 mg	119	NR	NR	NR	NR
	Placebo	125	NR	NR	NR	NR
TEMPO-3[32]	Tavapadon 5mg to 15 mg	252	NR	NR	NR	NR
	Placebo	255	NR	NR	NR	NR

CI: confidence interval, EQ-5D: EuroQoL 5D measure, LSM: least squares mean, N: number, NR: not reported, PDQ-8: Parkinson's Disease Questionnaire 8. PDQ-39: Parkinson's Disease Questonnaire-39, SE: standard error, SF-36: Short-Form Health Survey.

Table D2.9. Overview of Safety Outcomes and Discontinuations for Early Parkinson's Disease Therapy Trials

Study	Arm	N	Week	DC, n (%)	DC due to AE's, n (%)	Serious AEs, n (%)	Impulse Control Disorder, n (%)	Dyskinesia, n (%)	Hypotension, n (%)	Somnolence, n (%)	Hallucination, n (%)
Whone et al. (2003)[7]	Levodopa 50 mg to 1000 mg	75	48	20 (27%)	4 (5%)	17 (23%)	NR	20 (26.7%)	NR	7 (9.3%)	1 (1.3%)
	Ropinirole 0.75 mg to 24 mg	87	48	23 (26%)	13 (15%)	18 (21%)	NR	3 (3.45%)	NR	33 (37.9%)	6 (6.8%)
Rascol et al. (1998)[8]	Levodopa 50 mg to 1200 mg	89	24	12 (13.5%)	12 (13.5%)	8 (8.99%)	NR	2 (2.47%)	5 (5.62%)	12 (13.5%)	NR
	Ropinirole 0.75 mg to 24 mg	179	24	19 (10.6%)	14 (7.8%)	14 (7.8%)	NR	1 (0.6%)	8 (4.46%)	22 (12.3%)	NR
Holloway et al. (2000)[9]	Carbidopa/levodopa 37.5/150 mg or 75/300 mg	150	102	19 (12.7%)	NR	NR	NR	46 (30.7%)	15 (10%)	26 (17.3%)	5 (3.3%)
	Pramipexole 0.75 mg to 3 mg	151	102	23 (15.2%)	NR	NR	NR	15 (9.9%)	9 (6%)	49 (32.5%)	14 (9.27%)
Adler et al. (1997)[10]	Ropinirole 0.75 mg to 4.5 mg	116	24	37 (32%)	27 (23.3%)	NR	NR	NR	NR	42 (36.2%)	2 (1.7%)
	Placebo	125	24	20 (16%)	13 (10.4%)	NR	NR	NR	NR	6 (4.8%)	0
Singer et al. (2007)[11]	Ropinirole up to 24 mg	202	39	95 (47%)	48 (23.8%)	17 (8.4%)	NR	NR	NR	63(31.2%)	NR
	Placebo	203	39	108 (53.2%)	17 (8.4%)	12 (6%)	NR	NR	NR	17 (8.4%)	NR

Study	Arm	N	Week	DC, n (%)	DC due to AE's, n (%)	Serious AEs, n (%)	Impulse Control Disorder, n (%)	Dyskinesia, n (%)	Hypotension, n (%)	Somnolence, n (%)	Hallucination, n (%)
Giladi et al. (2007)[12]	Rotigotine 2 mg, 4 mg, 6 mg, or 8 mg	215	41	75 (35%)	37 (17.2%)	22 (10.2%)	NR	NR	NR	22 (10.2%)	NR
	Ropinirole 0.75 mg, 1.5 mg, 3 mg, 6 mg, or 15 mg	228	41	60 (26.3%)	29 (12.7%)	30 (13.2%)	NR	NR	NR	28 (12.3%)	NR
	Placebo	118	41	41 (34.7%)	6 (5%)	9 (7.6%)	NR	NR	NR	20 (17%)	NR
Zhang et al. (2016)[28]	Rotigotine 2 mg, 4 mg, 6 mg, or 8 mg	124	24	11 (8.9%)	6 (4.8%)	6 (4.8%)	NR	NR	1 (0.8%)	10 ((8%)	2 (1.6%)
	Placebo	123	24	16 (13%)	7 (5.7%)	1 (0.8%)	NR	NR	0	4 (3.25%)	0
Watts et al. (2007)[13]	Rotigotine 2 mg, 4 mg, or 6 mg	181	28	39 (21.5%)	25 (13.8%)	NR	NR	NR	4 (2.2%)	60 (33%)	0
	Placebo	95	28	15 (15.78%)	6 (6.3%)	NR	NR	NR	4 (4.2%)	19 (20%)	1 (1%)
Poewe et al. (2011)[14]	Pramipexole extended release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, or 4.5 mg	223	33	49 (21.9%)	24 (10.7%)	16 (7.17%)	4 (1.8%)	0	NR	70 (31.4%)	NR
	Pramipexole immediate release 3.75 mg, 0.75 mg, 1.5 mg,	213	33	37 (17.4%)	20 (9.4%)	11 (5.2%)	3 (1.4%)	0	NR	81 (38%)	NR

Study	Arm	N	Week	DC, n (%)	DC due to AE's, n (%)	Serious AEs, n (%)	Impulse Control Disorder, n (%)	Dyskinesia, n (%)	Hypotension, n (%)	Somnolence, n (%)	Hallucination, n (%)
	2.25 mg, 3 mg, 3.75 mg, or 4.5 mg										
	Placebo	103	33	12 (11.7%)	4 (3.9%)	4 (3.9%)	1 (0.97%)	0	NR	15 (14.56%)	NR
Shannon et al. (1997)[15]	Pramipexole 0.375 mg to 4.5 mg	164	33	28 (17%)	22 (13.4%)	NR	NR	0	16 (9.8%)	31 (18.9%)	20 (12.2%)
	Placebo	171	33	34 (19.9%)	24 (14%)	NR	NR	1 (0.6%)	10 (5.8%)	14 (8.2%)	3 (1.8%)
Viallet et al. (2013)[22]	Pramipexole 0.375 mg to 1.5 mg	56	15	NR	8 (14.3%)	1 (1.8%)	21 (37.5%)	NR	3 (5.4%)	NR	3 (5.4%)
	Rasagiline 1 mg	53	15	NR	3 (5.7%)	1 (1.9%)	11 (20.8%)	NR	1 (1.9%)	NR	0
Barone et al. (2015)[16]	Rasagiline 1 mg	58	12	9 (15.5%)	4 (6.9%)	2 (3.4%)	NR	NR	NR	NR	NR
	Placebo	65	12	8 (12.3%)	0	1 (1.5%)	NR	NR	NR	NR	NR
Olanow et al. (2009)[17]	Rasagiline 1 mg	288	36	15 (5.2%)	9 (3.125%)	NR	NR	NR	2 (0.7%)	2 (0.7%)	0
	Placebo	595	36	50 (8.4%)	17 (2.9%)	NR	NR	NR	5 (0.84%)	9 (1.5%)	1 (0.17%)
Hanagasi et al. (2011)[23]	Rasagiline 1 mg	23	12	NR	0	NR	NR	NR	NR	NR	NR
	Placebo	25	12	NR	0	NR	NR	NR	NR	NR	NR
Hattori et al. (2019)[29]	Rasagiline 1 mg	118	26	7 (5.9%)	3 (2.5%)	4 (3.4%)	NR	NR	NR	NR	NR
	Placebo	126	26	26 (20.6%)	8 (6.35%)	8 (6.35%)	NR	NR	NR	NR	NR
	Rasagiline 1 mg	84	48	21 (25%)	14 (16.7%)	29 (34.5%)	NR	NR	8 (9.5%)	2 (2.4%)	NR

