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AbbVie's Response to ICER's Draft Evidence Report for Tavapadon in Parkinson's Disease – August 2026

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 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.

Methodological and procedural concerns with ICER's Draft Evidence Report

The basis for ICER's flawed conclusions can be understood in two categories: methodological concerns and procedural concerns. Methodologically, the assessment does not adequately reflect the comparative evidence standards, patient-relevant outcomes, real-world treatment pathways, safety and tolerability considerations, long-term disease consequences, or societal and care-partner impacts needed to evaluate tavapadon's value. Procedurally, limited transparency into the model and its assumptions further reduces confidence in the robustness, validity, and reliability of the reported results.

Methodological concern	Implication
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.
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

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	care-partner burden, leading to an incomplete evaluation of treatment benefit.
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.
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 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]
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

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	weight to these outcomes, the analysis understates the value of treatments that may help PwP remain active, independent, productive, and better manage daily life.

Procedural concern	Implication
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.
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.
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.

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 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.

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 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]

Tavapadon as a meaningful therapeutic innovation in Parkinson's disease

Tavapadon is designed to address the gaps outlined above. Currently 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.

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, 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.

AbbVie's position

AbbVie unequivocally disagrees with ICER's Draft Evidence Report conclusions regarding tavapadon. The Draft Evidence Report materially understates the unmet need experienced by PwP, undervalues tavapadon's potential contribution to real-world PD care, and does not provide a reliable basis for assessing tavapadon's value. ICER's conclusions are undermined by both methodological and procedural concerns: methodologically, the assessment underrepresents outcomes that matter most to PwP and their care partners, does not fully reflect the real-world context of PD or the populations likely to benefit in clinical practice, and gives insufficient weight to safety, tolerability, treatment complexity, long-term disease consequences, and societal and care-partner impacts; procedurally, limited transparency, limited reproducibility, and limitations in ICER's ability to conduct the assessment with appropriate scientific rigor fundamentally reduce confidence in the robustness, validity, and reliability of the reported results.

Tavapadon represents a meaningful therapeutic innovation as the first selective oral D1/D5 receptor agonist designed for once-daily administration. An assessment that fails to fully recognize the unmet need in PD, the value of expanded treatment choice, and the real-world limitations and trade-offs of current therapies cannot credibly support a definitive conclusion regarding tavapadon.

ICER's Draft Evidence Report should therefore be regarded as incomplete, methodologically constrained, procedurally limited, and unsuitable as a definitive benchmark for assessing tavapadon's value or informing decision-making.

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August 13, 2026

Institute for Clinical and Economic Review (ICER)

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Re: Tavapadon for Parkinson's Disease – Draft Background and Scope

Dear ICER Review Team,

GE HealthCare Pharmaceutical Diagnostics organization appreciates the opportunity to comment on the Draft Evidence Report (DER) for the evaluation of Tavapadon in Parkinson's disease (PD).

Parkinsonian syndromes represent a heterogeneous group of disorders that include PD as well as atypical parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, and dementia with Lewy bodies. More than one-third of patients are considered challenging to diagnose, particularly in early disease stages. Over the past decade, the diagnostic paradigm has evolved from reliance on clinical evaluation alone to incorporating objective biomarkers and imaging to improve diagnostic accuracy.[1-3] With a growing and aging population as well as a rapid rise in PD prevalence, this shift is increasingly important.[4-6]

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 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.

Conclusion

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.

Best regards,

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Genentech
A Member of the Roche Group

August 17, 2026

Dear ICER Review Panel,

Genentech, a member of the Roche Group, appreciates the opportunity to review and provide public comments on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report on *Tavapadon for Parkinson's Disease (PD): Effectiveness and Value*.

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 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.

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):

1. **Incorporate Specified Societal Perspective From Patient & Care partner Testimonies: fully capture informal care partner & patient impact from key clinical milestones within base-case evaluations**
2. **Integrate The Full Disease Continuum And Heterogeneity: explicitly incorporate non-motor symptoms (NMS) and discrete clinical progression milestones**
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.**

We expand on these recommendations with supporting rationale below:

1. 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 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 .

2. Integrate The Full Disease Continuum And 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 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.

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 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.

We appreciate ICER’s dedication to conducting transparent, evidence-based reviews and encourage the panel to incorporate these recommendations to ensure the final report fully reflects the needs of patients and families living with Parkinson’s disease.

Sincerely,

Elaine Yu, PharmD, MS
Head of Evidence for Access
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AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

August 25, 2026

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Submitted Electronically: publiccomments@icer.org

Re: Tavapadon for Parkinson's Disease: Effectiveness and Value – Draft Evidence Report

Dear ICER Review Team,

On behalf of the American Parkinson Disease Association (APDA), we appreciate the opportunity to provide comments on the **Tavapadon for Parkinson's Disease: Effectiveness and Value – Draft Evidence Report**.

We commend ICER for its comprehensive approach and for incorporating patient and caregiver perspectives into the process of assessing the potential value of Tavapadon as compared to the other available treatment options. We respectfully offer the following comments for consideration:

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 agonists[i]. 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 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.

