AbbVie Response to ICER's Draft Scope for the Assessment of Tavapadon for Parkinson's Disease

AbbVie appreciates the opportunity to comment on ICER's draft scoping document for the tavapadon assessment. We commend ICER for highlighting the profound and persistent unmet needs in Parkinson's disease (PD) in its draft scope. For more than thirty years, innovation in the PD treatment landscape has stagnated, leaving patients trapped in a relentless cycle of benefit-risk tradeoffs. As PD progresses, treatment regimens with existing therapies become increasingly complex, demanding higher doses, more frequent administration, and additional adjunctive medications. These escalations can increase the risk of developing potentially debilitating side effects as well as decrease treatment adherence. This "safety-versus-symptom-control" tradeoff perpetuates escalating personal distress, care partner strain, financial hardship, and societal costs that remain largely unaddressed. The Michael J. Fox Foundation (MJFF) first estimated the annual economic burden of PD in the US at $52.1 billion, and their new report demonstrates an even greater economic impact, particularly with higher indirect, non-medical, and out-of-pocket costs.[1] Tavapadon, currently under review by the US Food and Drug Administration (FDA), has the potential to fill critical gaps as a novel PD treatment and the first and only selective D1/D5 receptor agonist. Through precision targeting, it may enable predictable and sustained motor control while potentially minimizing the risk of certain burdensome side effects. Its once-daily administration streamlines dosing and reduces treatment complexity. Drawing upon AbbVie's decades of experience advancing innovative therapies for people with Parkinson's disease (PwP), we submit our comments to inform ICER's scope based on our strong commitment to elevating the standard of care.

Population: *ICER should define the target population for this evaluation as PwP who have initiated treatment and require subsequent therapy adjustment due to inadequate motor symptom control or tolerability limitations.*

- PD is exceptionally heterogeneous, with each patient's clinical journey shaped by unique pathways of disease progression, symptom burden, age, comorbidities, cognitive function, treatment response, and patient preference. As a result, a diverse range of treatment options is needed to address these complex and evolving individual needs.
- Oral levodopa/carbidopa (levodopa) is recommended as first-line (1L) treatment per American Academy of Neurology (AAN) guidelines for early PD,[2] accounting for >70% of treatment initiations in PwP.[3,4] As tavapadon enters the market, it is unlikely to displace levodopa as 1L therapy.
- Nearly all PwP receiving oral levodopa will eventually require treatment adjustments (e.g., levodopa dose escalation, fractionation, or adjunctive therapies) as motor symptoms advance and/or side effects grow less tolerable.[5] This transition period marks a critical decision point for a population with significant unmet needs, compelling clinicians to identify treatment strategies that are both effective and well-tolerated to optimize outcomes.
- Given the individualized nature of PD, segmenting PwP into two distinct populations creates artificial analytical constructs and limits the applicability of findings to real-world decision making. Evaluating tavapadon across the full continuum of PD better reflects clinical practice and enhances generalizability.

Intervention: *AbbVie recognizes ICER's interest in assessing tavapadon and agrees it represents a novel mechanism of action (MOA) as the first and only selective D1/D5 agonist. After decades of limited advancement in PD treatment, tavapadon represents an innovative therapeutic option. It introduces a new MOA, provides once-daily dosing, and addresses a critical unmet need by providing effective motor symptom control while lowering the risk of certain life-altering AEs that frequently limit the tolerability of current treatment options.*

- Preclinical data demonstrate that tavapadon selectively binds with high affinity to D1 and D5 receptors, with minimal activity at D2/D3 receptors.[6,7] D1/D5 receptors are predominantly expressed in the striatum and cortical regions and play a central role in motor control by activating the direct pathway and enhancing neuronal signaling. This supports improved motor function and may also contribute to cognitive benefits.

- By selectively activating D1/D5 receptors, tavapadon is hypothesized to deliver effective motor symptom control while reducing the risk of certain burdensome AEs associated with D2/D3 agonism.[7–9] This mechanistic differentiation offers the potential for improved tolerability while maintaining efficacy.
- In the TEMPO pivotal trial programs, which included over 1,300 PwP, tavapadon demonstrated clinically meaningful motor symptom control and low rates of AEs of interest, supporting a favorable benefit-risk profile in clinical practice.[10–13]

Comparators: *Of ICER's selected comparators in this draft scope, ICER should avoid direct comparisons with levodopa and fully account for the safety and societal burden associated with D2/D3 DAs. Tavapadon, as a selective D1/D5 agonist, represents a novel mechanism with no direct mechanistic comparators and, if approved by the FDA, may offer an alternative to the burdensome side effects of existing therapies.*

- Levodopa remains the predominant PD treatment and is recommended as 1L therapy by AAN guidelines, accounting for >70% of 1L use.[3,4] As tavapadon enters the market, it is not likely to displace this standard of care as 1L therapy.
- D2/D3 DAs (including pramipexole, ropinirole, rotigotine) are characterized by highly unfavorable risk-benefit profiles, leading to a significant decline in use in the US (now limited to ~10% of patients) and high early discontinuation rates (44% within 3 months).[3,14] Tavapadon is expected to have a meaningfully different AE profile given its D1/D5 selectivity. Due to the extremely burdensome AE profiles of current D2/D3 DAs, we urge ICER to fully account for the significant individual and societal impacts of these medications as part of the assessment.
    - Unlike tavapadon, traditional DAs target D2/D3 receptors that are highly expressed in nigrostriatal and mesolimbic pathways that regulate reward, motivation, and behavior.[8] This activity is associated with debilitating AEs, including impulse control disorders (ICDs), hallucinations, and excessive daytime sleepiness, which are the most burdensome AEs reported by patients.[9,15]
    - In a cross-sectional study of >3,000 patients, approximately 14% of PwP receiving D2/D3 DAs developed at least one ICD, which includes behaviors like gambling, binge eating, hypersexuality, and compulsive shopping.[16,17] This risk is even greater when used adjunctively with oral levodopa. One patient described the experience, stating she began compulsively gambling and buying frivolous things, leaving her feeling like there was something "that's controlling me." This loss of autonomy resulted in £30,000 (~$40,000 USD) in losses.[18] These debilitating AEs trigger a cascade of negative consequences affecting patients, care partners, and broader society, undermining patient quality-of-life, decreasing workforce participation and productivity, intensifying care partner burden, destabilizing family life, and escalating healthcare costs. The severity of behavioral AEs, particularly ICDs, has repeatedly resulted in costly litigation, underscoring the societal risks associated with these medications.[18]
    - Additional AEs include somnolence, affecting approximately 22% of patients receiving DAs;[19] hallucinations, occurring in approximately 40% of PwP creating frightening and disorienting experiences for both patients and care partners; and peripheral edema (6–19%) which limits mobility and increases fall risk particularly in older patients.[20,21]
    - Furthermore, cessation can trigger dopamine agonist withdrawal syndrome (DAWS) in up to 1 in 5 patients, with half of those affected experiencing chronic symptoms lasting months or years, thus requiring slow tapering over time. The risk of DAWS is increased in patients discontinuing due to ICDs.[22,23]
    - The constraints and safety concerns inherent to existing treatment options complicate comparative assessments, particularly when evaluating an innovative MOA that fundamentally represents different therapeutic approaches.

