INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Tavapadon for Parkinson's Disease
Response to Public Comments on Draft Evidence Report

September 16, 2026

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Manufacturers		
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1.	**AbbVie unequivocally disagrees with ICER's Draft Evidence Report conclusions regarding tavapadon.** The Draft Evidence Report materially understates the unmet need experienced by people living with Parkinson's disease (PwP), undervalues tavapadon's potential contribution to real-world Parkinson's disease (PD) care, and does not provide a scientifically sound basis for assessing tavapadon's value. It relies on a comparative evidence base that does not meet rigorous methodological standards and a modeling framework that fails to represent real-world clinical practice, the experiences of PwP, and outcomes that matter to PwP and their care partners. As a result, the conclusions systematically undervalue key treatment benefits, including symptom control, functional improvement, safety and tolerability, convenience, care-partner burden, and real-world trade-offs that persist despite currently available therapies. These omissions are especially consequential for tavapadon, which is currently under FDA review and not yet approved. Tavapadon is the first selective oral D1/D5 receptor agonist designed for once-daily administration, with clinical trials demonstrating clinically meaningful motor symptom control and low rates of	Thank you for your comments. We strive to adhere to best-practice standards in all the work we do, including synthesis of available clinical evidence, economic evaluation, and our interactions with patients and caregivers. We feel quite strongly that we have tried to accurately capture what patients, and care partners have told us about the daily and longer-term burdens of Parkinson's disease (PD). With regard to tavapadon's benefits, risks, and possible place in therapy our approach (as would be the case in any rigorous comparative effectiveness analysis) was to summarize the evidence on any direct treatment comparisons and to perform indirect comparisons to alternative therapies described in clinical guidelines and/or recommended by clinical experts. We explored the sensitivity of our results to numerous structural changes and alternative specifications for these indirect comparisons and found that our conclusions remained unchanged. We also want to note that we departed from some of our indirect comparison data in development of the cost-effectiveness model, where our access to contemporary real-world data allowed for estimation of discontinuation rates and incidence of selected adverse events such as impulse control disorders (ICDs) among older agents for PD. Use of this information and comparison to the TEMPO trial data resulted in comparisons that were actually quite favorable to tavapadon. In the course of our review we did uncover an error in how switch therapy costs were calculated for Model 2. While this did not change our overall conclusions, the threshold prices for tavapadon (and therefore our health benefit price benchmarks) increased substantially.

	adverse events of interest, supporting a favorable benefit-risk profile in clinical practice. ICER's conclusions should therefore not be used as a definitive benchmark for decision-making.	
2.	**Methodological concern: Insufficient evidence rigor** ICER's approach to systematic literature reviews and indirect treatment comparisons does not adhere to established guidelines (e.g., PRISMA, NICE DSU, ISPOR).[1–3] These methodological limitations impair the validity of the comparative evidence base and compromise the reliability of any conclusions drawn from the assessment.	We strongly disagree with this comment. Our process was documented publicly at each stage and follows best practices for Health Technology Assessment that ICER has followed for many years. We published our scope for comment and revised it in response to stakeholder inputs. We then posted our full research protocol, outlining the entire systematic review process, including following PRISMA, and network meta-analysis (NMA) approach. Most importantly, our supplement section D in the draft report includes detailed literature review and NMA methods. While updating two previous NMAs, we provided reasons for the excluded studies as well. We also have cited PRISMA guidelines and included the PRISMA flow chart. These steps are consistent with the three guidelines cited and support the goal that our work be transparent and reproducible. This is also a general comment with no specifics on particular gaps or deficits in our work, so there are no feasible steps to take.
3.	**Methodological concern: Failure to prioritize outcomes that matter most to PwP and their care partners** Currently available pharmacologic treatments for PD are primarily used to manage symptoms rather than modify the underlying progression of the disease. The assessment places insufficient emphasis on symptom control, functioning, independence, quality of life, and care-partner burden, leading to an incomplete evaluation of treatment benefit.	Our review started by talking with patients and their care partners. The outcomes that they prioritized are our primary outcomes. We agree that currently available therapies do not modify disease, so symptom control is paramount. Our review therefore focused on what was measured in terms of symptoms as well as other outcomes we could feasibly link to symptom control.

4.	**Methodological concern: Incomplete capture of eligible PwP who may benefit from new treatment options and populations relevant to real-world practice** ICER's simplified approach, which relies on two disconnected PD cohorts and restrictive treatment assumptions, does not adequately reflect the heterogeneity of PD, the complexity of contemporary treatment pathways, or the evolving treatment decisions made by PwP and clinicians over the course of the disease. Evaluating tavapadon as a direct alternative to first-line oral levodopa may not reflect likely treatment patterns. As tavapadon enters the market, it is unlikely to displace levodopa as first-line therapy. At the same time, ICER's assumptions regarding adjunctive use appear overly narrow and do not adequately capture the range of clinical circumstances in which tavapadon could potentially be used. Together, these limitations constrain the applicability of ICER's findings to real-world clinical practice and decision-making.	Any effort to understand the potential impact of a newly emerging therapy must follow the available evidence. We modeled two distinct candidate populations for tavapadon (monotherapy in early PD and as an adjunct to levodopa in later-stage disease) to reflect the design and entry criteria of the pivotal clinical trials. We agree that our modeling effort does not capture the full heterogeneity of disease. Our evidence synthesis strives to capture heterogeneity, when possible, but subgroup data and information on stratified treatment effects were limited or missing in available trial data.
5.	**Methodological concern: Incomplete assessment of safety and long-term value** The model does not fully account for tolerability, adverse-event burden, treatment complexity, or long-term outcomes, thereby understating the value of sustained symptom control and treatment over time. Specifically, ICER's model inputs do not appear to	The model incorporates somnolence and ICD for both tavapadon and its comparators using the best available evidence from trials and observational studies. We are unsure precisely what is meant by "underestimate the burden of…ICDs", as we have integrated evidence-based projections of costs as well as quality-of-life impacts of these events. There are no available data or studies on the gain to PD patients from reduced pill burden.

	accurately capture the rates of somnolence associated with comparator D2/D3 dopamine agonists. The model also appears to underestimate the burden of impulse-control disorders (ICDs) and does not adequately account for the potential value of once-daily administration or the impact of treatment complexity on PwP and their care partners. Further, long-term efficacy and tolerability evidence from the TEMPO-4 open-label extension appears to be minimally incorporated into the model, limiting its ability to capture the potential benefits of sustained treatment over time.[4]	To examine the potential impact of a gain to patients and caregivers from reduced pill burden, we added a scenario analysis that applies a time savings of 1 hour per week each to patients and caregivers as a benefit of reduced pill burden. Finaly, while we look forward to the complete results of TEMPO-4, the results have not yet been fully published, limiting our ability to incorporate them into the simulation model.
6.	**Methodological concern: Undervaluation of societal and care-partner benefits** ICER's modified societal perspective fails to meaningfully link PwP productivity and care-partner burden costs to the Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) in early PD. As a result, the model implies that improvements in PD symptoms have no impact on societal outcomes (e.g., ability to work, work productivity, and care-partner burden). This is not reflective of the lived experiences of PwP or their care partners. This model simplification increases the absolute costs while leaving incremental results unchanged, thereby downplaying the value of treatments that improve symptoms in people with early PD. By assigning insufficient weight to	Currently, there is very limited publicly available evidence that could be used to link productivity or caregiver burden to MDS-UPDRS in early PD which limits our ability to conduct analyses that make these assumptions. Nonetheless, we have added a scenario where we assign 50% of the utility gain to patients in model 1 to caregivers as an added benefit in the modified societal perspective analysis. We also have made this limitation explicit in the report. Because the Model 1 treatment effect operates through MDS-UPDRS scores, not linking productivity and care-partner costs to these scores means any societal offsets from motor and functional improvement are not counted. We also reviewed the sources identified by other commenters (the NICE foslevodopa-foscarbidopa appraisal and Pahwa et al. 2023) as potential bases for linking care-partner burden to disease severity and describe in the Uncertainties and Controversies section of the report that unfortunately no unredacted information was available for use. We also describe this issue further below in Genentech comment 2.