Study	Arm	N	Week	DC, n (%)	DC due to AE's, n (%)	Serious AEs, n (%)	Impulse Control Disorder, n (%)	Dyskinesia, n (%)	Hypotension, n (%)	Somnolence, n (%)	Hallucination, n (%)
Poewe et al. (2015)[18]	Placebo	90	48	15 (16.7%)	7 (7.8%)	23 (25.6%)	NR	NR	3 (3.33%)	5 (5.6%)	NR
Siderowf et al. (2002)[147]	Rasagiline 1 mg	134	26	8 (6%)	NR	6 (4.5%)	NR	NR	NR	NR	NR
	Placebo	138	26	4 (2.9%)	NR	4 (2.9%)	NR	NR	NR	NR	NR
Allain et al. (1993)[20]	Selegiline 5 mg	43	12	10 (23.3%)	1 (2.3%)	NR	NR	NR	NR	NR	NR
	Placebo	42	12	4 (9.5%)	4 (9.5%)	NR	NR	NR	NR	NR	NR
Larsen et al. (1997)[24]	Selegiline 10 mg	73	12	NR	16 (21.9%)	NR	NR	12 (16.4%)	NR	NR	NR
	Placebo	81	12	NR	11 (13.6%)	NR	NR	22 (27%)	NR	NR	NR
Palhagen et al. (1998)[21]	Selegiline 10 mg	81	24	9 (11.1%)	NR	NR	NR	NR	NR	NR	NR
	Placebo	76	24	7 (9.2%)	NR	NR	NR	NR	NR	NR	NR
TEMPO-1[25]	Tavapadon5 mg	177	31	43 (24.3%)	29 (16.4%)	4 (2.3%)	2 (1.2%)	NR	7 (4%)	6 (3.4%)	0
	Tavapadon15 mg	177	31	59 (33.3%)	35 (19.8%)	10 (5.6%)	1 (0.56%)	NR	9 (5%)	5 (2.8%)	11 (6.2%)
	Placebo	175	31	27 15.4%)	6 (3.4%)	11 (6.3%)	0	NR	4 (2.3%)	6 (3.4%)	0
TEMPO-2[26]	Tavapadon 5 mg to 15 mg	151	27	57 (37.7%)	36 (23.8%)	7 (4.6%)	2 (1)	0	6 (3.9%)	5 (3.3%)	6 (4)
	Placebo	153	27	23 (15%)	6 (3.9%)	2 (1.3%)	0	0	0	6 (3.9%)	0

AE: adverse event, DC: discontinuation, N: number, NR: Not reported

Table D2.10. Overview of Safety Outcomes and Discontinuations for Adjunctive Parkinson's Disease Therapy Trials

Study	Arm	N	Week	DC, n (%)	DCs due to AE's, n (%)	Serious AE's, n (%)	Impulse Control Disorders, n (%)	Dyskinesia, n (%)	Somnolence, n (%)	Hypotension, n (%)	Hallucinations, n (%)
LeWitt et al. (2006) [40]	Rotigotine8 mg	120	24	37 (30.8%)	18 (15%)	NR	NR	16 (13.3%)	38 (31.7%)	2 (1.7%)	8 (6.7%)
	Placebo	120	24	26 (21.7%)	11 (9.2)	NR	NR	8 (6.7%)	33 (27.5%)	8 (6.7%)	3 (2.5%)
Zhang et al. (2017) [41]	Rotigotine 4 mg, 6 mg, or 8 mg	174	12	14 (8%)	8 (4.6%)	6 (3.4%)	0	11 (6.3%)	NR	NR	NR
	Placebo	172	12	21 (12.2%)	7 (4.1%)	6 (4.5%)	0	7 (4.1%)	NR	NR	NR
Nicholas et al. (2014)[42]	Rotigotine8 mg	94	16	14 (14.9%)	5 (5.3%)	0	5 (1.2%)	14 (14.89%)	4 (4.3%)	2 (2.1%)	10 overall (2.5%)
	Rotigotine 6 mg	104	16	22 (21.2%)	12 (11.5%)	2 (1.9%)		11 (10.5%)	8 (7.7%)	0	
	Rotigotine 4 mg	107	16	23 (21.5%)	15 (14%)	3 (2.8%)		4 (3.7%)	6 (5.6%)	1 (0.9%)	
	Rotigotine 2 mg	101	16	22 (21.7%)	12 (11.9%)	4 (4%)		5 (5%)	7 (6.9%)	3 (3%)	
	Placebo	108	16	27 (25%)	17 (15.7%)	5 (4.6%)	0	3 (2.8%)	9 (8.3%)	7 (6.5%)	1 (0.9%)
Poewe et al. (2007)[43]	Pramipexole 0.375 mg to 4.5 mg	201	20	30 (14.9%)	14 (6.9%)	15 (7.5%)	NR	31 (15.4%)	24 (11.9%)	10 (5%)	4 (2%)
	Rotigotine 4 mg to 16 mg	204	20	23 (11.3%)	11 (5.4%)	19 (9.3%)	NR	24 (11.8%)	25 (12.3%)	7 (3.4%)	0
	Placebo	101	20	26 (25.7%)	6 (6%)	9 (9%)	NR	3 (3%)	8 (8%)	5 (5%)	0
Lieberman et al. (1998)[59]	Ropinirole 0.75 mg to 9 mg	95	24	21 (22%)	15 (15.7%)	NR	NR	32 (33.7%)	18 (18.9%)	16 (16.8%)	NR
	Placebo	54	24	19 (35%)	9 (16.7%)	NR	NR	7 (12.9%)	6 (11.1%)	10 (18.5%)	NR

Study	Arm	N	Week	DC, n (%)	DCs due to AE's, n (%)	Serious AE's, n (%)	Impulse Control Disorders, n (%)	Dyskinesia, n (%)	Somnolence, n (%)	Hypotension, n (%)	Hallucinations, n (%)
Mizuno et al. (2007)[144]	Ropinirole 0.75 mg to 15 mg	121	16	23 (19%)	13 (10.7%)	6 (5%)	NR	14 (11.6%)	15 (12.4%)	NR	12 (9.9%)
	Placebo	122	16	26 (21.3%)	14 (11.5%)	3 (2.5%)	NR	2 (1.6%)	10 (8.3%)	NR	2 (1.6%)
Pahwa et al. (2007)[57]	Ropinirole 2 mg, 4 mg, 6 mg, 8 mg, 12 mg, 16 mg, 20 mg, or 24 mg	202	24	34 (16.8%)	13 (6.4%)	8 (4%)	NR	27 (13.4%)	14 (7%)	11 (5.4%)	12 (5.9%)
	Placebo	191	24	57 (30%)	10 (5.2%)	7 (3.7%)	NR	5 (2.6%)	7 (3.7%)	3 (1.6%)	2 (1%)
Lieberman et al. (1997)[58]	Pramipexole 0.375 mg to 4.5 mg	181	32	30 (16.6%)	24 (13.2%)	NR	NR	111 (61%)	NR	29 (16%)	38 (20.9%)
	Placebo	179	32	39 (21.8%)	30 (16.8%)	NR	NR	73 (40.8%)	NR	20 (11.2%)	10 (5.6%)
Schapira et al. (2011)[150]	Pramipexole immediate release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3.0 mg, 3.75 mg, or 4.5 mg	175	18	10 (5.7%)	8 (4.6%)	7 (4%)	2 (1.1%)	32 (18.3%)	24 (13.7%)	2 (1.1%)	9 (5%)
	Pramipexole extended release 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg,	164	18	16 (9.8%)	8 (4.9%)	5 (3%)	3 (1.8%)	27 (16.5%)	18 (10.9%)	3 (1.8%)	9 (5.5%)

Study	Arm	N	Week	DC, n (%)	DCs due to AE's, n (%)	Serious AE's, n (%)	Impulse Control Disorders, n (%)	Dyskinesia, n (%)	Somnolence, n (%)	Hypotension, n (%)	Hallucinations, n (%)
	3.0 mg, 3.75 mg, or 4.5 mg										
	Placebo	178	18	19 (10.7%)	7 (3.9%)	6 (3.4%)	1 (0.56%)	14 (7.8%)	24 (13.5%)	2 (1.1%)	1 (0.56%)
Poewe et al. (2003)[19]	Entacapone 200 mg	197	24	48 (24.4%)	41 (20.8%)	NR	NR	67 (34%)	NR	NR	7 (3.6%)
	Placebo	104	24	15 (14.4%)	10 (9.6%)	NR	NR	27 (25.9%)	NR	NR	4 (3.8%)
Reichmann et al. (2005)[45]	Entacapone 200 mg	174	13	27 (15.5%)	18 (10.3%)	NR	NR	16 (9.2%)	NR	NR	NR
	Placebo	96	13	18 (18.75%)	8 (8.3%)	NR	NR	5 (5.2%)	NR	NR	NR
Brooks et al. (2003)[46]	Entacapone 200 mg	203	24	49 (24%)	38 (18.7%)	NR	NR	44 (21.7%)	NR	NR	6 (3%)
	Placebo	97	24	16 (16.5%)	14 (14.4%)	NR	NR	10 (10.3%)	NR	NR	1 (1%)
Fenelon et al. (2003)[47]	Entacapone 200 mg	99	12	21 (21%)	17 (17%)	9 (9%)	NR	31 (31%)	NR	NR	0
	Placebo	63	12	16 (25.4%)	7 (11.1%)	6 (9.5%)	NR	8 (12.6%)	NR	NR	4 (6.3%)
Ferreira et al. (2016)[48]	Opicapone 50 mg	116	14-15	9 (7.75%)	5 (4.3%)	4 (3.4%)	8 (6.9%)	1 (0.86%)	NR	NR	5 (4.3%)
	Entacapone 200 mg	122	14-15	15 (0.8%)	8 (6.6%)	8 (6.6%)	10 (8.2%)	0	NR	NR	1 (0.8%)
	Placebo	121	14-15	11 (9%)	8 ((6.6%)	6 (5%)	5 (4%)	0	NR	NR	2 (1.6%)
Lees et al. (2017)[49]	Opicapone 50 mg	150	14-15	26 (17.3%)	18 (12%)	9 ((6%)	NR	36 (24%)	NR	NR	NR
	Opicapone 25 mg	121	14-15	11 (9%)	5 (4%)	4 (3.3%)	NR	30 (24.7%)	NR	NR	NR
	Placebo	136	14-15	14 (10.3%)	10 (7.4%)	5 (3.7%)	NR	11 (8.1%)	NR	NR	NR