Outcomes: *AbbVie appreciates the inclusion of quality-of-life measures, care partner burden, and AEs. Building on this, we underscore the need to fully capture the holistic impact of PD on clinical, economic,*

humanistic, and societal outcomes given that PD is a lifelong, chronic, progressive disease with significant impacts on patients, families, care partners, and society.

- AbbVie supports the inclusion of key efficacy measures such as MDS-UPDRS Parts II and III and Hauser Diary motor states (OFF time and ON time without troublesome dyskinesia). These outcomes should be assessed across PwP, rather than separate cohorts (early-stage PD versus those with motor fluctuations), to ensure generalizability and relevance across a highly heterogeneous population.
- Given the substantial, life-altering risks associated with D2/D3 DAs, it is imperative to comprehensively account for AEs, such as ICDs, excessive daytime sleepiness, hallucinations, and peripheral edema. Qualitative evidence in PwP suggests that impulse control behaviors may arise from medication side effects and coping mechanisms and may not be recognized until negative consequences occur, limiting capture in traditional assessments.[24] AE assessments should reflect all clinical, economic, and humanistic burden affecting patients and care partners, including but not limited to, hospitalizations, emergency care, institutionalization, accidents (including falls) and injuries, increased comorbid burden, productivity consequences, and other societal impacts.
- ICER's economic analysis should also include productivity losses and other indirect costs affecting both PwP and their care partners, as indirect costs comprise at least 50% of total PD costs.[1,25] The economic and humanistic toll of PD extends far beyond direct medical costs. In 2017, the total economic burden of PD in the US was estimated at $51.9 billion, including $25.4 billion in direct medical costs and $26.5 billion in indirect and non-medical costs for PwP and their care partners. Key components of indirect costs included $7.5 billion in non-medical expenses and $4.8 billion in disability income. Additionally, care partners alone accounted for $6.6 billion in indirect costs, driven by reduced employment, absenteeism, presenteeism, and social productivity losses.[25,26] More recent evidence suggests that this burden has continued to grow. A recently released 2026 report now reveals an even higher total economic impact, reinforcing the need for comprehensive value assessments that fully capture the holistic burden associated with PD.[1]

Time Horizon and Setting: *AbbVie agrees with ICER's proposal to include studies of any duration and a lifetime time horizon. Additionally, we recommend applying a societal perspective as the base case and expanding beyond any specific focus on outpatient settings to enable comprehensive consideration across all care settings. This ensures the assessment captures the full clinical, economic, humanistic, and societal impact of PD.*

- AbbVie recommends adopting a societal perspective as the base case to reflect the total impact of PD across all relevant clinical, economic, humanistic, and societal outcomes as noted through our comments above. Given the extensive burden on families, care partners, and society, a narrow healthcare-system perspective is misleading and insufficient.
- The assessment should encompass the full patient journey across all settings, including home-based, institutional, and emergency settings, to accurately reflect real-world resource utilization. A recent 2026 report demonstrates direct medical costs are driven by non-acute institutional care, and that inpatient hospital care also has higher costs than outpatient settings.[1] Evidence thus should not be limited to a focus on outpatient settings given the associated broad disability across the health care system.
- A lifetime horizon is the most appropriate duration for assessment in PD due to the progressive and chronic nature of the disease. Evaluating outcomes over a lifetime further allows for the inclusion of the catastrophic and potentially long-term consequences associated with D2/D3 DAs, such as ICDs, hallucinations, and excessive daytime sleepiness.

AbbVie continues to encourage ICER to adopt a comprehensive, patient-centered assessment framework that reflects the complexity of PD management and fully evaluates tavapadon's transformative potential as a novel, selective D1/D5 agonist. After decades of limited therapeutic advancement, tavapadon could offer PwP, their care partners, and clinicians, a well-tolerated innovative once-daily oral treatment that directly addresses longstanding unmet needs.

References:

1. The Lewin Group Inc. *Economic Burden of Parkinson's and Atypical Parkinsonism in the United States Full Study Report*. 2026. https://www.michaeljfox.org/sites/default/files/media/document/Economic%20Burden%20of%20Parkinson%E2%80%99s%20and%20Atypical%20Parkinsonism%20in%20the%20United%20States_0.pdf

2. Pringsheim T, Day GS, Smith DB, et al. Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary. *Neurology*. 2021;97(20):942-957. doi:10.1212/wnl.0000000000012868

3. Song Y, E JY, Guo T, et al. Treatment Patterns and Healthcare Resource Use in Medicare Beneficiaries with Parkinson's Disease. *Clin Outcomes Res*. 2023;15(0):631-643. doi:10.2147/ceor.s422023

4. Houghton R, Boess F, Verselis L, et al. Treatment Patterns in Patients with Incident Parkinson's Disease in the United States. *J Park's Dis*. 2019;9(4):749-759. doi:10.3233/jpd-191636