	these outcomes, the analysis understates the value of treatments that may help PwP remain active, independent, productive, and better manage daily life.	
7.	**Procedural concern: Lack of transparency** AbbVie did not have full access to the economic model through ICER's Model Transparency Program. This procedural limitation makes it difficult to fully evaluate the model structure, assumptions, and internal consistency, and therefore further reduces confidence in the robustness, validity, and reliability of the reported results. **Procedural concern: Limited reproducibility of reported results** Certain model outputs, cost inputs, terminology, and budget-impact calculations are not presented with sufficient detail to allow independent verification. This limits confidence that the reported results are fully reproducible and appropriate for use as a decision-making benchmark.	We acknowledge that the model transparency effort did not operate as intended but note that such agreements are between manufacturer and collaborating institution, and ICER is not directly involved. When it was clear that access to the model in a timely fashion was not feasible, ICER and its collaborator offered alternative solutions (i.e., a walkthrough presentation and discussion, extended model review time period), which were declined by the manufacturer. There are no details provided on what is contributing to "limited reproducibility of reported results." Nevertheless, we have reviewed the model section of the report and the Supplement and added further details where we felt necessary.
8.	**Procedural concern: Compressed evidence- review process** ICER's compressed assessment timeline is insufficient to support a rigorous, fit-for-purpose evaluation, particularly given the complexity and heterogeneity of PD. As a result, ICER's process forces material simplifications that critically undermine the scientific rigor and real-world relevance of its assessment of tavapadon.	We recognize that for treatments undergoing FDA review there are often limited data available. However, patients, clinicians and insurers are still immediately faced with decisions about how best to use these new agents once approved for use. As such, we view comparative clinical effectiveness research and cost-effectiveness modeling as a useful and important way to identify the key inputs that impact the effectiveness and cost of a new therapy. Even when there is uncertainty about the actual values used in the models, sensitivity analyses can highlight the range of plausible values and their impact on overall cost-

		effectiveness. This report uses data that are currently available and highlights the limitations of these data as well as the qualitative input of a range of stakeholders.
9.	**Parkinson's disease remains an area of significant unmet need:** AbbVie is deeply committed to advancing innovation for PwP. PD is a complex, progressive neurological condition affecting more than 1 million people in the US,[5] and it imposes a substantial burden on PwP, care partners, families, and society. In 2024, the economic burden of PD in the US was estimated at $68.0 billion in annual costs.[5] Including an additional $2.8 billion in indirect costs associated with care-partner productivity loss brings the total economic burden to over $70 billion.[5] Nearly 40% of PwP rely on unpaid care partners, more than 20% of whom reduced their work hours or retired early, and 34% missed their own routine health care visits because of caregiving demands.[5] Despite decades of research and multiple available therapies, significant unmet need persists. PD progressively takes away individuals' independence, making everyday activities such as walking, dressing, eating, or simply rising from a chair challenging. As the disease advances, many PwP	We agree. This is described extensively in the Background and in Section 2 (Patient and Other Stakeholder Perspectives) and is also quantified in Table 5.1.

	experience worsening motor symptoms, including but not limited to tremor, rigidity, bradykinesia, gait impairment, and debilitating motor fluctuations characterized by unpredictable transitions between periods of adequate symptom control ("ON" time) and the return of disabling symptoms ("OFF" time). These changes are not isolated clinical events; they can drive progressive disability, greater dependence on care partners, increased need for supportive services, medication adjustments, emergency or unplanned care, and other health care resource utilization over time. Beyond motor symptoms, PD affects a breadth of non-motor symptoms, including but not limited to sleep, cognition, and mood.[6] The worsening motor and non-motor symptoms have significant impacts on social engagement and overall quality of life, extending their toll well beyond the individual patient and placing considerable physical, emotional, and financial strain on care partners and families.	
10.	**Parkinson's disease remains an area of significant unmet need:** Current treatment options fall short of fully addressing this burden. Oral levodopa remains the first-line treatment for PD, but it can become less effective at managing symptoms as the disease progresses. Levodopa-induced	Again, we agree. See Table 5.1.

	dyskinesia has been found to affect 40–50% of PwP treated for five years, and the majority of PwP would experience it after 10 years of treatment.[7] As PD progresses, many PwP require adjustments to oral levodopa dose and dosing frequency, as well as additional medications, to maintain motor control. These changes can contribute to increasingly complex treatment regimens and pill burden. Additionally, higher oral levodopa doses (above 600 mg/day) are associated with a substantially higher risk of developing dyskinesias compared with doses <400 mg/day, contributing to a difficult clinical balancing act between symptom control and long-term motor complications.[8] Alternative therapies, such as D2/D3 dopamine agonists, can be used to address PD, but are often limited by life-altering side effects, including ICDs, hallucinations, excessive daytime sleepiness, and peripheral edema.[9] These side effects can profoundly affect PwP and their families, leading to loss of independence, financial consequences, care-partner burden, treatment discontinuation, and reduced quality of life. PwP and clinicians today are often forced to choose between inadequate symptom control and a heightened risk of side effects.[9]	
11.	**Tavapadon as a meaningful therapeutic innovation in Parkinson's disease:** Tavapadon is designed to address the gaps outlined above. Currently	We agree, as highlighted in our evidence ratings, that tavapadon is more effective than placebo in measures of symptom control. Yet there are residual uncertainties in terms of adverse events and rates of discontinuation.

	under FDA review, tavapadon represents a new approach to oral symptomatic PD therapy as the first selective oral D1/D5 receptor agonist designed for once-daily administration. In the Phase 3 program, treatment with tavapadon demonstrated statistically significant and clinically meaningful improvements in motor symptom control, when used with or without levodopa, across the stages of PD compared with placebo at week 26.[10,11] The efficacy with tavapadon was sustained for an additional 52 weeks of treatment (TEMPO-4 open-label extension), with >90% of patients not requiring initiation of oral levodopa (rollover from TEMPO-1 and -2) or escalation of oral levodopa (rollover from TEMPO-3).[4,12] Additionally, rates of adverse events typically associated with D2/D3 dopamine agonism (e.g., ICDs and somnolence) remained low through the 26-week parent studies and 52-week open-label extension studies. Tavapadon offers clinicians and PwP an additional treatment option for navigating the complex trade-offs inherent to PD management.	You noted above that it is not more effective than levodopa in early PD. The real question is whether it has fewer adverse events than older, less receptor-specific dopamine agonists. Given the lack of head-to-head studies, this is highly uncertain. A recent systematic review and meta-analysis of tavapadon, independent of ICER's work, also raises concerns about the adverse event profile of tavapadon.[1]
12.	**Tavapadon as a meaningful therapeutic innovation in Parkinson's disease:** The value of tavapadon should also be considered in the broader context of therapeutic innovation. Beyond the clinical data, tavapadon represents a meaningful new treatment option in a disease characterized by relentless progression, loss of independence,	The indirect comparisons that we and others have performed (see above) do not show clear benefits of tavapadon compared with the older dopamine agonist therapies. The best way to demonstrate such evidence is to perform head-to-head randomized trials versus the older dopamine agonists.

	and increased mortality. For PwP, families, and clinicians, innovation brings not only measurable clinical benefits but also hope and expanded treatment choice in an area where new options have been limited. Recognizing the value of novel therapies is therefore essential to a complete assessment of treatments intended to help PwP maintain symptom control, function, and quality of life over time.	
GE HealthCare		
1.	GE HealthCare manufactures DaTscan™ (ioflupane I 123 injection), the first FDA-approved imaging agent indicated as an adjunct to other diagnostic evaluations for striatal dopamine transporter visualization using SPECT brain imaging in adult patients with suspected parkinsonian syndromes and, in these patients, to help differentiate essential tremor from tremor due to parkinsonian syndromes, including idiopathic Parkinson's disease.[7] Published evidence from prospective, meta-analytic, and observational studies supports the clinical utility of DaTscan in settings of diagnostic uncertainty, including effects on diagnostic confidence, diagnosis, and subsequent clinical management.[8-11] In this context, we note that the proposed cost-effectiveness models in the DER are based on clinically diagnosed PD populations derived from the TEMPO-1 and TEMPO-3 trials, which enrolled patients meeting the UK	Thank you for your comments. This project focuses on medications used by patients with diagnosed PD, and while misdiagnosis may lead to spending on medications that will not help, this is outside of the scope of our review. The model population comprises patients with established Parkinson's disease, following the design of the TEMPO trials that represent the best available evidence on the effects of tavapadon. A scenario focused on diagnostic confirmation would therefore not address questions about the incremental benefits and risks of tavapadon.

	Parkinson's Disease Society Brain Bank Diagnostic Criteria. However, the model does not include a diagnostic confirmation step or imaging-related costs for clinically uncertain cases. As a result, the model does not evaluate the potential impact of diagnostic confirmation on treatment cohort composition in patients with clinically uncertain parkinsonism. We respectfully suggest that ICER consider a scenario analysis in clinically uncertain cases that incorporates diagnostic confirmation and associated imaging costs, with patients subsequently classified according to the presence or absence of evidence of dopaminergic deficit. Such an analysis could evaluate the impact of reclassifying patients without evidence of dopaminergic deficit outside the PD treatment cohort, including avoidance of unnecessary treatment costs and the resulting effect on clinical and economic outcomes. This approach may provide additional insight into how diagnostic heterogeneity encountered in routine clinical practice could influence model results. Parkinson's disease is the fastest growing neurodegenerative disorder worldwide. In the context of an expanding aging population, the need for accurate diagnosis and effective, individualized treatment strategies is paramount, not only to improve patient outcomes but also	

	to enhance quality of life for patients and their caregivers. While we recognize that the proposed model appropriately reflects the populations evaluated in the pivotal TEMPO trials, we respectfully encourage ICER to consider the potential impact of diagnostic confirmation in clinically uncertain cases. A scenario analysis incorporating diagnostic confirmation, patient reclassification, and associated costs may may better reflect the impact of diagnostic uncertainty on treatment utilization, clinical outcomes, and economic results in real-world practice. We appreciate ICER's commitment to incorporating stakeholder perspectives and thank you for the opportunity to provide input on this important assessment.	
Genentech		
1.	PD imposes a substantial clinical, humanistic, and economic burden on patients, care partners, and healthcare systems. While current symptomatic treatments provide motor symptom management, significant unmet needs persist, particularly regarding slowing disease progression, unpredictability of symptom control, medication side effects, long-term complications, and care partner burden. Genentech and Roche are evaluating multiple approaches to slow down disease progression in PD. Currently, we are investigating a monoclonal	Thank you for your comments. We appreciate your commendation of our work.