Study	Arm	N	Week	DC, n (%)	DCs due to AE's, n (%)	Serious AE's, n (%)	Impulse Control Disorders, n (%)	Dyskinesia, n (%)	Somnolence, n (%)	Hypotension, n (%)	Hallucinations, n (%)
Takeda et al. (2020)[50]	Opicapone50 mg	145	14-15	18 (12.4%)	8 (5.5%)	3 (2.1%)	NR	18 (12.4%)	NR	NR	NR
	Opicapone25 mg	145	14-15	12 (8.3%)	6 (4.1%)	8 (5.5%)	NR	13 (9%)	NR	NR	NR
	Placebo	147	14-15	6 (4%)	3 (2%)	2 (1.4%)	NR	4 (2.7%)	NR	NR	NR
Hattori et al. (2018)[51]	Rasagiline1 mg	129	26	26 (20%)	21 (16.3%)	10 (7.8%)	NR	21 (16.3%)	4 (3.1%)	NR	5 (3.9%)
	Rasagiline 0.5 mg	133	26	29 (21.8%)	18 (13.5%)	10 (7.5%)	NR	11 (8.3%)	1 (0.75%)	NR	5 (3,8%)
	Placebo	141	26	22 (15.6%)	9 (6.4%)	4 (2.8%)	NR	10 (7.1%)	1 (0.7%)	4 (2.8%)	1 (0.7%)
Rascol et al. (2005)[52]	Entacapone 200 mg	227	18	30 (13.2%)	16 (7%)	12 (5.3%)	NR	14 (6.2%)	3 (1.3%)	5 (2.2%)	8 (3.5%)
	Rasagiline 1 mg	231	18	23 (10%)	7 (3%)	12 (5.2%)	NR	12 (5.2%)	3 (1.2%)	0	5 (2.2%)
	Placebo	229	18	35 (15.3%)	11 (4.8%)	17 (7.4%)	NR	9 (3.9%)	2 (0.87%)	NR	3 (1.3%)
Schwid et al. (2005)[53]	Rasagiline 0.5 mg	164	26	22 (13.4%)	NR	21 (12.8%)	NR	30 (18.3%)	NR	NR	NR
	Rasagiline1 mg	149	26	17 (11.4%)	NR	18 (12%)	NR	27 (18%)	NR	NR	NR
	Placebo	159	26	19 (11.9%)	NR	14 (8.8%)	NR	16 (10.1%)	NR	NR	NR
Zhang et al. (2018)[54]	Rasagiline 1 mg	163	16	12 (7.4%)	6 (3.7%)	7 (4.3%)	NR	11 (6.7%)	1 (0.6%)	6 (3.7%)	2 (1.2%)
	Placebo	158	16	10 (6.3%)	5 (3.2%)	5 (3.2%)	NR	12 (7.6%)	2 (1.3%)	0	0
Zhang et al. (2013)[55]	Rasagiline 1 mg	119	12	11 (9.2%)	3 (2.5%)	1 (0.8%)	NR	0	0	NR	NR
	Placebo	125	12	14 (11.2%)	6 (4.8%)	1 (0.8%)	NR	1 (0.8%)	1 0.8%)	NR	NR

Study	Arm	N	Week	DC, n (%)	DCs due to AE's, n (%)	Serious AE's, n (%)	Impulse Control Disorders, n (%)	Dyskinesia, n (%)	Somnolence, n (%)	Hypotension, n (%)	Hallucinations, n (%)
TEMPO-3[32]	Tavapadon 5 mg to 15 mg	251	27	93 (37%)	43 (17%)	17 (6.8%)	6 (2.4%)	25 (10%)	11 (4.4%)	15 (6%)	14 (5.6%)
	Placebo	254	27	49 (19.3%)	23 (9.1%)	14 (5.5%)	3 (1.2%)	4 (1.6%)	13 (5.1%)	3 (1.2%)	3 (1.2%)

AE: adverse event, DC: discontinuation, N: number, NR: Not reported

D3. Ongoing Studies

No records were found.

D4. Previous Systematic Reviews and Technology Assessments

Our review found no ongoing health technology assessments or systematic literature review related to tavapadon and Parkinson's disease. However, we identified several systematic literature reviews and network meta-analyses evaluating the effectiveness and safety of our comparators of interest, four of which are summarized below.

Comparison for Efficacy and Tolerability among Ten Drugs for Treatment of Parkinson's Disease: A Network Meta-Analysis[6]

This systematic review and network meta-analysis aimed to evaluate the efficacy and tolerability of ten selected monotherapies in patients with either early PD or advanced PD or both. The review included 110 RCTs involving more than 24,000 patients with PD that assessed UPDRS scores and/or discontinuations. Levodopa ranked high in efficacy outcomes and had low discontinuation rates; however, long term side effects including dyskinesia and motor complications were a concern. Dopamine agonists (i.e., pramipexole, ropinirole, and rotigotine patch) and one MAO-B inhibitor (selegiline) also ranked higher in efficacy outcomes compared to placebo. Ropinirole demonstrated a lower risk of discontinuation compared to placebo whereas selegiline appeared to have a higher discontinuation rate compared to levodopa, ropinirole, and rotigotine patch. One key limitation of this study was evaluating monotherapies in patients with advanced PD as such patients typically use adjunct therapies (e.g., dopamine agonists, MOAB inhibitors, or COMT inhibitors etc.) to levodopa in clinical practice.

Comparative efficacy and safety of adjunctive drugs to levodopa for fluctuating Parkinson's disease - network meta-analysis[31]

This systematic review and network meta-analysis compared the efficacy, tolerability, and safety of adjunctive therapies to levodopa in patients experiencing motor fluctuations. The review included 48 RCTs of 12 drugs that evaluated changes in OFF time as an efficacy endpoint and five safety outcomes including discontinuations due to AEs, incidence of AEs, dyskinesia, hallucinations, and orthostatic hypotension. Two dopamine agonists (pramipexole and ropinirole) and one MAO-B inhibitor (safinamide) ranked the highest in efficacy endpoint. There was no drug that ranked consistently higher across all tolerability and safety endpoints. One key limitation of this study was using a frequentist framework since many health technology assessment bodies currently prefer Bayesian framework over the frequentist framework to undertake a NMA.[151]

Dopamine agonists versus levodopa monotherapy in early Parkinson's disease for the potential risks of motor complications: A network meta-analysis[152]

This systematic review and network meta-analysis compared dopamine agonists versus levodopa monotherapy in early-stage PD. The review included nine RCTs that assessed one of these outcomes: UPDRS scores, discontinuations, dyskinesia, nausea, insomnia, somnolence, orthostatic hypotension, headache, and dizziness. Levodopa ranked higher in all efficacy endpoints and had a lower discontinuation rate compared to dopamine agonists; however, it showed a higher risk of dyskinesia. Pramipexole demonstrated a better efficacy profile than other dopamine agonists whereas ropinirole generally had a lower risk of adverse events. The primary limitation of this study was the exclusion of MAO-B inhibitors as a comparator in this population.

Efficacy and safety of adjunctive oral therapy in Parkinson's disease with motor complications: a systematic review and network meta-analysis[153]

This systematic review and network meta-analysis compared the efficacy and safety of dopamine agonists, MAO-B inhibitors, and COMT inhibitors as adjunctive treatment to levodopa in patients with PD experiencing motor fluctuations. The review included 18,693 patients from 74 RCTs that assessed outcomes including changes in daily OFF times, UPDRS scores, HRQoL scores, risk of dyskinesia, risk of hallucinations, and risk of ICD etc. All adjunct therapies demonstrated better efficacy compared to levodopa alone, with pramipexole appeared to be the highest in ranking. All three therapies were associated with a higher risk of dyskinesia. Only studies evaluating dopamine agonists reported the risk of ICD events. We believe this study was well conducted, with one minor drawback being the use of JADAD scale for quality assessment instead of the traditional Cochrane risk of bias (ROB2) approach.