5. Kulisevsky J. Pharmacological management of Parkinson's disease motor symptoms: update and recommendations from an expert. *Rev Neurol*. 2022;75(Supl 4):S1-S10. doi:10.33588/rn.75s04.2022217

6. Jones-Tabah J, Mohammad H, Paulus EG, Clarke PBS, Hébert TE. The Signaling and Pharmacology of the Dopamine D1 Receptor. *Front Cell Neurosci*. 2022;15:806618. doi:10.3389/fncel.2021.806618

7. Bezard E, Gray D, Kozak R, Leoni M, Combs C, Duvvuri S. Rationale and Development of Tavapadon, a D1/D5-Selective Partial Dopamine Agonist for the Treatment of Parkinson's Disease. *CNS Neurol Disord - Drug Targets*. 2024;23(4):476-487. doi:10.2174/1871527322666230331121028

8. Isaacson SH, Hauser RA, Pahwa R, Gray D, Duvvuri S. Dopamine agonists in Parkinson's disease: Impact of D1-like or D2-like dopamine receptor subtype selectivity and avenues for future treatment. *Clin Park Relat Disord*. 2023;9:100212. doi:10.1016/j.prdoa.2023.100212

9. Kaye AD, Ford BM, Abbott BM, Broocks KM, Novacic S, Shekoohi S. Emerging Clinical Role of Tavapadon, a Novel Dopamine Partial Agonist, in the Treatment of Parkinson's Disease. *Diseases*. 2025;13(9):290. doi:10.3390/diseases13090290

10. Pahwa R, Moro E, Espay A, et al. Efficacy and Safety of Fixed-Dose Tavapadon, an Oral, Once-Daily, Selective D1/D5 Partial Dopamine Agonist for the Treatment of Early Parkinson's Disease. In: 2025.

11. Fernandez H, Bhatia P, Cloud L, et al. Efficacy and Safety of Flexible-Dose Tavapadon, an Orally Administered, Once-Daily, Selective D1/D5 Partial Dopamine Agonist for the Treatment of Early Parkinson's Disease. In: 2025.

12. Fernandez H, Isaacson S, Hauser R, et al. Efficacy and Safety of Tavapadon, an Orally Administered, Once-daily, Selective D1/D5 Partial Dopamine Agonist, Adjunctive to Levodopa for Treatment of Parkinson's Disease with Motor Fluctuations. In: 2025.

13. Pahwa R, Dhall R, Mari Z, et al. TEMPO-4: A Phase 3 Open-Label Trial to Investigate the Safety and Efficacy of Long-Term Administration of Tavapadon in People With Parkinson's Disease. In: 2025.

14. Frazer M, Arcona S, Le L, Sasane R. Dopamine agonist monotherapy utilization in patients with Parkinson's disease. *Clin Park Relat Disord*. 2023;8:100173. doi:10.1016/j.prdoa.2022.100173

15. Richards K, Avanceña AL, Johnsrud M, et al. Quantifying the Tolerability of Dopamine Agonist Antiparkinsonian Medication Side Effects: A Best-Worst Scaling Survey. *Patient Preference Adherence*. 2026;20(0):570840. doi:10.2147/ppa.s570840

16. Voon V, Sohr M, Lang AE, et al. Impulse control disorders in parkinson disease: A multicenter case–control study. *Ann Neurol*. 2011;69(6):986-996. doi:10.1002/ana.22356

17. 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

18. Titheradge N. "It's ruined my life": Hundreds tell BBC how medication triggered gambling and other addictions. *BBC News*. February 21, 2026. https://www.bbc.com/news/articles/ce948d9gxevo

19. Avorn J, Schneeweiss S, Sudarsky LR, et al. Sudden Uncontrollable Somnolence and Medication Use in Parkinson Disease. *Arch Neurol*. 2005;62(8):1242-1248. doi:10.1001/archneur.62.8.1242

20. Tan EK. Peripheral Edema and Dopamine Agonists in Parkinson Disease. *Arch Neurol*. 2007;64(10):1546-1547. doi:10.1001/archneur.64.10.1546-b

21. Kleiner-Fisman G, Fisman DN. Risk Factors for the Development of Pedal Edema in Patients Using Pramipexole. *Arch Neurol*. 2007;64(6):820-824. doi:10.1001/archneur.64.6.noc60158

22. Nirenberg MJ. Dopamine Agonist Withdrawal Syndrome: Implications for Patient Care. *Drugs Aging*. 2013;30(8):587-592. doi:10.1007/s40266-013-0090-z

23. Yu XX, Fernandez HH. Dopamine agonist withdrawal syndrome: A comprehensive review. *J Neurol Sci*. 2017;374:53-55. doi:10.1016/j.jns.2016.12.070

24. Delaney M, Simpson J, Leroi I. Perceptions of cause and control of impulse control behaviours in people with Parkinson's disease. *Br J Heal Psychol*. 2012;17(3):522-535. doi:10.1111/j.2044-8287.2011.02052.x

25. Yang W, Hamilton JL, Kopil C, et al. Current and projected future economic burden of Parkinson's disease in the U.S. *npj Park's Dis*. 2020;6(1):15. doi:10.1038/s41531-020-0117-1

26. The Lewin Group Inc. *Economic Burden and Future Impact of Parkinson's Disease Final Report*. 2019. https://www.michaeljfox.org/sites/default/files/media/document/2019%20Parkinson%27s%20Economic%20Burden%20Study%20-%20FINAL.pdf

AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

March 27, 2026

Institute for Clincial and Economic Review (ICER)
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Submitted Electronically: publiccomments@icer.org

Re: Tavapadon for Parkinson's Disease – Draft Background and Scope (March 9, 2026)

Dear ICER Review Team,

On behalf of the American Parkinson Disease Association (APDA), we appreciate the opportunity to provide comments on the draft scoping document for the evaluation of Tavapadon for Parkinson's disease (PD).

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 available treatment options. We respectfully offer the following comments for consideration broken down according to the PICOTS framework:

Population:

"Early-stage PD" (defined as modified Hoehn and Yahr stages 1-2) is one of the populations under study. It should be noted that the definition of "early-stage PD" varies across studies[1] and should therefore not be limited to Hoehn and Yahr stages 1 and 2. Some trials use years since diagnosis or MDS-UPDRS scores in their definitions.