	antibody that targets alpha-synuclein aggregation—a hallmark pathology we now understand drives Parkinson's progression. We commend ICER for incorporating several progressive, state-of-the-art modeling principles based on 2 methodological reviews on published economic models to evaluate PD therapies— Dams 2011 and Dams 2023- in this draft report. In particular, we are in agreement with the following: • **Natural History Calibration:** utilizing the longitudinal Parkinson's precision medicine initiative (PPMI) cohort to derive Hoehn and Yahr (HY) transition matrices and excess mortality standardized mortality ratios (SMRS). **Multi-Domain Within-Stage Tracking:** incorporating continuous movement disorder society–unified parkinson's disease rating scale (MDS-UPDRS) part II, part III, and daily OFF-time hours within discrete HY states. • **Co-Base Case Modified Societal Perspective:** evaluating patient productivity loss and care partner formal labor and unpaid caregiving time, alongside direct medical costs. • **Long-Term Behavioral Hazard Modeling:** explicitly	

	integrating cumulative time-varying risks for dopaminergic complications, such as impulse control disorders.	
2.	To build upon these strengths and ensure that the final Evidence Report reflects the realities of living with PD and aligns with rigorous health-economic methodology, we present three key recommendations based on 30 papers that we had systematically reviewed, including 20 papers that met Dams 2023 criteria (Ruoss, et al. Value in Health 2025). We expand on these recommendations with supporting rationale below:	We too would like to ensure that we fully capture how patients and their care partners are impacted by the disease. To the extent feasible, we used perspectives gleaned from patient interviews and multiple interactions with key patient advocacy groups to obtain both additional perspective and direction to available and useful data. That being said, we focused attention on what we could feasibly model about the effects of the therapy under review given the available evidence.
3.	**Incorporate Specified Societal Perspective From Patient & Care partner Testimonies: fully capture informal care partner & patient impact from key clinical milestones within base-case evaluations.** **Recommendation**: ICER should refine its societal perspective by incorporating functional improvements (MDS-UPDRS Parts II/III) into productivity models, applying care-partner disutility offsets from existing literature, and factoring in discrete event disutilities and cost drivers for key clinical milestones identified in patient interviews. **Rationale:** While ICER's modified societal perspective focused on	We agree that linking functional improvement to productivity and incorporating care-partner disutility would strengthen the societal perspective, and we examined the NICE foslevodopa-foscarbidopa appraisal (2023), the underlying Adelphi Disease Specific Program estimates, and the Pahwa et al. (2023) citation you provided. The Adelphi-based caregiver disutilities in the NICE appraisal were reported as commercial-in-confidence and the key metrics were redacted, which prevented us from applying them directly. Appeals to both NICE and the manufacturer of record for that appraisal to obtain unredacted data were unsuccessful.

	daily OFF-time hours only, without accounting for functional impairment and care partner health-related quality of life (HRQoL). ICER's report stated that caregiver utility inputs could not be identified to link care-partner disutility to patient disease severity or OFF-time (pp. 49–50). However, published literature and health technology assessments had established caregiver disutilities based on Adelphi Disease Specific Program that directly linked to patient severity level (e.g. The NICE Technology Appraisal for foslevodopa–foscarbidopa (2023)), and associated informal care hours by Pahwa et al. (2023, Mov Disord). In addition, ICER's qualitative feedback (Section 2) highlighted cognitive decline, recurrent falls, loss of independence, and institutionalization as pivotal concerns for patients and care partners. Nevertheless, in the draft model, falls were entered only as disutility from orthostatic hypotension (p. 34), institutionalization was embedded inside broad HY 3–5 stage costs (p. 36), and dementia was omitted. **Implications:** Excluding caregiver HRQoL spillover and restricting productivity offsets to OFF-time duration yields an incomplete analysis that fails to reflect the true specified societal burden identified by ICER's qualitative findings from patient and care-partner interviews	
4.	**Integrate The Full Disease Continuum And**	The primary aim of the model is to capture the average incremental treatment effect when comparing treatments. The H&Y stage does

	Heterogeneity: explicitly incorporate non-motor symptoms (NMS) and discrete clinical progression milestones. **Recommendation:** ICER should explicitly incorporate NMS —such as cognitive decline, depression, sleep disturbances, autonomic dysfunction (or MDS-UPDRS Part I scores)—as core drivers of patient daily functioning, overall health-related quality of life, care partner burden, and resource utilization. **Rationale:** While symptomatic treatments do not reverse underlying neurodegeneration, targeted symptomatic therapy significantly improves daily functioning, sleep architecture, mood stability, gastrointestinal motility, and overall HRQoL (Pedrosa & Timmermann, 2013; Tibar et al., 2018). As recognized in ICER's original Tavapadon Background and Scope document, NMS represent major determinants of long-term patient burden and cost. In the current draft report, NMS were captured only indirectly through general HY-stage utility mappings or specific adverse event inputs (e.g., hallucinations or impulse control disorders). Similarly, major clinical milestones—such as cognitive impairment, recurrent falls, and transition to institutional care—were aggregated into broad stage-based costs rather than modeled as explicit event transitions. Explicitly modeling NMS progression and clinical milestones ensures that the	indirectly capture non-motor symptoms, although rates do not differ between treatments given the focus of available trial evidence. The model does directly capture adverse events that have been shown from randomized controlled trials to vary between treatments. We have clarified in the report that non-motor symptoms enter through the HY-stage utility and cost structure and through the modeled adverse events that differ between treatments, and that milestones such as falls, cognitive decline, and institutionalization are captured within stage-level costs rather than as explicit events. We identify explicit event-level modeling of these milestones as a priority for future work when data linking them to treatment become available.

	full clinical trajectory and economic offsets of therapy are accurately evaluated. **Implications:** Omitting explicit pathways for NMS and bundling discrete high-cost milestones understates the true disease burden and misses critical drivers of healthcare utilization and long-term care costs.	
5.	**3. Shift from Short-Term Symptom Control to Lifetime Disease Progression: transition toward a flexible modeling framework capable of separating underlying neurodegeneration disease progression from transient symptomatic treatment effects.** **Recommendation:** ICER should transition toward flexible modeling architectures (e.g., individual-level microsimulations or hybrid state-transition models) capable of separating underlying neurodegenerative disease trajectory (slope change) from transient symptomatic treatment effects (reversible intercept shift), as formally defined by Vu et al. (2012, Br J Clin Pharmacol) and Ribba et al. (2024, J Parkinsons Dis). **Rationale:** The current ICER draft model relies on a traditional de novo semi-Markov cohort framework structured around discrete HY stages 1–5. As ICER noted in Supplement E7, cohort Markov models structured around discrete HY states struggle to integrate joint continuous trajectories. While HY staging	Microsimulation and hybrid state-transition approaches are valuable when individual-level heterogeneity, history dependence, or the separation of disease-modifying from symptomatic effects materially affects the incremental result. For a symptomatic therapy evaluated against comparators that also target symptoms only and given that the available evidence supports average treatment effects rather than differential progression, a cohort semi-Markov structure was deemed as most appropriate for this assessment. We agree that a hybrid architecture may be an important direction for future PD models, particularly as disease-modifying therapies emerge, and trials should provide more detailed evidence of treatment effect heterogeneity or lack thereof.

	provides a recognized global disability framework, it lacks the granularity required to track continuous disease trajectory and cannot differentiate between a therapy that alters underlying neurodegeneration and one that merely provides temporary symptomatic control. Furthermore, applying constant symptomatic shifts across static transition probabilities fails to reflect real-world treatment patterns, disease heterogeneity, or long-term persistence. A hybrid microsimulation framework—combining integrating HY stage, OFF-time, and MDS-UPDRS scores simultaneously, —would provide a more structurally faithful and credible basis for lifetime economic evaluations as noted by Chandler et al. (2021, J Mark Access Health Policy). **Implications:** Relying solely on standard HY cohort models obscures treatment dynamics and risks misestimating the long-term value of Parkinson's therapies.	