E. Long-Term Cost-Effectiveness: Supplemental Information

E1. Detailed Methods

Table E1.1. Impact Inventory

Sector	Type of Impact (Add additional domains, as relevant)	Included in This Analysis from […] Perspective?		Notes on Sources (if quantified), Likely Magnitude & Impact (if not)
		Health Care Sector	Societal	
Formal Health Care Sector				
Health Outcomes	Longevity effects	X	X	
	Health-related quality of life effects	X	X	
	Adverse events	X	X	
Medical Costs	Paid by third-party payers	X	X	
	Paid by patients out-of-pocket	¨	¨	
	Future related medical costs	X	X	
	Future unrelated medical costs	X	X	
Informal Health Care Sector				
Health-Related Costs	Patient time costs	NA	¨	
	Unpaid care partner-time costs	NA	X	
	Transportation costs	NA	¨	
Non-Health Care Sector				
Productivity	Labor market earnings lost	NA	X	
	Cost of unpaid lost productivity due to illness	NA	X	
	Cost of uncompensated household production	NA	¨	
Consumption	Future consumption unrelated to health	NA	¨	
Social Services	Cost of social services as part of intervention	NA	¨	
Legal/Criminal Justice	Number of crimes related to intervention	NA	¨	
	Cost of crimes related to intervention	NA	¨	
Education	Impact of intervention on educational achievement of population	NA	¨	
Housing	Cost of home improvements, remediation	NA	¨	
Environment	Production of toxic waste pollution by intervention	NA	¨	
Other	Other impacts (if relevant)	NA	¨	

NA: not applicable

Adapted from Sanders et al[154]

Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[155]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

Target Population

The economic evaluation comprised two models, each with a distinct target population reflecting a different point in the Parkinson's disease course. Model 1 evaluated patients with early Parkinson's disease initiating first-line symptomatic therapy and its base-case cohort emulated the populations of the TEMPO-1 trials of tavapadon monotherapy, with a mean age of 63.7 years and a baseline distribution across modified Hoehn and Yahr (HY) stages of 23.7% in stage 1 and 76.3% in stage 2. Model 2 evaluated patients with Parkinson's disease established on levodopa and experiencing motor fluctuations and its base-case cohort emulated the TEMPO-3 trial population, with a mean age of 64.9 years and a baseline HY-stage distribution of 66.6% in stage 2 and 33.4% in stage 3. In both models, the underlying cohort was assigned the mean MDS-UPDRS Part II and Part III scores and mean daily OFF-time corresponding to its HY stage, estimated from the Parkinson's Progression Markers Initiative (PPMI) cohort and then treatment effects were assigned across the arms as described below. Baseline characteristics are shown in Table E1.2.

Table E1.2. Base-Case Model Cohort Characteristics

	Model 1 (Early PD)	Model 2 (PD with Motor Fluctuations)	Primary Source
Age	63.7	64.9	TEMPO-1 and -3
Sex, male	64.7%	63.3%	TEMPO-1 and -3
Modified HY Stage at Baseline	Stage 1: 23.7% Stage 2: 76.3% Stage 3: 0% Stage 4: 0% Stage 5: 0%	Stage 1: 0% Stage 2: 66.6% Stage 3: 33.4% Stage 4: 0% Stage 5: 0%	TEMPO-1 and -3

HY: Hoehn and Yahr**, PD: Parkinson's disease**

Treatment Strategies

Interventions and comparators were identified with input from patient organizations, clinicians, manufacturers, and payers. In both models, the intervention was tavapadon, dosed per the regimen evaluated in the TEMPO trials (5 to 15 mg orally once daily) and modeled as chronic therapy. In Model 1, the comparator was levodopa, modeled as carbidopa/levodopa 25 mg/100 mg taken eight times daily. In Model 2, the comparator was a market basket of other dopamine agonists used as add-on therapy to levodopa, comprising ropinirole, pramipexole, and rotigotine, weighted by their relative use in practice (Table E1.3).

Table E1.3. Treatment Regimen Recommended Dosage:

	Tavapadon	Levodopa (Model 1)	Dopamine Agonist Market Basket (Model 2)
Route	Oral	Oral	Oral / transdermal
Dosing	5–15 mg once daily	Carbidopa/levodopa 25/100 mg, eight times daily	Ropinirole 3 mg TID; pramipexole 1 mg TID; rotigotine 2 mg/24-hr patch daily
Duration	Chronic	Chronic	Chronic

hr: hour, mg: milligram, TID: three times a day

E2. Model Inputs and Assumptions

Unless otherwise noted, model inputs were identical across Model 1 and Model 2. The two models differed only in the baseline population and in the treatment-effect inputs (MDS-UPDRS score changes and OFF-time), which were drawn from the relevant trials and network meta-analyses. Detailed inputs and sources described below. All costs were inflated to 2026 US dollars.

Model Inputs

Clinical Inputs

Model 1 and Model 2 Discontinuation

In Model 1, treatment discontinuation for tavapadon was estimated using TEMPO-1 and -2 for the first cycle and then using the discontinuation pattern of dopamine agonists (DA) observed in an analysis of MarketScan Medicare data anchored to the rate from the first cycle. Rather than applying the observed cycle-specific rates directly, we fit parametric survival distributions to the DA time-to-discontinuation data, with the log-normal distribution providing the best fit. Per-cycle (6-month) discontinuation probabilities were then derived from the fitted survivor function for cycles 1-25, the period over which data were available; beyond cycle 25, the probability was held constant at the cycle-25 value (6.24%).

To anchor these DA-based probabilities to tavapadon, we drew on the pooled TEMPO-1 and TEMPO-2 trials, in which 32.12% of patients discontinued over the trial period. As no head-to-head data were available, this trial-period estimate was compared with the corresponding DA discontinuation (30.7%) to yield a discontinuation rate ratio of 1.0642(= 32.67/30.7). Applying this multiplier to the log-normal DA per-cycle probabilities produced the tavapadon per-cycle probabilities, which were likewise held constant beyond cycle 25 (6.53% = 6.24% × 1.0463). No discontinuation was applied to the comparator arm (levodopa) or to patients after switching from tavapadon to levodopa.

In Model 2, treatment discontinuation for the dopamine agonist plus levodopa (DA + levodopa) comparator was estimated from the MarketScan Medicare database. As above, rather than applying the observed cycle-specific rates directly, we fit parametric survival distributions to time-to-discontinuation; the log-normal provided the best fit. Per-cycle (6-month) discontinuation probabilities were derived from the fitted survivor function for cycles 1-25, the period over which data were available. Beyond cycle 25, the probability was held constant at the cycle-25 value (9.52%).

Tavapadon plus levodopa discontinuation was further informed by the TEMPO-3 trial, in which 38% of patients discontinued over the trial period. As no head-to-head data were available, tavapadon plus levodopa was modeled relative to DA + levodopa: the trial-period tavapadon discontinuation (38%) was compared with the corresponding DA + levodopa discontinuation (48%), yielding a discontinuation rate ratio of 0.7917 (= 38/48). This multiplier was applied to the log-normal DA + levodopa per-cycle probabilities to obtain the tavapadon plus levodopa per-cycle probabilities, and was likewise held constant beyond cycle 25 (7.53% = 9.52% × 0.7917). Once patients moved to the monotherapy market basket, no further discontinuation was assumed.