Interventions:

Parkinson's disease (PD) is a highly variable condition, and optimal medication regimens differ across individuals[2]. As a result, APDA is eager to see new treatment options that can address this heterogeneity. The benchmark for evaluating Tavapadon's value should therefore be whether it provides meaningful benefit for those who need alternative options to what is currently available. Its novel mechanism of action, with greater selectivity for specific dopamine receptor subtypes, suggests it may offer distinct advantages within the PD treatment landscape. For people with PD who experience inadequate benefit or intolerable side effects from existing therapies, Tavapadon may represent an important additional option.

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[1] Mov Disord. 2018 Oct;33(10):1643-1646. doi: 10.1002/mds.27431.
[2] Lancet. 2024 Jan 20;403(10423):305-324. doi: 10.1016/S0140-6736(23)01429-0

Comparators:

The scoping document explains that ICER considered a wide range of comparators and decided to focus on comparators with a similar mechanism of action to Tavapadon. We would respectfully disagree with this limitation. In real-world movement disorders practice, Tavapadon would be an option alongside a wide range of choices and all these should be considered in this comparative study. For Population 1 (adults with early-stage PD), we recommend expanding the list of comparators to include monoamine oxidase B inhibitors, as well as all currently available long and short acting dopamine agonists.

For Population 2 (adults with PD and on levodopa who are experiencing motor fluctuations), we also recommend expanding the list of comparators to include all the medications used to increase the time that a dose of levodopa is effective. This would include not only the currently available long-acting dopamine agonists as you indicate, but COMT inhibitors, MAOB inhibitors, adenosine inhibitors and others. It should also be noted that there are currently multiple long-acting levodopa formulations (carbidopa/levodopa ER, Rytary, Crexont) that are used in people experiencing motor fluctuations and these should be considered comparators as well.

Outcomes:

We suggest that not only MDS Parts II and III be included as outcome measures, but Part IV as well, which captures motor fluctuations and dyskinesias.

We also suggest that the outcomes related to adverse events be expanded to explicitly include hallucinations and a broader category of adverse neuropsychiatric effects, such as increased confusion, agitation etc. These neuropsychiatric symptoms are very relevant to patients with more advanced disease and are typically the adverse events that limit the usage of other dopamine agonists in this population. We also recommend broadening "impulse control disorders" to "impulse-control and related behavioral disorders[3]" which includes conditions such as dopamine dysregulation syndrome and punding[4].

Benefits beyond health and special ethical priorities

Finally, we encourage ICER to further consider other "benefits beyond health and special ethical priorities". In addition to those already identified, Tavapadon may offer important economic and societal benefits by potentially delaying the need for continuous supervision of a person with advanced PD, thereby reducing reliance on family members or home health aides. It may also enable individuals with PD to more fully participate in daily activities, including volunteer work and other forms of economic and social contribution.

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[3] Mov Disord. 2024 Feb;39(2):235-248. doi: 10.1002/mds.29700. Epub 2024 Jan 17
[4] Mov Disord Clin Pract. 2023 Apr 23;10(7):1035-1047.doi: 10.1002/mdc3.13748.

The APDA Voices of Parkinson's Council comments

The APDA Voices of Parkinson's Council consists of people with PD and their care partners. It ensures that the perspectives and priorities of the PD community always inform and enhance our work. We posed ICER's patient experience questions to this group and provided their thoughts below. We hope that these insightful comments will help highlight the potential value of an additional treatment option for the PD community.

- My husband experienced great benefit from the rotigotine patch, but it had to be stopped because of a rash. Tavapadon may be a great solution for him.
- A long-acting medication like Tavapadon may be helpful because now when my Levodopa stops working, it is like a switch turns off.
- I have predictable dystonia that you can set a clock by. My neurologist wants to prescribe a dopamine agonist to increase the time that my Levodopa works, but I have heard such bad things about dopamine agonists that I am afraid to try it. Maybe Tavapadon will be a good choice if it is a dopamine agonist that has fewer side effects.
- In the past, I was on a medication that I had a very difficult time getting insurance to approve. Eventually, I gave up and came off of the medication. I hope that this new medication will not have similar issues.

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

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Foundation for Parkinson's
Inform. Connect. Inspire.

Submitted to publiccomments@icer.org, March 27, 2026

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

Thank you for the opportunity to comment on the draft scoping document for the evaluation of tavapadon for Parkinson's disease (PD).

As an organization focused on helping people with Parkinson's live well today, we offer comments centered on the lived experience of individuals and families and how that experience should be reflected in modeling assumptions, outcome selection, and value determination.

Ground Modeling in the Reality of Parkinson's Progression

Parkinson's is highly heterogeneous. Individuals experience a wide range of motor and non-motor symptoms, variable rates of progression, and differing responses to treatment. While clinical scales and staging frameworks are useful, they do not fully capture the day-to-day or long-term variability and unpredictability that define life with Parkinson's. We encourage ICER to ensure that modeling approaches reflect this variability and acknowledge the inherent uncertainty in predicting long-term disease trajectories.

Consider Treatment Patterns in Real-World Care

Parkinson's treatment is not static. Individuals typically move through multiple therapies and combinations over time as symptoms evolve. Medications are frequently adjusted, added, or discontinued based on effectiveness, tolerability, and changing needs. A drug such as tavapadon— one that is likely to be used both as monotherapy and as adjunctive therapy, as well as introduced at various stages depending on the individual, provider, and goal of the intervention—should be assessed with a wide lens.

We encourage ICER to model multiple plausible treatment pathways that reflect real-world care, including therapy switching, combination use, and variation in timing of initiation, and to use definitions that reflect real-world clinical practice when defining groups such as those with "early Parkinson's disease," recognizing the variability in symptoms, treatment history, and timing of intervention. Evaluating tavapadon within a single, fixed-line treatment sequence risks underestimating its potential role and value in clinical practice.