#	Comment	ICER Response
Patient/Patient Groups		
American Parkinson Disease Association (APDA)		
1.	**Comparative Clinical Effectiveness** As mentioned in the report, currently available dopamine agonists primarily target D2/D3 receptors, whereas Tavapadon selectively targets D1-like receptors. This receptor proclivity was one of the major drivers for the development of Tavapadon, with an anticipated lower rate of neuropsychiatric side effects than other dopamine agonists. Despite this, the report notes that it is very hard to directly compare neuropsychiatric side effects in clinical trials involving Tavapadon versus the clinical trials of other dopamine agonists as the reported data is inconsistent across trials. It would be valuable for reviewers of this report to be aware of post-clinical trial data available on currently available dopamine agonists. One large study showed that the odds of having an individual impulse control disorder are 2 to 3.3 times higher in patients treated with dopamine agonists as compared with patients not treated with dopamine agonistsi. This "real world" data can't be directly compared to the TEMPO study during which exposure to Tavapadon was much shorter than the analysis in the paper. However, it seems reasonable to include this data for context for those accessing this ICER report. The report, as currently written, does not fully reflect how challenging the side	Thank you for your comments. We agree and have cited this observational study in the report. However, it is worth reviewing a recent systematic review and meta-analysis of the tavapadon trials, independent from ICER's work, that found the incidence of ICDs was 2 times higher with tavapadon than with placebo over a short follow-up period.[1] The real-world evidence suggests a steady increase in the incidence of ICD events over at least 3 years. It is unclear whether the hypothesized receptor specificity of tavapadon translates into fewer ICD events, particularly over the long term, although limited data from the TEMPO-4 study suggest relatively steady rates over an additional year of follow-up. Furthermore, the discontinuation rates in the tavapadon groups were very high and appear higher than those observed in the pivotal trials of the other dopamine agonists. Again, this is indirect evidence, which contributes to the uncertainty in these comparisons and the overall uncertainty in the net health benefits of tavapadon compared with other dopamine agonists. Ideally, we would have head-to-head randomized trials comparing tavapadon to the earlier dopamine agonists. It remains unclear whether tavapadon will have fewer ICDs than other DAs over longer periods of follow-up. We have expanded our discussion of this issue in the uncertainties and controversies section of the clinical assessment.

	effects and management of side effects can be with currently available dopamine agonists, and as such, may not fully reflect the value of Tavapadon for patients.	
2.	**Long Term Cost Effectiveness** The report aims to determine whether Tavapadon is cost effective in two clinical situations – as a first line agent in comparison with Levodopa (Model 1) and as an adjunctive therapy along with Levodopa in comparison to other available dopamine agonists (Model 2). In real-world movement disorders practice, when a first line agent is being selected, especially in cases in which Levodopa is not well tolerated because of nausea, dizziness or somnolence, Tavapadon would be considered along with all currently available long and short acting dopamine agonists. Therefore Model 1 presents a limited use case for Tavapadon which should be acknowledged in the report. The report takes into account drug costs, non-drug costs and societal costs, with additional costs applied when a patient experienced an adverse event (dyskinesia, hypotension, somnolence, hallucinations, Impulse Control Disorders). Societal costs include productivity losses of the person with PD, as well as care partner formal and informal labor costs.	We have added a sentence acknowledging that Model 1 (tavapadon monotherapy versus levodopa) represents a specific first-line scenario and that, in practice, a patient for whom levodopa is poorly tolerated would be considered for tavapadon or other dopamine agonists. We have also taken care throughout the report to distinguish outcomes that are unmeasured from outcomes shown to be absent.

3.	Both the non-drug costs and societal costs are linked almost exclusively to H+Y stage and amount of OFF time experienced. However, the report independently acknowledges based on extensive input from patients, care partners and other stakeholders that non-motor symptoms (which are not limited to the 5 included in the model as the costs associated with adverse events), are often the main drivers of disability. In addition, the model does not fully capture other symptoms that are not directly linked to H+Y scale or OFF time and are reflected in a decreased quality of life in PD for both the person with PD and care partner. These include increased frailty, more predilection for falls, and decreased independence. The cost calculations in this report, therefore, likely do not fully reflect the lived experience of people with Parkinson's disease and their care partners, which must be central to any analysis of the benefits of a new medication. The PD research community acknowledges that a PD progression scale that reflects non-motor symptom burden of PD would be a valuable tool to develop as a resource for future clinical trials and analyses. More generally, the PD community is in need of additional tools to help fully understand the potential benefit (or lack thereof) of any new intervention that is introduced. These tools would better quantify the relationship between PD progression, both	We agree that non-motor symptoms, frailty, falls, and loss of independence matter to the lived experience of Parkinson's disease and are not captured explicitly by HY stage and OFF-time. To the extent these symptoms track with disease severity, they are captured indirectly through the HY-stage utility and cost structure, and the non-motor symptoms measured in the trials and shown to differ between treatments (such as impulse control disorders and somnolence) are captured directly. We agree that this reflects a gap in available measurement tools rather than an absence of benefit and have distinguished throughout the report between outcomes that are unmeasured and those shown to be absent**.**

	motor and non-motor, on quality of life and societal productivity of both the person with PD and care partner. It is important to note however, that the lack of data on these relationships should not be conflated with lack of benefit.	
Davis Phinney Foundation for Parkinson's		
1.	In reviewing the report, we appreciate its recognition of this complexity. The draft also highlights an important challenge extending well beyond this assessment: **our full understanding of what matters to people with Parkinson's is often not represented in the data we have available to quantify those outcomes.** In several areas, ICER appropriately acknowledges that available evidence is insufficient to incorporate important dimensions of lived experience into its quantitative analysis. For example, the model could not incorporate care-partner health-related quality of life and may therefore underestimate total care-partner impact. Similarly, available evidence allowed productivity and care-partner costs to be linked to OFF time, but not to improvements in motor function or activities of daily living, even though maintaining function and independence can have profound implications for individuals and families. We recognize that ICER cannot incorporate quantitative evidence that does not exist, nor should unproven benefits be attributed to	Thank you for your comments. We wholeheartedly agree. We started by speaking to patients with PD about their most important outcomes and found that many of them were not captured in the clinical trials. Our approach to lack of evidence is not to consider it evidence of lack of efficacy, but to consider it a marker for greater uncertainty. Our evidence ratings for tavapadon reflect this uncertainty. We have also edited several areas of the report to note that absence of evidence does not equate to absence of benefit.

	tavapadon or any individual therapy. However, **lack of evidence is not evidence of lack of benefit.** We encourage ICER to distinguish consistently between evidence demonstrating limited benefit and insufficient evidence to determine the presence or magnitude of benefit. Where meaningful outcomes cannot be adequately measured, their value should not inadvertently be treated as zero or characterized as unlikely to be meaningful. The discussion of care-partner quality of life provides a particularly clear example. The report acknowledges that available data do not permit care-partner quality of life to be incorporated into the model and that care-partner impact is therefore likely underestimated. Yet the Benefits Beyond Health section concludes that tavapadon is "unlikely to produce substantial improvements" in care-partner quality of life. We believe the available evidence supports describing this potential benefit as **unknown** or **not adequately measured**, rather than unlikely.	
2.	Finally, this review highlights an important opportunity for the Parkinson's community as a whole: **researchers, funders, advocacy organizations, industry, clinicians, and people living with Parkinson's share a role in building the evidence base needed to better translate lived experience into future value assessments.** We would welcome ICER's perspective	Thank you. We agree and have highlighted key uncertainties and their connection to future research in both Sections 3 and 4 of the report.

	on the evidence, measures, datasets, or research approaches that would have enabled these dimensions to be more meaningfully incorporated into this assessment. We appreciate ICER's continued engagement with the Parkinson's community and its transparency about the limitations of the available evidence. We hope the final report will preserve those limitations as uncertainties rather than conclusions about limited value, while helping all of us identify opportunities to build a stronger evidence base for future Parkinson's therapies.	
The Michael J. Fox Foundation (MJFF)		
1.	The Michael J. Fox Foundation for Parkinson's Research (MJFF) appreciates ICER's thoughtful consideration of stakeholder input in the Draft Evidence Report for tavapadon. We are pleased to see several priorities raised in our earlier comments reflected in the report, including the importance of patient experience, care partner outcomes, and broader societal burden. We particularly appreciate the depth of patient and care partner input reflected in the report. At the same time, the assessment highlights an important methodological challenge for the field: translating outcomes that matter to patients and families into evidence that can be appropriately incorporated into comparative effectiveness and economic evaluations.	Thank you for your comments. We greatly appreciate the engagement of the Michael J. Fox Foundation in the assessment.

	Our comments are intended to highlight methodological, and evidence gaps that extend beyond tavapadon and will become increasingly important as additional Parkinson's therapies are evaluated.	
2.	**Patient and Other Stakeholder Perspectives** Patients emphasized that even relatively small changes in motor function can have meaningful effects on independence and daily life and highlighted the importance of consistent symptom control and manageable medication regimens, non-motor symptoms, and access to trustworthy information and shared decision-making. Care partners described substantial physical, emotional, logistical, and financial impacts and emphasized that treatment value should consider not only effects on patient symptoms, but also the ability to reduce care partner burden, preserve independence, and improve quality of life for the family. While these perspectives are well reflected in the qualitative discussion, we encourage ICER to consider whether and how these patient- and care partner-important outcomes can be more explicitly reflected in the economic evaluation, where appropriate and supported by available evidence. MJFF is committed to partnering with people with Parkinson's and their families to generate evidence that reflects what matters most to them; advance opportunities for patient perspectives to inform	As noted in previous responses (for example, see responses to comment 3 from APDA and comment 3 from Genentech above), these outcomes are captured to the extent supported by available data, through HY stage, OFF-time, MDS-UPDRS scores, and modeled adverse events. We have expanded the discussion of the outcomes that could not be quantified and framed as evidence gaps rather than evidence of absent benefit. With regard to care partner impacts, we agree these are critically important and not fully captured in our model. Attempts to obtain relevant data linking PD symptoms and progression to care partner quality of life have been unsuccessful, as highlighted above in our response to comment 2 from Genentech above.