Table E2.1 Per Cycle Discontinuation Rates

		Model 1		Model 2	
Cycle	**Month**	**Tavapadon**	**DAs (not a comparator)***	**Tavapadon + Levodopa**	**DA + Levodopa**
1	6	26.15%	24.58%	30.09%	38.01%
2	12	26.35%	24.76%	30.34%	38.32%
3	18	22.57%	21.21%	25.98%	32.81%
4	24	19.79%	18.60%	22.76%	28.75%
5	30	17.70%	16.63%	20.35%	25.70%
6	36	16.07%	15.11%	18.46%	23.32%
7	42	14.76%	13.87%	16.94%	21.40%
8	48	13.68%	12.86%	15.69%	19.82%
9	54	12.78%	12.00%	14.64%	18.49%
10	60	12.00%	11.27%	13.73%	17.35%
11	66	11.32%	10.64%	12.95%	16.36%
12	72	10.73%	10.08%	12.27%	15.50%
13	78	10.21%	9.59%	11.66%	14.73%
14	84	9.74%	9.15%	11.12%	14.05%
15	90	9.32%	8.76%	10.63%	13.43%
16	96	8.94%	8.40%	10.19%	12.88%
17	102	8.59%	8.08%	9.79%	12.37%
18	108	8.28%	7.78%	9.43%	11.91%
19	114	7.99%	7.51%	9.09%	11.48%
20	120	7.72%	7.25%	8.78%	11.09%
21	126	7.47%	7.02%	8.50%	10.73%
22	132	7.24%	6.80%	8.23%	10.40%
23	138	7.03%	6.60%	7.98%	10.08%
24	144	6.83%	6.41%	7.75%	9.79%
25	150	6.64%	6.24%	7.53%	9.52%
26+	156+	6.64%	6.24%	-	-

DA: Dopamine agonist

*The dopamine agonist (DA) monotherapy discontinuation was used to derive the discontinuation rates for the tavapadon arm in Model 1, but was not included directly in the model.

Clinical Probabilities/Response to Treatment

Disease progression was modeled as movement across HY stage-based health states, with transitions restricted to forward (more severe) movement only. Annual HY-stage transition probabilities were estimated from the PPMI cohort,[62] restricted to patients enrolled for at least two years, and were identical across both models and across treatment arms, reflecting the assumption that none of the evaluated therapies modify the rate of progression. The full transition-probability matrices are reported in Table E2.2.

Treatment effects were applied to symptoms rather than to the rate of disease progression. In both models, the interventions were assumed not to alter the underlying trajectory of HY stage progression or mortality. HY-stage transition probabilities were therefore identical across arms, and the treatment effect operated entirely by improving the symptom scores experienced *within* each HY stage. This reflects the evidence base, in which the TEMPO trials and the comparator trials measured symptomatic change over trial follow-up rather than long-term modification of disease progression.

The specific symptom targeted differed by model, corresponding to the primary outcome of the relevant network meta-analysis (NMA). In Model 1 (early PD), the treatment effect was the relative difference in MDS-UPDRS Part II (patient-reported motor experiences of daily living) and Part III (clinician-assessed motor examination) scores for tavapadon versus each comparator. In Model 2 (PD with motor fluctuations), the treatment effect was the relative difference in daily OFF-time. In each case, the effect estimate was the pooled mean difference from the NMA (Section 3.2), which incorporated both the direct trial comparisons and the indirect evidence linking the treatments through common comparators.

Each effect was applied as a constant shift to the relevant within-stage mean value. For a given HY stage, the treatment arm was assigned the stage's mean MDS-UPDRS (Part II and Part III separately) or OFF-time value shifted by the NMA-estimated mean difference relative to the comparator arm, and this shift was applied uniformly across all HY stages. For example, if the NMA estimated that tavapadon reduced MDS-UPDRS Part III by a given number of points relative to the comparator, the mean Part III score in the treatment arm was reduced by that number of points in every HY stage the cohort occupied. The magnitude of the shift did not vary by stage, by time since treatment initiation, or by the patient's baseline score; it was a fixed additive difference between the treatment and comparator arms.

The treatment effect was applied only while a patient remained on therapy. Upon discontinuation, the symptom shift was removed and the remaining patients got the new symptom profiles for the corresponding HY stage, consistent with the treatment switching assumptions described above. Because the effect operated on within-stage symptom scores rather than on stage transitions, it influenced quality-adjusted life-years (through the utility adjustment) and, in Model 2, OFF-time-related costs, but did not change the number of life-years, the timing of HY-stage progression, or mortality, which were identical across arms.

Table E2.2. Annual Transition Probabilities

		To				
		HY 1	**HY 2**	**HY 3**	**HY 4**	**HY 5**
From	**HY 1**	0.490	0.506	0.004	0.000	0.000
	HY 2	0.000	0.930	0.065	0.004	0.001
	HY 3	0.000	0.000	0.815	0.146	0.039
	HY 4	0.000	0.000	0.000	0.845	0.155
	HY 5	0.000	0.000	0.000	0.000	1.000

HY: Hoehn and Yahr stages

Mortality

All-cause mortality was modeled using an excess-hazard approach. Background mortality was drawn from US life tables (National Center for Health Statistics)[74] and applied by age and sex at each cycle, so that background mortality rose as the cohort aged. Stage-specific mortality was estimated from the PPMI cohort[62] as incidence rate ratios (IRRs) of observed deaths to those expected from age- and sex-matched life-table rates over the same person-time at risk, functioning as stage-specific standardized mortality ratios applied multiplicatively to the background rate within each health state (Table E2.3). For HY Stages 1 and 2, the estimated ratios did not differ significantly from general-population expectations (p=0.148 and p=0.715), so no excess mortality was applied and the multiplier was set to 1.0. For HY stages 3 through 5, statistically significant excess mortality was applied using the estimated ratios of 2.84, 4.22, and 7.71, respectively. Because the PPMI cohort skews toward earlier-stage disease, deaths at advanced stages were limited and the corresponding estimates carried greater uncertainty, most evident in the wide confidence interval at HY 5 (3.68 to 16.17). Hence, alternative values from the published PD mortality literature were examined in sensitivity analyses. Mortality was unaffected by treatment in both models.

Table E2.3. Mortality Inputs

Parameter	Value (IRR)	95% CI	P value	Applied Multiplier*	Source
Background Mortality		—	—	—	US Life Tables (NCHS)[74]
HY Stage 1 Excess Mortality	0.43	0.14-1.35	0.148	1.00	PPMI[62] (authors' analysis)
HY Stage 2 Excess Mortality	1.04	0.84-1.30	0.715	1.00	PPMI[62] (authors' analysis)
HY Stage 3 Excess Mortality	2.84	1.98-4.09	<0.001	2.84	PPMI [62] (authors' analysis)
HY Stage 4 Excess Mortality	4.22	2.59-6.89	<0.001	4.22	PPMI (authors' analysis)
HY Stage 5 Excess Mortality	7.71	3.68-16.17	<0.001	7.71	PPMI [62] (authors' analysis)

CI: Confidence interval, HY: Hoehn and Yahr stages, IRR: Incidence rate ratios, PPMI: Parkinson's precision medicine initiative

Utilities

Health-state utilities were derived from Lowin et al. (2017),[65] stratified by HY stage and by the proportion of waking hours spent in the OFF state, capturing the combined effect of disease stage and motor-fluctuation burden (Table E2.4). These baseline utilities were further adjusted for within-stage variation in motor severity using the NICE (2016)[68] whereupon each one-point change in MDS-UPDRS Part II away from the within-state mean corresponded to a utility change of 0.04, and each one-point change in Part III by 0.02, with utilities bounded between 0 and 1.

We estimated the mean daily OFF-time for patients in each HY stage from the PPMI data. Then, based on the distribution of patients across HY stages at each cycle combined with these stage-specific OFF-time estimates, we calculated the occupancy-weighted mean OFF-time for the cohort at each cycle. Each treatment reduces daily OFF-time by a treatment-specific amount taken from TEMPO-3 and NMA. We subtract this reduction from the baseline stage OFF-time to obtain the reduced, on-treatment OFF hours at each HY stage, so the size of the reduction depends on which treatment a patient is receiving.

Chaudhuri et al. (2022) reported HY-stage-specific utilities for patients experiencing different percentages of their day in OFF.[63] Across our model cycles, the cohort's mean OFF-time stayed below 25% of the day, so we used the decrement Chaudhuri et al. (2022) reported for the 0-24% OFF band. We assumed this decrement corresponds to patients spending, on average, 12% of their day in OFF, and converted it into a per-OFF-hour disutility by dividing over that exposure (0.12 × 24=2.88 hours/day). Multiplying this per-hour disutility by the mean OFF hours at each HY stage yields the stage-specific OFF-related disutility.

Table E2.4. Utility Values for Health States

HY Stage	OFF 0%	OFF >0–24%	OFF 25–49%	OFF 50–75%	OFF >75%
1	0.820	0.790	0.760	0.730	0.707
2	0.710	0.680	0.650	0.621	0.598
3	0.590	0.570	0.540	0.510	0.480
4	0.480	0.460	0.430	0.400	0.376
5	0.389	0.357	0.324	0.293	0.268

HY: Hoehn and Yahr stages
OFF-time category: proportion of waking hours spent in the OFF state. Based on Chaudhuri 2022, Supplementary Table 13.