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Align Assessment with Realistic Goals of Treatment

For most people living with Parkinson's, the primary goal of treatment is not extending life, but maintaining function, independence, and quality of life. Outcomes that matter most include

- Stability and predictability of symptom control
- Ability to perform daily activities
- Reduction in OFF time and motor fluctuations
- Cognitive and emotional wellbeing
- Reduced burden on care partners

For many individuals, the predictability of symptom control is as important as the total duration of ON time. The ability to reliably function at a given time of day rather than experiencing unpredictable fluctuations has profound implications for independence, social participation, and planning. These outcomes are often insufficiently captured by traditional clinical endpoints and may be undervalued in cost-effectiveness models.We encourage ICER to ensure that patient-centered outcomes—particularly those related to function, predictability, and daily lived experience—are central to the assessment.

Understand the Impact of Treatment Burden

Many individuals manage complex medication schedules, often requiring multiple daily doses and careful timing around meals and activity. This complexity can impact adherence, independence, and quality of life. In this context, therapies that simplify treatment—such as once-daily options—may offer meaningful benefit beyond clinical measures alone. We encourage ICER to consider modeling and assessment approaches that take into account the value of reducing treatment burden for individuals and families.

Appropriately Value Reduction of Side Effects

Current dopamine agonists are associated with well-documented neuropsychiatric side effects, including impulse control behaviors, dopamine dysregulation syndrome, punding, and related challenges. These effects can have profound consequences for individuals and families, including financial harm, relationship strain, and loss of independence. While we appreciate that ICER has identified these side effects as important outcomes, we enourage the assessment to fully reflect

their real-world impact on individuals and families and to consider the value of a new treatment option that offers an improved tolerability profile.

Broaden the Lens: Societal and Care Partner Impact

Parkinson's carries a substantial and growing economic and societal burden, including impacts on employment, caregiving, and healthcare utilization. Recent analyses estimate this burden to be $82 billion annually in the United States, with significant costs borne by care partners through lost income and productivity. Therapies that improve symptom control, reduce treatment complexity, and delay functional decline may contribute to the following:

- Sustained workforce participation
- Reduced caregiver strain
- Fewer hospitalizations and complications

We encourage ICER to incorporate these broader impacts into its assessment framework.

Conclusion

We appreciate ICER's commitment to incorporating stakeholder input in this process. To ensure the assessment reflects the realities of Parkinson's, we encourage ICER to

- Reflect the heterogeneity and unpredictability of Parkinson's progression
- Incorporate real-world treatment patterns and burden
- Prioritize patient-centered outcomes related to function and daily life
- Consider neuropsychiatric risks and unmet needs in current therapies
- Recognize the broader societal and caregiver impacts of treatment

By grounding this evaluation in the lived experience of people with Parkinson's and their families, ICER can better capture the full value of emerging therapies such as tavapadon.

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

March 30, 2026

Re: Tavapadon for Parkinson's Disease - Draft Background and Scope — March 9, 2026

The Michael J. Fox Foundation for Parkinson's Research appreciates the opportunity to comment on the draft scoping document for the assessment of tavapadon for Parkinson's disease (PD). Our suggested refinements aim to ensure the assessment reflects the lived experience of people with Parkinson's and their caregivers, real-world clinical practice, and the economic and social impact of PD.

General Comments

A recent study commissioned by The Michael J. Fox Foundation and additional non-profit partners found the economic burden of PD and atypical parkinsonism in the United States totaled $82.2 billion in 2024 and projects the cost to be as high as $112.2 billion by 2045[1]. It takes into account new measures of indirect and non-medical costs, incorporates atypical parkinsonisms, quantifies the economic burden borne by care partners, and estimates medical costs in the year prior to formal diagnosis. The study finds care partners shouldered $8.3 billion in 2024 in lost earnings and productivity due to reduced work hours and premature retirement. These cost categories and findings could be considered for ICER's model framework. Much of the underlying data is available publicly in Fox Insight.

MJFF's Parkinson's Progression Markers Initiative (PPMI) is a source of high-quality observational data that may be utilized to analyze progression trajectories and subgroup heterogeneity. The MJFF-funded VALUE-PD microsimulation model integrates PPMI data with various real-world datasets and, in the future, may contribute model-ready input.

Population

Early PD definition**:** As part of an MJFF- and C-Path–supported Clinical Outcome Assessment (COA) initiative aimed at advancing asset-agnostic clinical development in early PD, the proposed operational definition of early-stage PD uses a cutoff of three years since diagnosis for the MDS-UPDRS Part III patient interview analyses. In parallel, a project to develop novel clinical anchors for use in early PD trials included a structured landscape review of Phase 2 or 3 early PD trials conducted in the past five years. As part of this review, the team performed case-by-case assessments of inclusion and exclusion criteria – primarily based on Hoehn & Yahr (H&Y) stage, time since diagnosis, and trial descriptions – to understand how early-stage populations are defined across the development landscape. As expected, the review of 28 trials found varying operational definitions of 'early PD', summarized below:

- Two years was the most common upper limit for time since diagnosis when this criterion was specified for participant inclusion, but the upper limit across all studies considered was much greater, ranging as high as 10 years since diagnosis.
- Average trial duration was ~56 weeks, with some studies lasting up to ~48 months.

Inclusion Criteria	# of studies that used this criteria	Most common threshold	Range
Time Since Diagnosis	19	<= 24 months (n=6)	<=6 - <= 120 months
H&Y Stage	19	<= 2 (n=11)	<=2 - <= 3
Age Minimum	27	40 yrs (n=11)	18 yrs – 50 yrs
Age Maximum	26	80 yrs (n=13)	70 yrs – 85 yrs

Many trials also included inclusion criteria around treatment status, as well as some specified MDS-UPDRS score threshold at screening. It may be helpful to note that 'de novo' Parkinson's generally refers to newly diagnosed, treatment-naïve patients, and is therefore a narrower subset of the early PD population.

Interventions

As noted, evidence indicates that certain dopamine agonists are associated with serious adverse effects, particularly impulse control disorders[2], hypersomnolence, and hallucinations, which restrict their use[3]. MJFF welcomes novel mechanisms with more selective dopamine receptor pharmacology that may offer an alternative first-line treatment option for early PD.