	research, regulatory, and payer decision-making; and co-create credible, accessible resources that support informed conversations and choices about care	
3.	**Comparative Clinical Effectiveness** We appreciate ICER's recognition that unpredictability of motor fluctuations and medication response is an important burden for people with Parkinson's. However, this important patient-centered outcome does not appear to be reflected in the comparative effectiveness or cost-effectiveness analyses, which focus primarily on total daily OFF time. As noted in our comments on the Draft Scope, relevant MDS-UPDRS Part IV items may provide complementary information to Hauser diary-based measures of OFF time by capturing aspects of OFF period predictability. We encourage ICER to identify OFF-time predictability as an important evidence gap and an area for future validation, including work to determine whether and how predictability contributes to patient utility independently of total OFF time. We view this as a broader evidence-generation opportunity for future PD therapeutic development rather than a recommendation specific to tavapadon.	Thank you. This is an important issue, and we include it as an important evidence gap/area for future research in our policy recommendations. We encourage you to highlight this during the policy roundtable portion of the public meeting. Unfortunately, the TEMPO trials did not report on part IV data from the MDS-UPDRS, but the modelling team did use part IV data from the PPMI data set to inform estimates of disease impacts and progression used in the economic model.
4.	**Comparative Clinical Effectiveness:** ICER points to uncertainty around minimal clinically important difference (MCID) in commonly used PD outcome measures. While	Thank you for highlighting this important work on the MCIDs. We cited Horváth et al. (2015) in our discussion of the MCIDs in the report. The lack of consensus about the MCIDs informed our assessment about the level of uncertainty assessing the net clinical benefits of tavapadon. It

	no single threshold resolves the interpretation of meaningful change across all contexts of use, Horváth et al. (2015) provides an important and widely cited empirical basis for interpreting clinically meaningful change on MDS-UPDRS Part III. More recent work continues to expand this evidence base, including an anchor- and consensus-based estimate of a 5-point threshold for meaningful motor progression in early PD assessed in the OFF state. While this threshold was developed to characterize progression rather than interpret between-treatment differences, we encourage ICER to consider this emerging evidence when characterizing the range of evidence available for interpreting meaningful change on the MDS-UPDRS1. Importantly, the evidence base extends beyond estimates of MCID. Patient-centered research has also examined the relevance and meaningfulness of individual MDS-UPDRS Part III items, providing complementary evidence that Part III captures motor symptoms that matter to people living with Parkinson's (Cleanthous et al., 20262; The Michael J. Fox Foundation, 20263). This evidence is important to consider alongside quantitative estimates of meaningful change when interpreting MDS-UPDRS outcomes.	is also important to consider the individual elements contributing to the MDS-UPDRS Part III, but they are not consistently reported separately in any of the TEMPO trial publications. Additional details from the trials, when available, may allow for more refined comparisons that may be particularly relevant to patients.
5.	Thresholds for clinically meaningful within-patient change should not be	We agree that presenting the results in 2x2 tables based on clinically accepted cut points for clinically meaningful changes is important for

	interpreted as direct thresholds for between-group treatment effects in randomized trials. Rather, they provide important context for interpreting the magnitude and clinical relevance of observed change at individual patient level. Applying within-patient change thresholds to between-group mean differences can lead to inappropriate conclusions about the clinical relevance of a treatment effect, as discussed by Trigg et al., 20254.	fully assessing the benefits of a therapy. Unfortunately, this was not the approach taken in designing the trials of tavapadon, designating the primary and secondary outcomes, or reporting the trial results. This limits our ability to address this for tavapadon versus no additional therapy (placebo) and makes it even more challenging for comparative effectiveness analyses.
6.	Additionally, the field has increasingly adopted the MDS-UPDRS in place of the original UPDRS, reflecting its improved standardization, broader capture of clinically relevant manifestations, and improved characterization of mild impairment relevant to contemporary trials testing therapies in early-stage Parkinson's5. The MDS-UPDRS is now widely used across contemporary PD therapeutic development. We encourage ICER to consider this evolution when interpreting historical UPDRS-based evidence and evaluating future MDS-UPDRS-based trials.	Thank you. We agree and note the uncertainties related to this evolution and that of other key measures. However, all the earlier trials and all prior NMAs used the original UPDRS. We felt that it was methodologically more rigorous to convert to the UPDRS scale for consistency with the prior literature using published, validated approaches to conversion.
7.	**Long-Term Cost-Effectiveness** We appreciate ICER's efforts to incorporate broader patient and societal impacts into the economic analysis, including patient productivity and care partner burden. The analysis also highlights important remaining evidence gaps. Care partner health-related quality of life could not be incorporated	Thank you for this comment. As described in our response to Genentech, we examined the NICE foslevodopa-foscarbidopa appraisal and associated Adelphi estimates as a basis for care-partner disutility, but the relevant metrics were redacted as commercial-in-confidence and could not be applied. We have identified this as an evidence gap and added a scenario reflecting a plausible (but nevertheless assumed) care-partner benefit.

	into the model because ICER did not identify suitable evidence to link care partner disutility to patient disease severity or OFF time. Published PD-specific literature and prior HTA assessments provide potential starting points for estimating care-partner disutility, although additional work is needed to establish how well these estimates map to contemporary PD populations and clinical severity.	
8.	**Long-Term Cost-Effectiveness** Similarly, available evidence allowed productivity and care partner costs to be linked to OFF time, but not to improvements in motor function or activities of daily living. As ICER notes, this may underestimate the broader societal value associated with functional improvements. We encourage ICER to identify this limitation and the need for future evidence linking clinical and functional outcomes to care partner quality of life, productivity, informal care needs, healthcare utilization, and other downstream societal outcomes.	We agree and have updated the report to reflect this and state the need for further evidence. Specifically, we note that productivity and care-partner costs are linked to OFF-time rather than to motor or functional improvement, that this may understate the societal value of functional gains, and that establishing these links is a priority for future evidence generation.
9.	**Long-Term Cost-Effectiveness** We also note that the model uses daily OFF time to characterize fluctuating motor and non-motor symptom burden. However, important non-motor symptoms may occur independently of OFF time and can have substantial effects on daily functioning, health-related quality of life, care partner burden, healthcare resource utilization, and long-term care needs. Clinically meaningful milestones such as cognitive	Please see our responses to several comments above. Non-motor symptoms and clinical milestones that occur independently of OFF-time are largely captured within the HY-stage utility and cost structure, and because they are applied identically across arms, they are unlikely to change the incremental result unless a treatment differentially affects them. We have stated this reasoning in the report and identified explicit milestone modeling as a product-agnostic evidence-generation priority.

	decline, recurrent falls, loss of independence, and transition to institutional care may similarly have consequences that are not fully captured by the current approach. We recognize that the evidence base does not yet support precise mapping between each of these clinical milestones and care partner utility, productivity, or other societal impacts. We view this as an important product-agnostic evidence-generation opportunity and encourage continued research to better quantify these relationships and assess the extent to which they are captured by OFF time, motor severity, or other measures relevant to future value assessments.	
10.	**Benefits Beyond Health and Special Ethical Priorities** We appreciate ICER's recognition of the substantial unmet need that remains in Parkinson's despite available symptomatic treatments. The analysis underscores the considerable health burden experienced by people with Parkinson's across the disease course and the continued need for therapies that meaningfully improve patient outcomes. We encourage ICER to characterize uncertainty regarding care partner benefit as evidence uncertainty rather than evidence of limited benefit. This is an important evidence gap for future research, particularly to quantify how changes in disease severity, function, and symptom burden	The issue of care partner benefit is nuanced. While we agree that the benefits have been poorly characterized in clinical trials and there is a need to future evidence on the link between key PD outcomes and care partner impacts, there is also uncertainty regarding the potential benefits to care partners of treatment with tavapadon, given the uncertainties in our assessment of the potential net health benefit to patients relative to alternative therapies.

	affect care partner quality of life and health utility. This distinction is also relevant to consideration of care partner quality of life and ability to pursue education, work, and family life.	
11.	**Future Evidence Generation** Taken together, these limitations point to evidence needs that extend beyond any individual therapy. MJFF views these as important opportunities for product-agnostic research to strengthen future Parkinson's disease health technology assessments. As the therapeutic landscape evolves – including treatments that improve symptoms and those that halt disease progression – it will become increasingly important to establish how changes in disease progression translate into preserved function and independence, quality of life, care needs, healthcare utilization, and broader societal impact. We appreciate ICER's continued engagement with people with Parkinson's, care partners, clinicians, and patient organizations and its incorporation of these perspectives throughout the assessment.	Thank you. We completely agree. We will incorporate this suggestion into our policy recommendations.
Parkinson's Foundation		
1.	The Parkinson's Foundation appreciates the opportunity to comment on the draft evidence report, *Tavapadon for Parkinson's Disease: Effectiveness and Value*. We commend ICER for incorporating several themes raised during the scoping process, including the importance of pill	Thank you for your comments and engagement with the ICER process. We encourage you to enumerate the underrepresented aspects of PD through oral comment at the public meeting to help the voting members make more informed decisions as they vote.