Adverse Events

Each event was assigned an incremental cost and, where applicable, a disutility, for one cycle applied to the arm in which it occurred. Disutility sources are described in the report (Section 4.2) and last for one-cycle.

The cost estimates for adverse events, except for orthostatic hypotension, are based on retrospective incidence cohort of all Medicare fee-for-service patients diagnosed between 2006 to 2020.[72] The estimates show the incremental spending associated with patients experiencing an event adjusted for clinical and demographic characteristics. Similarly, the orthostatic hypotension estimate was based on a retrospective cohort study using claims data (Merative MarketScan) to estimate the spending difference for patients with Parkinson disease who do and do not have orthostatic hypotension.[82]

We estimated utility using a variety of sources. Because no somnolence-specific health-state utility estimate was available, we used the disutility of sleep disturbance (0.12) from (Domingos, 2026),[80] a Parkinson's disease EQ-5D-5L vignette study, as a proxy; nighttime sleep disturbance and daytime somnolence are related but distinct, so this value is an approximation rather than a direct estimate. The dyskinesia disutility was derived from (Hjalte, 2025),[79] a Swedish National Parkinson's Disease Registry study (n=1,085) that estimated the association between daily hours in the OFF state or with dyskinesia and health-related quality of life measured by the EQ-5D; we applied the reported per-hour EQ-5D decrement for dyskinesia (0.01 per hour) multiplied by the mean daily dyskinesia hours observed in the TEMPO-3 trial to obtain the health-state disutility for patients experiencing dyskinesia. The impulse control disorder disutility was derived in two steps. First, we used (Leroi et al., 2011),[77] a study of 99 patients with Parkinson's disease that compared quality of life (measured by the eight-item Parkinson's Disease Questionnaire, PDQ-8) across patients with impulse control disorders, apathy, or neither, to estimate the difference in PDQ-8 score associated with impulse control disorder. Because the model requires utilities on the EQ-5D scale, we then mapped this PDQ-8 difference to an EQ-5D utility decrement using the published PDQ-8-to-EQ-5D crosswalk of Cheng et al. (2018),[78] yielding the health-state disutility applied to patients experiencing impulse

control disorder. For hallucinations, we could not identify a direct health-state disutility estimate suitable for the model, nor a disutility for another adverse event with a comparable quality-of-life burden that could serve as a proxy. We therefore applied an assumed disutility of 0.05 in the base case and tested its influence in sensitivity analysis, varying it from half to double this value (0.025 to 0.10).

For orthostatic hypotension/dizziness, no direct health-state utility estimate was available, so we attributed its disutility primarily to falls. We estimated the orthostatic-hypotension-attributable rate of medically attended falls as 4.5% per year, the adjusted difference in fall rates between PD patients with and without neurogenic orthostatic hypotension reported by François et al. (2017) in a claims analysis (25.6% versus 21.2% over a 12-month post-index window), and multiplied this rate by the per-faller EQ-5D fall disutility of 0.09 from Pillay et al. (2024), yielding a disutility of approximately 0.004 per patient with orthostatic hypotension.[81,82]

Table E2.5. Included Adverse Events

Adverse Event (Per Cycle Incidence)	Model 1		Model 2			Incremental Cost*	Disutility
	Tavapadon	Levodopa	Tavapadon + Levodopa	Other DAs + Levodopa	Mono-therapy market basket		
Dyskinesia	-	-	10%	4.2%	2.4	$5,164	0.02
Dyskinesia, Prevalence (cycle 1)†	0%	7%	-	-	-		-
Dyskinesia, Prevalence (year 5 Onwards)†	0%	50%	-	-	-		-
Somnolence / Excessive Daytime Sleepiness	3.1%	4.5%	5.2%	5.4%	5.7%	$7,548	0.12
Hallucination			5.6%	4.9%	1.4%	$13,463	0.05
Orthostatic Hypotension / Dizziness	5.3%	2.3%	6.0%	1.3%	1.9%	$6,606	0.004
Impulse Control Disorder (Cycle 1)†	1.0%	1.3%	2.4%	6.9%	3.2%	$14,505	0.08
Impulse Control Disorder (Year 5 Onwards)†	1.0%	12%	2.4%	51%	25.7%		

*Costs are incremental spending per 6-month model cycle, applied to the arm in which the event occurs. Costs from Song et al. (2023); orthostatic hypotension from François et al. (2017); inflated to 2026 USD.

†Dyskinesia (for Model 1) and impulse control disorder (ICD) are the only two events modelled with a time-varying incidence; all other adverse events are applied at a constant per-cycle rate across all cycles. For these two events, per-cycle incidence is predicted from an event-specific cumulative-hazard function through year 5 and then held constant per cycle thereafter. The hazard functions differ by event (and, for a given event, by arm and model): dyskinesia is based on Rascol et al (2000). The value shown is the cycle-1 (first 6-month) and cycles from year 5 onwards.

Economic Inputs

Because tavapadon had not received regulatory approval, a placeholder price of $15,000 per year (IPD Analytics) was used in both models. In Model 1, carbidopa/levodopa was costed at the median generic WAC from RED BOOK ($289 per year). In Model 2, the dopamine agonist comparator used a market-basket approach with shares derived from a 2024 Merative MarketScan Medicare Supplemental analysis (ropinirole 51.9%, pramipexole 41.6%, rotigotine 6.4%), yielding a weighted-average annual cost of $3,588.

Drug Acquisition Costs

Table E2.6. Drug Cost Inputs Intervention

	Dosing	Annual Drug Cost	Source
Tavapadon	5–15 mg once daily	$15,000 (placeholder)*	IPD Analytics
Levodopa (Model 1)	Carbidopa/levodopa 25/100 mg, 8×/day	$289	RED BOOK (median generic WAC)
Dopamine Agonist Market Basket (Model 2)	Ropinirole 3 mg TID; pramipexole 1 mg TID; rotigotine 2 mg/24-hr patch	$3,588 (weighted)	RED BOOK; SSR Health (rotigotine net); MarketScan shares
Monotherapy Market Basket (Model 2)	65% Carbidopa/levodopa 25/100 mg, 8×/day; 35% on DA market basket (Ropinirole 3 mg TID; pramipexole 1 mg TID; rotigotine 2 mg/24-hr patch)	$816	RED BOOK; SSR Health (rotigotine net); MarketScan shares

mg: milligram
*Placeholder price from IPD Analytics; no net price available.

Administration and Monitoring Costs

All interventions and comparators were orally or transdermally self-administered and required no provider-administered dosing; no administration or monitoring costs were applied. Health Care Utilization Costs

Annual direct medical costs were assigned by HY stage and daily OFF-time. HY-stage health-state costs were drawn from Johnson et al. (2013),[70] excess PD-related direct medical costs relative to an age- and sex-matched non-PD patient, ranging from $7,604 (HY 1) to $96,063 (HY 5) after inflation to 2026 USD. An OFF-time increment was added on top of the stage cost, based on the OFF-hour-stratified HCP consultation and hospitalization costs from Thach et al. (2021),[71] so that the between-arm difference captured the incremental cost attributable to the between-arm difference in OFF-time without double-counting the general burden in the stage costs.

Productivity Costs

In the modified societal perspective, we estimated patient productivity losses using the per-patient indirect cost estimates reported in the 2026 Lewin/MJFF economic burden report,[84] which applied a human capital approach to self-reported data from the 2024 PD and Related Disorders Impact Survey. The report attributes three components of labor market productivity loss to persons with Parkinson's disease: reduced employment ($5,557 per patient per year), absenteeism ($3,108 per patient per year), and presenteeism ($2,682 per patient per year), for a combined annual productivity loss of $11,347 per patient (2024 USD). These estimates were used to set a baseline for the per-patient level of productivity loss and were applied to each arm.

To allow productivity loss to respond to treatment, we also linked an OFF-hour attributable portion to each arm's OFF time. Here absenteeism and presenteeism among patients with Parkinson's disease were derived from Abeynayake et al. (2020), which reported the proportion of patients with and without OFF time exceeding successive monthly thresholds of missed and less-productive workdays.[85] Because these thresholds are cumulative, we converted them into non-overlapping frequency bins by differencing adjacent thresholds, weighted each bin by its midpoint (assuming approximately 22 days, a near-full working month, for the open-ended ≥20 category), and summed across bins to obtain the expected number of missed and less-productive days per month in each group. We took the difference between the with-OFF and without-OFF groups as the burden attributable to OFF, yielding 25.75 absentee days (absenteeism) and 42.43 less-productive days (presenteeism) per year. These losses were scaled to the average daily OFF hours (2.9 hours) experienced by US patients with OFF time reported in Thach et al to obtain a productivity loss per OFF hour,[86] which was then applied to each arm's daily OFF hours and converted to a per-cycle cost.