As PD progresses, patients often need to adjust to increasingly complex treatment regimens. Evidence shows that such complexity is associated with reduced adherence, whereas once-daily dosing may improve adherence and overall health outcomes[4].

Comparators

To ensure that the assessment reflects real-world clinical practice, we encourage inclusion of comparators and treatment patterns aligned with how PD is managed across the disease continuum. Early treatment may include levodopa, dopamine agonists, and MAO-B inhibitors, with selection guided by patient characteristics, symptom burden, and risk of adverse effects. While management of motor fluctuations in advanced PD typically involves optimization of levodopa and addition of adjunctive therapies such as COMT inhibitors, MAO-B inhibitors, dopamine agonists, and other agents targeting OFF periods. Accordingly, we recommend that the assessment consider comparators across these classes and reflect treatment patterns consistent with both initial therapy and real-world management of motor fluctuations.

Outcomes

We recommend aligning outcome measures of motor fluctuations by linking Hauser diary-based endpoints for quantifying OFF time with MDS-UPDRS Part IV items that assess the predictability of OFF periods as complementary measures, given their relevance to patients' lived experience and the meaningful impact of unpredictable OFF episodes on daily functioning[5].

An MJFF-funded study evaluating quality-of-life measurement tools emphasizes the importance of patient-centered assessment, indicating a preference for PD specific quality-of-life measures that more effectively capture the aspects of disease impact most meaningful to patients.

Current validated outcomes measures, largely focused on motor symptoms, do not fully capture the lived experience. Qualitative research highlights the importance of non-motor symptoms and their functional and psychosocial impacts, with a consensus conceptual model of early PD[6] identifying a broad range of patient-relevant domains beyond traditional scales. We recommend interpreting clinical outcomes in the context of patient-defined value, including functional and psychosocial impact, as well as predictability and durability of treatment effectiveness, and recognizing the role of narrative data in understanding patient experiences such as OFF periods[7].

Given the importance of accurately characterizing disease progression, recent research[8] highlights variability in how ON-OFF states and dopaminergic medication exposure are defined and documented across studies, complicating interpretation of treatment effects and progression. This underscores the need for standardized documentation of concomitant medication use in PD.

Settings

Limited access to movement disorder specialists, reaching only a small proportion of patients, can lead to delays in optimal treatment selection and management, negatively impacting outcomes and quality of life[9]. This underscores the need for effective therapies that can be initiated and managed across general neurology and primary care settings, helping to broaden equitable access to Parkinson's care and increase the standard of care across the board.

Contextual considerations

Patients experience meaningful benefit from existing therapies, yet disease variability, side effects, and progression create ongoing unmet needs.

In PD, where many patients rely on informal caregivers as symptoms progress[10], better management of OFF with lesser side effects may support greater independence, which in turn can influence overall quality of life for both patients and caregivers.

We appreciate the opportunity to provide feedback and look forward to continued engagement during subsequent public comment periods.

Sincerely,

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

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

REFERENCES

1. The Lewin Group, Inc. et al. Economic Burden of Parkinson's and Atypical Parkinsonism in the United States. Preprint at Zenodo. 2026; doi:10.5281/zenodo.19257591
2. 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
3. Pringsheim T, Day GS, Smith DB, et al. Dopaminergic therapy for motor symptoms in early Parkinson disease: practice guideline summary: a report of the AAN Guideline Subcommittee. Neurology. 2021;97(20):942-957. doi:10.1212/WNL.0000000000012868
4. Straka I, Minár M, Škorvánek M, et al. Adherence to Pharmacotherapy in Patients With Parkinson's Disease Taking Three and More Daily Doses of Medication. Front Neurol. 2019;10:799. doi:10.3389/fneur.2019.00799
5. Pahwa R, Isaacson SH. Pathophysiology, Patient Burden, and Recognition of OFF Episodes of Parkinson Disease. J Clin Psychiatry. 2020;81(6):SU19004BR1C. Published 2020 Oct 27. doi:10.4088/JCP.SU19004BR1C
6. Mammen JR, Adams JL, Mangrum R, et al. Systematic review and consensus conceptual model of meaningful symptoms and functional impacts in early Parkinson's Disease. NPJ Parkinsons Dis. 2025;11(1):65. doi:10.1038/s41531-025-00907-2
7. Chahine, L.M., Edison, B., Daeschler, et al. The Most Bothersome Aspects of Off Periods Reported by Individuals with Parkinson's Disease. Mov Disord Clin Pract, 7: 284-292. https://doi.org/10.1002/mdc3.12915
8. Spott M, Javidnia M, Pedata A, et al. Addressing the need for standardization of symptomatic medication documentation in Parkinson's disease clinical research: A call to action. J Parkinsons Dis. 2025;15(1):227-235. doi:10.1177/1877718X241305711
9. Pearson, C., Hartzman, A., Munevar, D. et al. Care access and utilization among medicare beneficiaries living with Parkinson's disease. NPJ Parkinsons Dis. 2023;9(1):108. doi:10.1038/s41531-023-00523-y
10. Oguh O, Kwasny M, Carter J, Stell B, Simuni T. Caregiver strain in Parkinson's disease: national Parkinson foundation quality initiative study. Parkinsonism Relat Disord. 2013;19(11):975-979. doi:10.1016/j.parkreldis.2013.06.015

March 27, 2026

Institute for Clinical and Economic Review
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Re: Draft Scoping Document for ICER Review: Tavapadon for Parkinson's Disease

As the largest, grassroots foundation serving and supporting the Parkinson's disease community, the Parkinson's Foundation thanks you for the opportunity to comment on ICER's Draft Scoping Document for Tavapadon for Parkinson's disease.

The mission of the Parkinson's Foundation is to make like better for people with Parkinson's disease (PD) by improving care and advancing research towards a cure. We are dedicated to supporting research and care that meets unmet needs in the Parkinson's community. As a result, we actively partner with a diverse group of stakeholders to find solutions to problems that affect those people living with Parkinson's disease (PwP). We welcome the focus of ICER upon Parkinson's disease and the upcoming review of the dopamine agonist Tavapadon, currently under consideration for approval by FDA.