	burden, motor fluctuations, caregiver impact, and the limitations of currently available therapies. We also appreciate the inclusion of patient and care partner perspectives throughout the report. However, we believe several important aspects of Parkinson's disease (PD) care remain underrepresented in both the clinical and economic evaluations. These limitations may lead to an incomplete assessment of the potential value of tavapadon and other future therapies.	
2.	**1. Unmet Need Associated with Pill Burden Is Underestimated** We appreciate that the report recognizes pill burden as a significant concern and notes the appeal of a once-daily treatment option. However, we do not believe the report fully captures the clinical, functional, and quality-of-life consequences of complex medication schedules. The report acknowledges that levodopa is commonly taken three to five times daily and that patients identified medication timing as a major challenge. For many people with Parkinson's disease (PwP), medication schedules become substantially more complex as disease progresses. Patients may require medication administration 5 to 10 times daily with careful coordination around meals, daily activities, and symptom fluctuations.[1,2] The burden extends	Thank you for this comment. We agree that less frequent dosing often results in improved adherence with therapy and thus improved outcomes. This is particularly challenging with levodopa, though there are extended-release forms to address this issue. And one of the dopamine agonists does come in a daily patch form. We have added a scenario analysis that incorporates a gain of one hour per week each to patients and caregivers for reduced pill burden. We have also added treatment simplification to the Benefits Beyond Health discussion. We note that the magnitude of the gain is uncertain given the mixed literature on the topic and is complicated by the relatively high rates of all-cause discontinuation from tavapadon seen in the TEMPO trials.

	beyond simple inconvenience and contributes to non-adherence, delayed dosing, worsening motor fluctuations, caregiver strain, and increased healthcare utilization.[3–5] This need has driven the development of device-aided therapies, which can be helpful for many, but are costly, invasive, and not accessible to all. By contrast, tavapadon's once-daily oral dosing is an attractive option for PwP, care partners, and clinicians alike. Importantly, the economic model developed by ICER does not appear to assign value to reductions in medication burden, treatment complexity, or medication management time. The societal model captures productivity and caregiver costs related to OFF time but does not account for the substantial caregiver and patient effort required to manage increasingly complex medication regimens or device-aided therapies.[6,7] As a result, the value associated with a once-daily treatment is likely underestimated. We encourage ICER to more prominently recognize treatment simplification as a meaningful benefit beyond health and to discuss this limitation explicitly within the economic model.	
3.	**2. Real-World Parkinson's Care Is More Heterogeneous Than Reflected in the Model** Parkinson's disease management differs substantially from many chronic diseases because there is no	We have acknowledged more explicitly that real-world treatment is individualized across patients, providers, and settings, and that the modeled pathways represent this variability only in aggregate given limitations in the available evidence for tavapadon. It is important that future trials and post-hoc analyses of trials

	single universally accepted treatment pathway. Although clinical guidelines exist, real-world care varies significantly across providers, regions, and health systems. The draft report appropriately discusses guideline recommendations but generally models PD treatment pathways as relatively standardized. In practice, clinicians personalize treatment decisions based on age, lifestyle, cognitive status, occupational demands, tolerance of adverse effects, caregiver availability, and patient preferences.[8,9] This heterogeneity is particularly important when evaluating therapies such as tavapadon, whose unique D1/D5 receptor mechanism may offer a different benefit-risk profile than traditional dopamine agonists.[10] We encourage ICER to acknowledge more explicitly that variability	explore the variation of the treatments' efficacy to better guide patients and providers' individualization of treatments. Nevertheless, the primary purpose of our model was to isolate the incremental effects of tavapadon where feasible rather than to depict the heterogeneity in the trajectory of PD that is undoubtedly present.
4.	**3. Early-Onset Parkinson's Disease Warrants Additional Consideration** We appreciate that ICER identified age as a prespecified subgroup in the review. However, we encourage greater emphasis on early-onset Parkinson's disease (EOPD), generally defined as diagnosis before age 50. Individuals with EOPD frequently experience a longer disease duration, greater cumulative exposure to dopaminergic therapies, and earlier development of both motor and non-motor	We agree that this is an important subgroup. However, we did not find any data on differential effects of tavapadon in this subgroup. We look forward to additional data focused on this population in the future. We have added a paragraph in the uncertainties and controversies section of the report to highlight this issue: "Early onset Parkinson's disease (usually defined as onset before the age of 50 years) is a subgroup of particular interest due to their long disease course and prolonged exposure to drug therapy. They remain under studied in clinical trials. We encourage future studies to report outcomes stratified by age of diagnosis to help elucidate potential benefits of

	complications.[11,12] Additionally, these individuals are typically in their prime productivity years and may be responsible for additional caregiving for young children or aging parents.[11,13] Consequently, therapies that may delay treatment complexity, reduce pill burden, or provide an alternative approach to symptom management could have different value implications for this population than for older adults.[14] Given these differences, we encourage ICER to discuss EOPD as a clinically meaningful subgroup even if available trial data do not permit formal subgroup analyses.	new therapies in this subgroup."
5.	**4. The Report May Underestimate the Potential Long-Term Advantages of a D1/D5 Selective Mechanism** The report appropriately notes the uncertainty surrounding impulse control disorders (ICDs), hallucinations, and other neuropsychiatric adverse effects because of limited long-term follow-up and the absence of head-to-head studies. However, we are concerned that the current framing gives disproportionate weight to short-term discontinuation rates while potentially undervaluing the theoretical and biologically plausible advantages of tavapadon's D1/D5 selectivity relative to D2/D3 dopamine agonists.[10] As ICER acknowledges, currently available dopamine agonists are associated with clinically significant adverse effects including ICDs, somnolence, hallucinations, and	We agree that the short trial follow-up duration limits the complete assessment of adverse effects such as impulse control disorders, which often develop over years rather than months, and we have made this more explicit. Importantly, the model does not rely on trial follow-up alone for this: the comparator dopamine agonist ICD risk is modeled as a cumulative, time-varying hazard that rises over the model horizon, precisely to capture the long-term accrual you describe, and is based on real-world rather than trial data. The current specification is favorable to tavapadon, whose ICD incidence is held constant while the comparator hazard grows. We agree that a genuine long-term advantage from D1/D5 selectivity is biologically plausible but not yet established by comparative data (indeed, ICDs occurred infrequently in the TEMPO trials but at a higher rate for tavapadon vs. placebo), and we have framed this as an uncertainty that could resolve in tavapadon's favor rather than as evidence of no difference.

	orthostatic hypotension, factors that often limit long-term use.[2,15] The absence of long-term comparative data should appropriately introduce uncertainty, but it should not obscure the possibility that important differences in neuropsychiatric outcomes may emerge over longer follow-up periods. We encourage ICER to more explicitly acknowledge that existing trials may be insufficient to assess outcomes such as ICDs, which often develop over years rather than months.	
6.	**5. Hospital and Institutional Care Settings Remain Underrepresented** We appreciate that ICER retained consideration of emergency department, hospital, and long-term care settings within the final scope. Nevertheless, the clinical and economic analyses largely focus on outpatient care and do not fully reflect the substantial risks faced by hospitalized individuals with PD. Hospitalized PwP frequently experience delayed, omitted, or incorrectly timed medication administration, resulting in worsening motor symptoms, complications, longer lengths of stay, and increased caregiver burden.[16–19] A once-daily therapy that is less dependent on precise administration timing could offer meaningful advantages during hospitalization and institutional care. These benefits are not readily	Thank you for these insights. We agree completely. However, the studies of tavapadon to date do not provide any data that support a reduction in ED visits, hospitalizations, or long-term care placement for patients with PD compared with other therapies. Whether the once daily dosing of tavapadon offers advantages over, for instance, the rotigotine patch, given that they are both typically used with levodopa given multiple times a day, remains an open question. There may be benefits, but head-to-head studies are needed to fully assess these comparative effectiveness/net benefits. Finally, in the economic analyses, we made several assumptions highly favorable to tavapadon (see discussions of ICD and discontinuation rates above) and performed scenario analyses of AEs highly favorable to tavapadon, none of which meaningfully changed the conclusions of our analyses.

	captured in the trials reviewed or in the current economic model but remain highly relevant from a patient-centered perspective. We recommend that ICER discuss this limitation more explicitly within the "Benefits Beyond Health" and "Uncertainty" sections.	
7.	**6. Health Equity Considerations Merit Greater Attention** We are concerned by the statement that no particular obligation was identified related to racial or ethnic inequities in Parkinson's disease care. A growing body of evidence demonstrates disparities in diagnosis, specialty care access, treatment intensity, and medication management among historically underserved populations.[20–23] Although PD may be diagnosed more frequently among non-Hispanic White individuals, substantial evidence suggests underdiagnosis and undertreatment among Black and other minority populations.[24–26] Therapies that simplify prescribing, reduce medication complexity, and lessen dependence on highly specialized PD expertise may particularly benefit populations that face barriers to specialty care. We encourage ICER to revise this section to acknowledge existing disparities and discuss whether treatment simplification may help reduce inequities in access and quality of care.	We agree and we have highlighted this in the Background section of the report, Section 2 on patient and other stakeholder perspectives, and in Table 5.1, which specifically addresses the issue of potential underdiagnosis.
8.	**7. Care Partner Impacts Are Likely Underestimated**	We agree that care-partner burden extends beyond care hours and productivity loss,

	We appreciate ICER's extensive inclusion of care partner perspectives and its acknowledgment that caregiver quality-of-life effects were not incorporated into the base-case model. However, caregiver burden in PD extends well beyond hours of care and productivity losses. Care partners frequently manage medication schedules, symptom fluctuations, transportation, communication with clinicians, financial challenges, and emotional burden over many years.[27,28] Given the central role medication management plays in caregiver responsibilities, therapies that simplify treatment administration may provide meaningful caregiver benefits not currently reflected in QALY-based analyses. We recommend that ICER emphasize this limitation more strongly when presenting overall value conclusions.	including the substantial role of medication management, and that these effects are not fully reflected in standard methods of economic evaluation. We have put more focus on this limitation in the value discussion and, as noted above, added a scenario reflecting reduced caregiver medication-management time under a once-daily regimen.
9.	The Parkinson's Foundation appreciates the thoughtful and comprehensive nature of this assessment. We agree that important uncertainties remain regarding the comparative clinical effectiveness of tavapadon. However, we believe the draft report underestimates several patient-centered dimensions of value, including medication burden, treatment simplification, caregiver impact, healthcare setting	Thank you, please see our responses above to the concerns articulated here. It will be important to have a robust discussion of these issues during the public meeting.