Care partner costs comprised lost formal (paid) labor, tied to OFF-time at 75 hours per year per additional daily OFF hour — and informal (unpaid) caregiving time, valued by the opportunity-cost method meaning population average wages are also used to assign costs. Informal caregiving increased with HY stage (Ciepielewska et al. 2025) plus an OFF-attributable increment of 3.04 care partner hours per week per additional daily OFF hour (derived from Abeynayake and Tanner 2020 and PPMI OFF-time).[62,85,87] Comparator-arm societal totals were anchored to the 2026 Lewin/MJFF benchmark.[2]

E3. Results

Model 1 (Early PD)

Over the lifetime horizon, both arms accrued 11.13 discounted life years, reflecting the assumption that neither tavapadon nor levodopa alters disease progression or mortality. Tavapadon accrued 6.701 discounted QALYs compared with 6.716 for levodopa, an incremental loss of approximately 0.015 QALYs, favoring levodopa. Because no incremental life years were generated, equal-value life years were numerically identical to QALYs in both arms. Under the health care sector perspective, total discounted costs were $1,083,000 for tavapadon and $1,056,000 for levodopa, an incremental cost of $27,308. This incremental cost is smaller than the difference in drug acquisition costs alone ($37,000 versus $3,200, a difference of $33,800), indicating that tavapadon was associated with approximately $6,500 in offsetting reductions in non-intervention costs over the lifetime horizon, attributable to lower adverse-event costs and to treatment discontinuation.

Model 2 (PD with Motor Fluctuations)

Both arms accrued 9.63 discounted life years. Tavapadon accrued 5.477 discounted QALYs compared with 5.467 for the dopamine agonist market basket, a gain of approximately 0.01 QALYs favoring tavapadon. This difference reflects the OFF-time results: tavapadon patients accrued 7,100 total discounted OFF hours compared with 7,015 for the market basket, a difference of 85 hours, indicating a modest increase in daily OFF-time for tavapadon than for the comparator. Under the health care sector perspective, total discounted costs were $1,182,000 for tavapadon and $1,153,000 for the market basket, an incremental cost of $28,700, which is marginally greater than the difference in acquisition costs alone ($39,700 vs. $5,300, a difference of $34,400). Because tavapadon was both more costly and less effective than the market basket, it was dominated.

Comparison Across Perspectives

The two perspectives behaved differently between the models, and the difference is informative about how the societal cost components enter each model. In Model 1, the incremental cost was $27,300 under the health care sector perspective and $36,600 under the modified societal perspective. In Model 2, by contrast, the incremental cost rose from $28,700 under the health care sector perspective to $30,400 under the modified societal perspective, a difference of $1,700.

Health-Related Quality of Life Burden

The ratio of QALYs to life years provides an indication of average health-related quality of life over the modeled horizon. In Model 1, patients accrued approximately 0.60 QALYs per life year in both arms, consistent with a cohort beginning in HY Stages 1 and 2 and progressing over a lifetime horizon. In Model 2, patients accrued approximately 0.57 QALYs per life year, reflecting the more

advanced baseline distribution (HY stages 2 and 3) and the additional utility decrement associated with time spent in the OFF state.

E4. Sensitivity Analyses

See table E4.1 below for details of the sensitivity results.

Table E4.1. Tornado Diagram Inputs and Results for Tavapadon versus Levodopa (Model 1) and Tavapadon versus Other Dopamine Agonists (Model 2)

Parameter	Lower Input	Upper Input	ICER at Lower Input*	ICER at Upper Input*
Model 1 (Tavapadon vs. Levodopa), Health Care System Perspective				
UPDRS II Per-Point Disutility	0.03	0.05	$7,700,000	-$783,000
UPDRS III Per-Point Disutility	0.02	0.03	-$1,100,000	-$5,000,000
Tavapadon vs. Placebo, UPDRS-II Change	-2.59	-1.15	$510,000	-$329,000
Tavapadon vs. Placebo, UPDRS-III Change	-8.86	-5.46	$424,000	-$282,000
Disutility, Dyskinesia	0.02	0.03	-$1,500,000	-$2,100,000
Levodopa vs. Placebo, UPDRS-III Change	-8.49	-4.19	-$229,000	$322,000
Somnolence/Excessive Daytime Sleepiness Prevalence, Levodopa Arm	0.03	0.06	-$1,500,000	-$2,000,000
ICD Disutility	0.06	0.10	-$1,600,000	-$2,000,000
Levodopa Proxy ICD Hazard, Per Year	0.02	0.03	-$1,600,000	-$2,000,000
Disutility, Somnolence	0.09	0.14	-$1,700,000	-$1,800,000
Model 1 (Tavapadon vs. Levodopa), Modified Societal Perspective				
UPDRS II Per-Point Disutility	0.03	0.05	$7,700,000	-$783,000
UPDRS III Per-Point Disutility	0.02	0.03	-$1,100,000	-$5,000,000
Tavapadon vs. Placebo, UPDRS-II Change	-2.59	-1.15	$510,000	-$329,000
Tavapadon vs. Placebo, UPDRS-III Change	-8.86	-5.46	$424,000	-$282,000
Disutility, Dyskinesia	0.02	0.03	-$1,500,000	-$2,100,000
Levodopa vs. Placebo, UPDRS-III Change	-8.49	-4.19	-$229,000	$322,000
Somnolence/Excessive Daytime Sleepiness Prevalence, Levodopa Arm	0.03	0.06	-$1,500,000	-$2,000,000
ICD Disutility	0.06	0.10	-$1,600,000	-$2,000,000
Levodopa Proxy ICD Hazard, Per Year	0.02	0.03	-$1,600,000	-$2,000,000
Disutility, Somnolence	0.09	0.14	-$1,700,000	-$1,800,000
Model 2 (Tavapadon vs. Other Dopamine Agonists), Health Care System Perspective				
ICD Disutility	0.06	0.10	$5,600,000	$1,900,000
Dopamine Agonist ICD Hazard, per Year	0.11	0.18	$5,300,000	$2,000,000
OFF-time Reduction (per day), Tavapadon	0.34	1.55	-$2,400,000	$878,000
Somnolence/Excessive Daytime Sleepiness Prevalence, Other DA Arm	0.04	0.07	$3,800,000	$2,300,000
Somnolence/Excessive Daytime Sleepiness Prevalence, Tavapadon Arm	0.04	0.07	$2,400,000	$3,700,000

HY2 0-24 Hour Disutility	0.02	0.04	$2,500,000	$3,400,000
Hallucination Prevalence, Tavapadon Arm	0.04	0.07	$2,600,000	$3,300,000
Hallucination Prevalence, Other DA Arm	0.04	0.06	$3,200,000	$2,600,000
Treatment Cost After Switching (Market Basket)	$541	$902	$2,600,000	$3,200,000
HY1 0-24 Hour Disutility	0.02	0.04	$2,600,000	$3,200,000
Model 2 (Tavapadon vs. Other Dopamine Agonists), Modified Societal Perspective				
ICD Disutility	0.06	0.10	$5,900,000	$2,100,000
OFF-time Reduction (per day), Tavapadon	0.34	1.55	-$3,000,000	$738,000
Dopamine Agonist ICD Hazard, per Year	0.11	0.18	$5,600,000	$2,100,000
Somnolence/Excessive Daytime Sleepiness Prevalence, Other DA Arm	0.04	0.07	$4,000,000	$2,500,000
Somnolence/Excessive Daytime Sleepiness Prevalence, Tavapadon Arm	0.04	0.07	$2,500,000	$3,900,000
HY2 0-24 Hour Disutility	0.02	0.04	$2,700,000	$3,600,000
Hallucination Prevalence, Tavapadon Arm	0.04	0.07	$2,700,000	$3,400,000
Hallucination Prevalence, Other DA Arm	0.04	0.06	$3,400,000	$2,800,000
Treatment Cost After Switching (Market Basket)	$541	$902	$2,800,000	$3,300,000
HY1 0-24 Hour Disutility	0.02	0.04	$2,800,000	$3,400,000

DA: Dopamine agonist, HY: Hoehn and Yahr, ICD: Impulse control disorder, CE: cost-effectiveness
*Note lower input may reflect either upper or lower incremental CE ratio value depending on the direction that the input has on the incremental CE ratio output.

E5. Scenario Analyses

See Table E5.1 for the full set of costs and effects (evLYs and QALYs which are equal in these models) for each of the six scenario analyses ran on Model 1 and Model 2.