New treatments like Tavapadon can provide life-changing value in the lives of PD patients. Approximately 1.2 million people in the United States live with Parkinson's disease or atypical parkinsonisms today. Parkinson's is the fastest-growing neurodegenerative disease, with 90,000 new people diagnosed each year (Willis et al. 2022). Given the prevalence, PD and atypical parkinsonisms place an increasing economic strain on people living with the disease, their families and the federal government, with total annual costs reaching $82.2 billion in 2024. Without intervention, the annual cost is expected to exceed $112 billion by 2045 (Lewin Group 2026). Tavapadon may provide a unique opportunity to reduce the burden of PD by addressing issues like those related to pill burden, side effects, and symptom management. Better treatment can also possibly contribute to lowering future healthcare costs if symptoms are better managed. PD requires individualized care and not every treatment works for every patient. This makes bringing new products to market critically important to create more and improved treatment options for those living with PD.

Our comments regarding the draft scoping document are:

1. We ask ICER to consider and strongly weigh the unmet need around pill burden in the treatment of PD. Simply put, pill burden is a major challenge for PwPs. The current gold standard therapy, levodopa, has a half-life of only a few hours, requiring administration three times a day even in the earliest stages of PD. As the disease progresses and motor fluctuations develop, administration may increase to 5, 6, even 10 times daily. This increases the likelihood of delayed administration (particularly for PwP who are hospitalized, institutionalized, or otherwise not in control of their medication timing, please see our comments regarding "setting"), adverse effects, and non-adherence. One study of 805 PwP using Medicaid claims data found that only about half of PwP taking levodopa, and only

40% of PwP taking dopamine agonists, remained adherent to their regimen over the 305-day study period (Johnsrud et al. 2021). A follow-up qualitative study found that pill burden was a major reason for discontinuation of medication, and even those who took medications only a few times a day expressed concern over their future medication needs (Richards et al. 2024). Moreover, meals containing protein can negatively impact the absorption of levodopa from the small intestine, further complicating burden of balancing the timing of medication with that of meals, especially with more advanced cases of PD (Rusch et al. 2023).

2. When considering treatment and medication options for PD, it is important to recognize the high level of variability in the approach of PD care. This is different from other disease areas where defined paths and plans of treatment have been established. In PD, even expert care centers that comprise the Parkinson's Foundation Global Care network approach patient care differently, though each shares the common goal of symptom management (Dahodwala et al. 2025). This may reflect regional or center differences but underscores the lack of uniformity in how PD is treated and therefore how fixed treatment approaches do not readily apply to PD.

3. Populations – The populations for the Scoping document currently describe the entire the spectrum of PD and could more easily be defined as those with or without motor fluctuations. We would also suggest that subgroup analysis specifically take into account age at diagnosis. Those with early onset PD (EOPD), defined as <50 years at diagnosis, typically have a different course to their disease and one for which motor fluctuations are more pronounced and appear earlier in the disease course (Mehanna et al. 2022).

4. Comparators – Unlike other currently approved dopamine agonists, which act upon the D2/D3 receptors and with downstream inhibitory impact on adenylyl cyclase, Tavapadon acts upon the D1 and D5 receptors but with downstream excitatory impact on adenylyl cyclase (Jones-Tabah et al. 2022). Thus, the effect and side effect profile of Tavapadon is unique in class. Specifically, Tavapadon is expected to produce less somnolence and fewer impulse control behaviors, both potentially serious adverse effects that have a major impact on quality of life for PwP and their care partners.

5. Settings – We agree that it is important to focus on the outpatient setting for those with living PD. However, we would like to highlight two separate issues with the care setting. First, it is important to recognize that the vast majority of PD care is not provided by those with expert training in PD care – movement disorders specialists who are neurologists with fellowship training in movement disorder. Only 9% of the PD population receives care from this group, 50% receives care from more generally trained community neurologists, and 29% receive their care from PCPs (Pearson et al. 2023). The complexity of prescribing levodopa for moderate to advanced PD may leave patients insufficiently medicated and grappling with motor complications.

The second issue is that the in-patient setting should not be discounted for its impact to a PwP. PwP have more frequent hospital encounters and are at a higher risk of complication and longer hospital stays than their peers (Azmi et al. 2020, Veilleux Carpentier et al. 2026). Despite the importance of medication timing in Parkinson's symptom management, hospitalized PwP rarely have their medications ordered according to their home schedule or administered within the recommended +/- 15 minutes of each scheduled time (Nance et al. 2020, Yu et al. 2023). Innovative medicines that provide symptom relief, especially with wide dosing windows, e.g., once daily, would greatly benefit the hospitalized PwP.

6. Special Ethical Priorities – As part of the scoping document it is important to consider that PD is no stranger to the persistent health gaps found in the United States. We recommend that ICER consider the benefits new medications may bring to those populations that are underrepresented in health care. For instance, Blacks living with PD are more likely to be under-medicated for the correct amount of levodopa/carbidopa to control their symptoms than their White counterparts – even at expert care centers (Luca et al. 2023). Medications that simplify prescribing may provide a ready benefit to these populations and ensure that even non-specialist prescribers can have an effective tool that meets the symptom needs of their patients.

Thank you for the opportunity to comment. The Parkinson's Foundation looks forward to continued engagement with ICER throughout the review process. If you have any questions, please contact Erin O'Quinn, Associate Vice President of Federal Public Policy, at 202-803-7523.