	considerations, and health equity implications. As ICER finalizes this report, we encourage greater emphasis on these factors and clearer acknowledgment that current models may not fully capture benefits that matter most to people living with Parkinson's disease and their families.	
PMD Alliance		
1.	At PMD Alliance, we work closely with people living with Parkinson's, care partners, family members, support group leaders, long-term care facilities, and healthcare providers. We consistently hear that the impact of Parkinson's is not just about symptoms, but about whether someone can keep doing the things that are important to them, how much help they need, whether they can continue working or participating in family life, and how much time and energy it takes to manage the disease. A change that may look small on a clinical scale can make a very real difference in daily life. We consistently hear from our community that disease burden is cumulative. Burden extends beyond any one symptom or caregiving responsibility and comes from the combined load of things like keeping track of medications, watching for changing symptoms, getting to appointments, helping with transportation, taking on more household responsibilities, and adjusting plans around what is	Thank you for your comments. We acknowledge that there could be unmeasured benefits either favoring tavapadon or its comparators in the model. We purposely limit our estimates of benefit in our primary analysis to those based on evidence. We note, however, that across a large number of scenario analyses with more flexible assumptions, our conclusions did not meaningfully change. We encourage broader efforts at data collection and study of cumulative benefits, heterogeneity, and other potential nuances in this and other patient populations.

	possible that day. This cumulative effect is difficult to truly capture in a model, but its impact on daily life is substantial. We recognize that ICER cannot assign a value to every outcome when the evidence is not available, and we are not suggesting that benefits should be assumed when they have not been demonstrated. We do think it is important, though, to distinguish between a benefit that has been shown not to exist and one that simply has not been measured well enough yet.	
2.	Care-partner impact is a clear example of this distinction. ICER acknowledges that care-partner health-related quality of life could not be incorporated into the model and that care-partner impact may therefore be underestimated. Yet the draft also concludes that substantial improvement in care-partner quality of life is unlikely. We think that goes further than the available evidence supports. If we do not yet have a reliable way to measure how changes in function, independence, treatment burden, or care needs affect people with Parkinson's and their families, then the better conclusion is that the impact is unknown or not adequately measured. Lack of evidence about the size of a benefit is not the same as evidence that the benefit is not there. We also encourage ICER to continue looking beyond what happens to the person taking the medication	We agree that care-partner burden is cumulative and should be treated as an outcome in its own right. Because the model could not incorporate care-partner health-related quality of life for lack of suitable evidence linked to changes in available outcome measures, we have revised the report to describe this impact as unknown or not adequately measured rather than unlikely, and have applied this framing consistently, distinguishing outcomes that are unmeasured from those shown to be absent. However, in order to see a substantial difference in care-partner burden a new treatment would also need to have a substantial treatment effect for primary patient outcomes relative to key comparators, the evidence of which we have found to be highly uncertain.

	and consider what happens to the family around them. Maintaining function or independence may allow a person with Parkinson's to stay employed longer, allow a spouse to keep working, reduce the amount of hands-on assistance needed at home, or delay the need for paid help or long-term care. Care-partner burden and care-partner quality of life should be treated as important outcomes in their own right, not simply as extensions of patient disability. We understand that stronger evidence is needed to connect changes in disease severity and function with outcomes such as independence, quality of life, productivity, informal caregiving, healthcare utilization, and long-term care. In the meantime, we would encourage ICER to be careful about how uncertainty is described. If an outcome has not been well measured, it should remain an uncertainty rather than becoming a conclusion about limited value. Thank you again for the opportunity to weigh in. We are passionate about this issue because we understand that value assessments can shape how treatments are viewed and, ultimately, how accessible they are to people living with Parkinson's. Treatment choices should not be preemptively narrowed due to	

	limitations in measuring some of the outcomes that matter most to people and families. We appreciate ICER's continued engagement with the Parkinson's ecosystem and its willingness to include lived experience in this process. As the report is finalized, we encourage ICER to clearly identify evidence gaps, preserve uncertainty where appropriate, and ensure that the experiences of people living with Parkinson's and their care partners remain central to conclusions about value.	
Patient living with Parkinson's		
1.	I was diagnosed with Parkinson's disease in January 2023. Like many people living with Parkinson's, my journey has been about much more than managing a tremor or a movement symptom. It has been about protecting my independence, maintaining my ability to stay active, and continuing to contribute to my family and my community. I participated in the Phase 3 clinical trial for tavapadon. During my time on the medication, I experienced improvements that were meaningful in my everyday life. My walking improved. My confidence improved. I became less concerned about falling. I was able to remain physically active and continue the activities that are important to me. One of the challenges in evaluating Parkinson's treatments is that some of the most meaningful benefits are difficult to capture in a clinical trial	Thank you for your comments. We are thrilled to learn about how much tavapadon helped you. We agree that tavapadon may offer meaningful benefit for some patients and expect that the FDA will approve it. The challenge is comparing tavapadon to existing therapies among all patients studied in clinical trials as well as the full spectrum of those who might be considering this therapy. It is likely that some will be better served with tavapadon and others better served with alternative therapies. The overall net benefit considering all the data from the TEMPO trials drives the assessment of the added clinical value of tavapadon. The lack of head-to-head trials limits our ability to draw conclusions with certainty. We look forward to additional head-to-head studies in the future.

	questionnaire. A change in a motor score or a quality-of-life measurement may appear modest on paper, but for a person living with Parkinson's, that change can mean the difference between avoiding activities and participating fully in life. For me, Tavapadon was not simply about improving a number on a chart. It was about feeling more capable and more confident in my daily routine.	
2.	I also want to emphasize the importance of looking beyond the individual patient. Parkinson's affects spouses, caregivers, families, and communities. When treatment helps someone remain independent, active, and engaged, the benefits extend beyond that person. It can reduce caregiver burden and help preserve quality of life for the entire family.	Thank you. We completely agree. That is why the societal perspective in the economic analysis was deemed to be essential.
3.	I understand and respect ICER's responsibility to carefully evaluate evidence, cost, and uncertainty. Long-term data are important, and continued research will help us better understand Tavapadon' s durability and safety profile. However, I encourage the panel to consider the full impact of Parkinson's treatments. Clinical evidence is essential, but patient experience provides important context about what those clinical improvements actually mean in real life. For people living with Parkinson's, preserving mobility, confidence, and independence is not a small benefit. It is often the difference between	Thank you. We agree with you. At the public meeting, the deliberative panel will consider not only the results of our quantitative analyses but also other societal priorities and contextual elements to inform their votes.

	simply managing the disease and continuing to live an active, meaningful life. I appreciate ICER's commitment to including the patient voice in this process, and I hope this perspective helps inform your evaluation of Tavapadon.	

#	Comment	ICER Response
Other		
Red Nucleus		
1.	Our comments concern the *internal validity and structural transparency* of the two de novo models: which assumptions are actually driving the reported estimates, and what the final report should disclose or test so that decision-makers can judge the uncertainty around the base case. The draft report is more transparent than most assessments of this type. The assumption log in Table 4.1 is explicit. Section 4.3 explains why several scenario analyses left the results unchanged rather than simply reporting that they did. The Uncertainty and Controversies section is candid about what the models cannot do. Our observations depend on that openness, and all six are intended to be achievable within the existing model structure.	We thank Red Nucleus for this detailed and constructive review. We address each of the six points below; several are adopted as added disclosures or scenarios within the existing model structure, as suggested.
2.	**1. Neither model allows direct medical costs to respond to treatment. This should be stated, and tested.** **Recommendation:** State in the final report that no symptomatic treatment effect, of any magnitude, can produce a direct medical cost offset in either model, and add a scenario in which within-stage functional improvement is allowed to attenuate stage-level resource use . **Rationale:** Three modeling choices combine to this effect. Direct medical costs are assigned by Hoehn and Yahr (HY) stage alone, with "no further stratification by MDS-UPDRS Part II or Part III score" (p. 36). HY transitions run forward only and are not modified by treatment (pp. 25–	We appreciate this comment and make the structure explicit, with one clarification. Direct medical costs in both models do respond to treatment through adverse-event costs, which differ between arms and are themselves direct medical costs; in Model 2 they also respond through the OFF-time increment. What treatment does not affect is the HY-stage-assigned resource use, because direct medical costs are assigned by HY stage without further stratification by MDS-UPDRS Part II or Part III score, and because HY transitions are not modified by treatment. We now state explicitly that a symptomatic effect operating through within-stage MDS-UPDRS scores produces no offset in the HY-stage cost component, while noting that adverse-