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.

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 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.

We appreciate ICER's commitment to a thorough and patient-centered evaluation process and thank you for the opportunity to provide input. We look forward to continued engagement as this review progresses.

Sincerely,

Leslie Chambers, MSPH
President and CEO
American Parkinson Disease Association

Rebecca Gilbert, MD, PhD
Chief Mission Officer
American Parkinson Disease Association

[i] Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol*. 2010;67(5):589-595. doi:10.1001/archneurol.2010.65

DAVIS PHINNEY
Foundation for Parkinson's
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August 25, 2026

Re: Tavapadon for Parkinson's Disease: Effectiveness and Value Draft Evidence Report, JULY 29, 2026

Dear ICER Review Team:

On behalf of the Davis Phinney Foundation, thank you for the opportunity to respond to the Draft Evidence Report for tavapadon and for your ongoing engagement with our organization and the Parkinson's community. Throughout this process, we have seen ICER make a concerted and genuine effort to learn about Parkinson's, understand what matters to our community, and take care in capturing the nuances of this complex disease that effects individuals and the families in nearly every dimension of life.

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 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,

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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.

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 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.

Sincerely,

Jenna Deidel
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Davis Phinney Foundation

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THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

August 25, 2026

Re: Tavapadon for Parkinson's Disease: Effectiveness and Value Draft Evidence Report, JULY 29, 2026

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.

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.

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 research, regulatory, and payer decision-making; and co-create credible, accessible resources that support informed conversations and choices about care.

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

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.

ICER points to uncertainty around minimal clinically important difference (MCID) in commonly used PD outcome measures. While 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-UPDRS[1].

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., 2026[2]; The Michael J. Fox Foundation, 2026[3]). This evidence is important to consider alongside quantitative estimates of meaningful change when interpreting MDS-UPDRS outcomes.

Thresholds for clinically meaningful within-patient change should not be 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., 2025[4].

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's[5]. 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.

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 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.

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 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 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.

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 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.

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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.

MJFF is committed to supporting product-agnostic evidence generation that helps ensure future evaluations can appropriately capture outcomes that matter to people with Parkinson's and their families.

Sincerely,

Sohini Chowdhury Chief Program Officer
The Michael J. Fox Foundation for Parkinson's Research

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August 25, 2026

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Parkinson's Foundation Comments on ICER Draft Evidence Report: Tavapadon for Parkinson's Disease

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 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.

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 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.

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 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 in real-world PD treatment limits the applicability of rigid comparative treatment assumptions.

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 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.

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 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.

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 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.

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.

7. Care Partner Impacts Are Likely Underestimated

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.

Conclusion

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 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.

Respectfully submitted on behalf of the Parkinson's Foundation

Sneha Mantri, MD, MS, FAAN
Chief Medical Officer

James C. Beck, PhD
Chief Scientific Officer

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Re: Tavapadon for Parkinson's Disease: Effectiveness and Value – Draft Evidence Report

Dear ICER Review Team,

On behalf of Parkinson & Movement Disorder Alliance (PMD Alliance), thank you for the opportunity to comment on the draft evidence report. We appreciate the effort ICER has made to hear directly from people living with Parkinson's and their care partners.

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 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.

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.

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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 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.

Sincerely,

Andrea Merriam
Chief Executive Officer
Parkinson & Movement Disorder Alliance

August 24, 2026

Dear ICER Review Panel,

Red Nucleus welcomes the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report, *Tavapadon for Parkinson's Disease: Effectiveness and Value* (July 29, 2026).

We are an independent health economics and outcomes research organization, and our interest here is methodological. In 2025 we updated the systematic review of published economic evaluations in Parkinson's disease (PD) compiled by Dams et al. (2011, 2023), the two methodological reviews ICER used to benchmark its own structural choices (Supplement E7). The update brought the evidence base to 30 evaluations and was presented at ISPOR Europe 2025 (Ruoss et al., Value in Health 2025;28(12):S130). Working through that literature left us with a clear view of which modeling choices in PD tend to decide results.

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.

Disclosure: Red Nucleus provides health economics and outcomes research services to pharmaceutical manufacturers. The systematic review cited above was conducted under contract to, and funded by, F. Hoffmann-La Roche Ltd, and was co-authored with Roche employees. Red Nucleus has no financial interest in tavapadon or in any comparator evaluated in this review, and no manufacturer commissioned, funded, or reviewed this comment.

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. 25–26). 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.

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 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.

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.

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.

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.

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.

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, 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 encourage the panel to take these up in the final report. Better-characterized uncertainty makes for better coverage decisions, and those decisions are what patients with Parkinson's disease and their families ultimately depend on.

Sincerely,

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Members of the ICER Panel,

Thank you for the opportunity to provide a patient perspective on tavapadon and its potential role in the treatment of Parkinson's disease.

My name is REDACTED,

and 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 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.

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.

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 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.

Thank you for your time and consideration.