Table E5.1 Scenario Analysis Results

Scenario	Treatment Arm	Health Care System Perspective		Modified Societal Perspective	
		Total Cost	QALYs / evLYs*	Total Cost	QALYs / evLYs*
Model 1. Early Parkinson's Disease Model: Tavapadon vs. Levodopa					
Base Case	Tavapadon	$1,082,000	6.701	$1,698,000	6.701
	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Shorter Time Horizon (2 years)	Tavapadon	$82,200	1.591	$161,000	1.591
	Levodopa	$62,300	1.607	$141,000	1.607
Shorter Time Horizon (10 years)	Tavapadon	$386,000	4.981	$780,000	4.981
	Levodopa	$360,000	4.996	$754,000	4.996
	Tavapadon	$1,121,000	6.721	$1,737,000	6.721

Scenario	Treatment Arm	Health Care System Perspective		Modified Societal Perspective	
		Total Cost	QALYs / evLYs*	Total Cost	QALYs / evLYs*
No Discontinuation After Cycle 1 (Tavapadon)	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Distribution of Part II/III Scores and OFF-Time	Tavapadon	$1,082,000	6.701	$1,698,000	6.701
	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Exclude Future Unrelated Health Care Costs	Tavapadon	$369,000	6.701	$984,000	6.701
	Levodopa	$342,000	6.716	$958,000	6.716
No Adverse Event in Tavapadon Group After Cycle 1	Tavapadon	$1,080,000	6.708	$1,696,000	6.708
	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Model 2. Adjunct Therapy Model: Tavapadon vs. Other Dopamine Agonists					
Base Case	Tavapadon	$1,182,000	5.477	$1,910,000	5.477
	Other DAs	$1,153,000	5.467	$1,879,000	5.467
Shorter Time Horizon (2 years)	Tavapadon	$111,000	1.480	$221,000	1.480
	Other DAs	$95,800	1.482	$204,000	1.482
Shorter Time Horizon (10 years)	Tavapadon	$484,000	4.331	$1,015,000	4.331
	Other DAs	$458,000	4.322	$987,000	4.322
No Discontinuation After Cycle 1 (Tavapadon)	Tavapadon	$1,223,000	5.563	$1,936,000	5.563
	Other DAs	$1,153,000	5.467	$1,879,000	5.467
Exclude Future Unrelated Health Care Costs	Tavapadon	$421,000	5.477	$1,149,000	5.477
	Other DAs	$392,000	5.467	$1,118,000	5.467
No Adverse Event in Tavapadon Group After Cycle 1	Tavapadon	$1,177,000	5.491	$1,905,000	5.491
	Other DAs	$1,153,000	5.467	$1,879,000	5.467
OFF-Time Related Disutility Halved	Tavapadon	$1,182,000	5.621	$1,910,000	5.621
	Other DAs	$1,153,000	5.605	$1,879,000	5.605
	Other DAs	$1,156,000	5.465	$1,881,000	5.465
Model 1. Early Parkinson's Disease Model: Tavapadon vs. Levodopa					
Base Case	Tavapadon	$1,082,000	6.701	$1,698,000	6.701
	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Shorter Time Horizon (2 years)	Tavapadon	$82,200	1.591	$161,000	1.591
	Levodopa	$62,300	1.607	$141,000	1.607
Shorter Time Horizon (10 years)	Tavapadon	$386,000	4.981	$780,000	4.981
	Levodopa	$360,000	4.996	$754,000	4.996
	Tavapadon	$1,121,000	6.721	$1,737,000	6.721

Scenario	Treatment Arm	Health Care System Perspective		Modified Societal Perspective	
		Total Cost	QALYs / evLYs*	Total Cost	QALYs / evLYs*
No Discontinuation After Cycle 1 (tavapadon)	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Distribution of Part II/III Scores and OFF-Time	Tavapadon	$1,082,000	6.701	$1,698,000	6.701
	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Exclude Future Unrelated Health Care Costs	Tavapadon	$369,000	6.701	$984,000	6.701
	Levodopa	$342,000	6.716	$958,000	6.716
No Adverse Event in Tavapadon Group After Cycle 1	Tavapadon	$1,080,000	6.708	$1,696,000	6.708
	Levodopa	$1,056,000	6.716	$1,671,000	6.716
Model 2. Adjunct Therapy Model: Tavapadon vs. Other Dopamine Agonists					
Base Case	Tavapadon	$1,182,000	5.477	$1,910,000	5.477
	Other DAs	$1,153,000	5.467	$1,879,000	5.467
Shorter Time Horizon (2 years)	Tavapadon	$111,000	1.480	$221,000	1.480
	Other DAs	$95,800	1.482	$204,000	1.482
Shorter Time Horizon (10 years)	Tavapadon	$484,000	4.331	$1,015,000	4.331
	Other DAs	$458,000	4.322	$987,000	4.322
No Discontinuation After Cycle 1 (Tavapadon)	Tavapadon	$1,223,000	5.563	$1,936,000	5.563
	Other DAs	$1,153,000	5.467	$1,879,000	5.467
Distribution of Part II/III Scores and OFF-Time	Tavapadon	$1,182,000	5.477	$1,910,000	5.477
	Other DAs	$1,153,000	5.467	$1,879,000	5.467
Exclude Future Unrelated Health Care Costs	Tavapadon	$421,000	5.477	$1,149,000	5.477
	Other DAs	$392,000	5.467	$1,118,000	5.467
No Adverse Event in Tavapadon Group After Cycle 1	Tavapadon	$1,177,000	5.491	$1,905,000	5.491
	Other DAs	$1,153,000	5.467	$1,879,000	5.467
OFF-Time Related Disutility Halved	Tavapadon	$1,182,000	5.621	$1,910,000	5.621
	Other DAs	$1,153,000	5.605	$1,879,000	5.605
	Other DAs	$1,156,000	5.465	$1,881,000	5.465

DAs: Dopamine agonists, evLYs: equal-value life year, QALY: quality-adjusted life year

*QALYs equal evLYs in both models

E6. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

E7. Prior Economic Models

Our systematic literature review did not identify any published cost-effectiveness analyses of tavapadon for Parkinson's disease. We therefore could not benchmark our results against a prior model of the same intervention. We did, however, identify a body of prior decision-analytic models in Parkinson's disease, cataloged in two methodological reviews, against which we compared our structural and methodological choices.[156-158]

Consistent with the majority of prior Parkinson's disease models, our models used a Markov structure with health states defined by Hoehn and Yahr (HY) stage and unidirectional (forward-only) progression.[70] The Johnson et al. (2013) model used a six-state framework (HY stages 1 through 5 plus death) and a societal perspective. For our motor-fluctuation model (Model 2), in which the treatment effect operates through daily OFF-time rather than HY-stage progression, we additionally aligned with Parkinson's disease models that structure outcomes around OFF-time burden.[159] Our approach of layering an OFF-time effect onto an HY-stage structure has been used in other work as well (Chaudhuri 2022, van Boven 2014).[63,160] While prior Markov models in Parkinson's disease have defined health states by Hoehn and Yahr stage and OFF-time category,[63] and others have used MDS-UPDRS Part III as a progression measure (Fundament 2016, Fann 2020),[161,162] we did not identify a prior cohort Markov model that simultaneously incorporated Hoehn and Yahr stage, OFF-time, and continuous MDS-UPDRS Part II and Part III scores to fully capture patients experience with the disease. The only identified model integrating these dimensions jointly used an individual-patient simulation rather than a cohort Markov structure.[163]

Direct numerical comparison of our discounted cost and outcome estimates to prior models was not appropriate. No prior model evaluated tavapadon, and the available prior models differ substantially from ours in comparator, population, time horizon, and, most importantly, in their measurement of treatment effect, with the most frequently cited models (e.g., the entacapone and pramipexole analyses) predating both the MDS-UPDRS and contemporary OFF-time data. These

models were therefore informative for validating our structural and methodological choices but not for benchmarking our absolute results. When comparing results to other studies such as Dams 2013 and Chaudhuri 2022, we find the estimated costs vary from over $900,000 to under $200,000 2026 USD with total costs in our models falling between these two estimates. However, these models do estimate expected life years at roughly 10 years, where both of our models are less than this estimate (7.7 and 8.6). This may be due to the US life expectancy being lower than that of the countries studied (UK and Germany).

F. Potential Budget Impact: Supplemental Information

Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons.

ICER's methods for estimating potential budget impact are described in detail in the Value Assessment Framework. The intent of our approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility.

As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent five-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2025-2026, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $821 million per year for new drugs.