	26). In Model 1, OFF-time is tracked but "was not connected to costs or utilities" (p. 31). The arms in Model 1 therefore cannot differ in direct medical cost except through drug acquisition and adverse-event management, and in Model 2 only through the OFF-time increment. Whether functional improvement really produces no resource-use offset is an empirical question. At present it is an assumption, it is untested, and it works in one direction. **Implication:** Readers may take the absence of cost offsets for a finding of the analysis. It is a property of the architecture, and the report should say so.	event costs and, in Model 2, OFF-time costs do respond to treatment.
3.	**2. The utility mapping chain, not the clinical evidence, is driving the Model 1 result.** **Recommendation:** Estimate an MDS-UPDRS to EQ-5D mapping directly in the Parkinson's Progression Markers Initiative (PPMI) cohort and report it as a scenario. Failing that, treat the mapping coefficients in Model 1 as a structural rather than a parametric uncertainty. **Rationale:** Utilities reach Model 1 through four steps. Trial MDS-UPDRS scores are crosswalked to pre-2008 UPDRS units (p. 27). Those are put through the NICE (2016) linear mapping at 0.04 per Part II point and 0.02 per Part III point. The result enters only as a deviation from within-state means (p. 34). All of it is layered on the Lowin et al. (2017) HY-by-OFF-time matrix. Each step is defensible on its own, but the composite draws on four populations and two instruments, and the one-way sensitivity analysis in the evidence report shows what follows. The largest single driver of the Model 1 ratio is	We agree that the Model 1 result is sensitive to the MDS-UPDRS-to-utility mapping, and that the UPDRS Part II per-point disutility is the single largest driver in the one-way analysis. A direct EQ-5D-on-MDS-UPDRS mapping estimated in PPMI would be preferable, but the subset of PPMI participants with EQ-5D data is quite small and sparsely distributed across HY stages, particularly in the advanced stages, so a stage-robust mapping could not be estimated. We have added this point to the Uncertainties section.

	the UPDRS Part II per-point disutility, which moves the result from −$783,000 to $7.7 million per QALY (p. 40). The Part III coefficient ranks second. The relative treatment effects estimated in the network meta-analysis rank below both. The data to shorten this chain are already in hand, since PPMI collects EQ-5D alongside MDS-UPDRS and supplies the transition probabilities, within-stage means, and mortality hazards. **Implication:** A coefficient derived from a superseded instrument currently carries more weight in the early-PD conclusion than any measured clinical effect.	
4.	**3. Long-term persistence carries more weight than any clinical parameter and is not treated as such.** **Recommendation:** Treat the persistence assumption as a formally characterized structural uncertainty rather than a scenario, report the range it generates alongside the base case, and test at least one intermediate assumption. **Rationale:** No trial data describe tavapadon persistence beyond the first cycle, so long-term discontinuation is proxied from a MarketScan analysis of comparator dopamine agonist regimens with rate-ratio anchoring (p. 32). Scenario 3 shows how much rests on it. Setting tavapadon discontinuation to zero after cycle 1 moves Model 1 from "more costly, less effective" to $15.2 million per QALY, reversing the direction of the incremental effect, and moves Model 2 from $2.9 million to $726,000 per QALY (Table 4.6). The plausible value lies somewhere between the base case and that scenario, but both sit at opposite ends of the same axis.	We agree that long-term persistence is an influential input and that no tavapadon-specific data describes it beyond the trial period. However, across the full range of persistence assumptions we examined, including setting tavapadon discontinuation to zero after the first cycle, the resulting ICERs remain far above commonly accepted cost-effectiveness thresholds in both models. An additional persistence scenario would therefore not change the conclusion, and we have characterized this input as a structural uncertainty in the report.

	Implication: The qualitative conclusion for early PD turns on an unobserved parameter borrowed from a different drug class. A persistence curve declining more slowly than the dopamine agonist proxy would be more informative to the decision-makers than either bound.	
5.	**4. The ICD hazard is specified asymmetrically across arms, in the parameter pair that dominates Model 2.** **Recommendation:** Apply a time-varying cumulative impulse control disorder (ICD) hazard to both arms, or state the clinical rationale for the asymmetry and test its removal. **Rationale:** ICD incidence for tavapadon comes from the TEMPO trials and is "kept constant across model cycle," while comparator incidence rises over time following the Corvol et al. (2018) cumulative hazard (p. 33). We support the inclusion of time-varying behavioural hazards; our concern is that only one arm receives one. A mechanistic distinction may well be defensible for a D1/D5-selective partial agonist, but the report does not make that argument, and 26 weeks of trial follow-up cannot on its own support a constant lifetime rate. ICD disutility and the dopamine agonist ICD hazard ratio are the two largest drivers of the Model 2 results (pp. 40–43), and removing adverse events altogether moves Model 2 from $2.9 million to $1.0 million per QALY (Scenario 6, Table 4.6). **Implication:** The most influential parameter pair in Model 2 rests on an asymmetry the report asserts but does not justify.	We agree that the ICD hazard is currently specified asymmetrically, with a constant tavapadon incidence and a time-varying comparator hazard, and that this pair is among the largest drivers of the Model 2 result. We have added the clinical rationale for treating a D1/D5-selective partial agonist differently from older dopamine agonists, and, because 26 weeks of follow-up cannot on its own support a constant lifetime rate, we have added a scenario applying the same time-varying cumulative hazard structure to both arms to show the effect of removing the asymmetry. We do note, however, that while data are currently limited, information from TEMP0-4 suggests a flattening of the ICD rate with tavapadon over an additional year of follow-up.

6.	**5. The two models are architecturally separate, so the transition into motor fluctuations carries no value.** **Recommendation:** State that neither model represents progression from the early-PD population into the motor-fluctuation population, and consider reporting time to onset of motor fluctuations as a model outcome. **Rationale:** Model 1 evaluates first-line therapy in early PD and Model 2 evaluates add-on therapy in patients with motor fluctuations. A patient in Model 1 who develops motor fluctuations does not enter the Model 2 structure. Any difference between first-line strategies in time to onset of motor fluctuations, time to levodopa initiation, or time to advanced therapy is therefore unrepresentable, for either arm and in either direction. Neither model is at fault on its own; the gap follows from evaluating a chronic progressive disease through two disjoint cross-sections of its course. Delaying motor complications is a long-standing clinical rationale for first-line non-levodopa strategies, and the draft report discusses long-term comparative evidence on the risk of motor fluctuations elsewhere, so what is missing here is structure rather than evidence. **Implication:** A principal claimed benefit of first-line non-levodopa strategies sits outside the analysis by construction, and the report does not currently say so.	We agree that neither model represents progression from the early-PD population (Model 1) into the motor-fluctuation population (Model 2), and that any difference between first-line strategies in time to onset of motor fluctuations is therefore not represented. Use of two models is an artifact of the design of the TEMPO trials, which were conducted in two distinct populations and treatment paradigms. We now state this explicitly as a structural limitation.
7.	**6. Advanced-stage inputs warrant external validation, and Model 1's directional uncertainty warrants clearer presentation.** **Recommendation:** Validate modelled stage occupancy and survival against a cohort with substantial HY 4–5 follow-up,	These are two distinct points. On external validation of advanced-stage inputs: because tavapadon is assumed not to modify disease progression or mortality, both arms occupy the HY stages identically over time and incur the stage-assigned costs, including the HY-5 cost, in equal amounts. These costs therefore

	using pre-specified acceptance criteria, and report in the summary the probability that tavapadon is more effective than levodopa. **Rationale:** ICER notes that the PPMI cohort "skews toward earlier-stage disease" and that estimates for advanced HY stages are "correspondingly more uncertain" (p. 50). Those same inputs dominate lifetime cost. The HY 5 annual health-state cost is $96,063 against $7,604 at HY 1 (Table 4.2), a more than twelvefold gradient taken from a single 2013 source and inflated forward. The report also observes that modelled life expectancy of 7.7 and 8.6 years falls below prior published models at roughly 10 years, and attributes this to national life tables (Supplement E7); external validation would establish whether that fully accounts for the difference. On presentation, the summary describes tavapadon as "more costly and slightly less effective" than levodopa in early PD, while the probabilistic analysis finds it cost-effective in 23.2% of simulations at $200,000 per QALY (Table 4.5) and the report acknowledges "uncertainty in the direction of the comparison." Reporting that probability in the summary would make it harder to read a directionally uncertain result as a dominance finding. **Implication:** The inputs with the greatest lifetime leverage are the least externally corroborated, and the headline characterization of the early-PD result is firmer than the analysis behind it. Most of what we have set out asks for disclosure and targeted scenarios rather than a different model, and we have framed it that way deliberately. We would	cancel when the incremental difference between arms is taken, so uncertainty in the advanced-stage cost inputs, stage occupancy, and survival affects the absolute results in each arm but not the incremental cost-effectiveness result on which the comparison rests. We now make this cancellation explicit in the report so that the limited external corroboration of these inputs is not mistaken for a limitation of the incremental analysis. On presentation of the early-PD result: we agree, and report in the summary the probability that tavapadon is more effective than levodopa, so that a directionally uncertain result is not read as a conclusive finding that tavapadon is more costly and less effective.

	encourage the panel to take these up in the final report. Better-characterized uncertainty makes for better coverage decisions, and those	

References

1. Rashid AA, Mohammad A, Malik U, et al. “Efficacy, safety and certainty of evidence for selective D1/D5 dopamine receptor partial agonists in Parkinson’s disease: a systematic review, meta-analysis and GRADE assessment”. *Neurological Sciences*. 2026/08/15 2026;47(9):708. doi:10.1007/s10072-026-09306-8