Respectfully submitted on behalf of the Parkinson's Foundation

James C. Beck, PhD
Chief Scientific Officer

Sneha Mantri, MD, MS, FAAN
Chief Medical Officer

References

Willis, A. W., Roberts, E., Beck, J. C., Fiske, B., Ross, W., Savica, R., Eeden, S. K. V. D., Tanner, C. M., Marras, C., Alcalay, R., Schwarzschild, M., Racette, B., Chen, H., Church, T., Wilson, B., & Doria, J. M. (2022). Incidence of Parkinson disease in North America. *Npj Parkinson's Disease*, *8*(1), 170. https://doi.org/10.1038/s41531-022-00410-y

Lewin Group, Inc. Economic Burden of Parkinson's and Atypical Parkinsonism in the United States (2026). https://www.michaeljfox.org/sites/default/files/media/document/Economic%20Burden%20of%20Parkinson's%20and%20Atypical%20Parkinsonism%20in%20the%20United%20States_0.pdf

Johnsrud M, Richards K, Arcona S, Sasané R, Leoni M. An assessment of Parkinson's disease medication treatment patterns in the Medicaid population. *Clin Park Relat Disord*. 2021 Sep 27;5:100109. doi: 10.1016/j.prdoa.2021.100109. PMID: 34693271; PMCID: PMC8512608.

Richards K, Mantri S, Brown CM, Johnsrud M, Arcona S, Sasané R. A Qualitative Study on Perspectives of Parkinson's Disease Medications: Insights from Patient Focus Groups. *Patient Prefer Adherence*. 2024 Sep 18;18:1919-1928. doi: 10.2147/PPA.S473991. PMID: 39310087; PMCID: PMC11416774.

Rusch C, Flanagan R, Suh H, Subramanian I. To restrict or not to restrict? Practical considerations for optimizing dietary protein interactions on levodopa absorption in Parkinson's disease. *NPJ Parkinsons Dis*. 2023 Jun 24;9(1):98. doi: 10.1038/s41531-023-00541-w. PMID: 37355689; PMCID: PMC10290638.

Dahodwala, N., Kapogiannis, T., Cruz, A., Beck, J. C., Davis, T. L., Liu, H., Luo, S., Naito, A., Neault, M., Rafferty, M. R., Ramirez-Zamora, A., & Marras, C. (2025). Longitudinal Study of Treatment Variability for Parkinson's Disease across Specialized Centers. *Movement Disorders Clinical Practice*, 12(12), 2207–2216. https://doi.org/10.1002/mdc3.70232

Mehanna, R., Smilowska, K., Fleisher, J., Post, B., Hatano, T., Piemonte, M. E. P., Kumar, K. R., McConvey, V., Zhang, B., Tan, E., Savica, R., Savica, R., Tan, E., Mehanna, R., Smilowska, K., Marras, C., Ross, O., Kumar, K., Fleisher, J., … Salari, M. (2022). Age Cutoff for Early-Onset Parkinson's Disease: Recommendations from the International Parkinson and Movement Disorder Society Task Force on Early Onset Parkinson's Disease. *Movement Disorders Clinical Practice*, *9*(7), 869–878. https://doi.org/10.1002/mdc3.13523

Jones-Tabah J, Mohammad H, Paulus EG, Clarke PBS, Hébert TE. The Signaling and Pharmacology of the Dopamine D1 Receptor. *Front Cell Neurosci*. 2022 Jan 17;15:806618. doi: 10.3389/fncel.2021.806618. PMID: 35110997; PMCID: PMC8801442.

Pearson, C., Hartzman, A., Munevar, D., Feeney, M., Dolhun, R., Todaro, V., Rosenfeld, S., Willis, A., & Beck, J. C. (2023). Care access and utilization among medicare beneficiaries living with Parkinson's disease. *Npj Parkinson's Disease*, *9*(1), 108. https://doi.org/10.1038/s41531-023-00523-y

Veilleux Carpentier, A., Malaty, I.A., LeWitt, P.A., Azmi, H., Brooks, A., Pollak, E., Air, E.L., Simpson, H., Thomas, J., Thomas, F.P., Cocoziello, L., Rosenfeld, S. and Okun, M.S. (2026), A Systematic Review of the Parkinson's Foundation Hospital Care Recommendations. *Mov Disord Clin Pract*, 13: 29-43. https://doi.org/10.1002/mdc3.70247

Yu JRT, Sonneborn C, Hogue O, et al. Establishing a framework for quality of inpatient care for Parkinson's disease: a study on inpatient medication administration. *Parkinsonism Relat Disord* 2023; 113:105491. https://doi.org/10.1016/j.parkreldis.2023.105491.

Azmi H, Cocoziello L, Nyirenda T, et al. Adherence to a strict medication protocol can reduce length of stay in hospitalized patients with Parkinson's disease. *Clin Park Relat Disord* 2020; 3:100076. https://doi.org/10.1016/j.prdoa.2020.100076.

Nance MA, Boettcher L, Edinger G, et al. Quality improvement in Parkinson's disease: a successful program to enhance timely Administration of Levodopa in the hospital. *J Parkinsons Dis* 2020; 10(4): 1551–1559. https://doi.org/10.3233/JPD-202024.

Luca, D. G. D., Luo, S., Liu, H., Cohn, M., Davis, T. L., Ramirez-Zamora, A., Rafferty, M., Dahodwala, N., Naito, A., Neault, M., Beck, J., & Marras, C. (2023). Racial and Ethnic Differences in Health-Related Quality of Life for Individuals With Parkinson Disease Across Centers of Excellence. *Neurology*, 100(21), e2170–e2181. https://doi.org/10.1212/wnl.0000000000207247

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March 27, 2026

Institute for Clinical and Economic Review (ICER)
14 Beacon St., Suite 800
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Submitted electronically: publiccomments@icer.org
Re: Tavapadon for Parkinson's Disease – Draft Background and Scope

Dear ICER Review Team,

On behalf of Parkinson & Movement Disorder Alliance (PMDA), we appreciate the opportunity to comment on the draft scoping document for the evaluation of tavapadon for Parkinson's disease (PD). PMDA works to improve quality of life for people living with Parkinson's through education, support, and community building. Our comments reflect both patient and healthcare provider perspectives, including some in their own words. We aim to ensure that ICER's assessment captures outcomes most meaningful to those living with PD.

Quality of Life and Function as Primary Outcomes
For people living with Parkinson's, the goal of treatment is not just living longer, but being able to function, stay independent, and count on their bodies in daily life. Our community consistently emphasizes outcomes such as:

- Ability to perform activities of daily living
- Predictability of symptom control
- Reduction in motor fluctuations
- Cognitive and emotional stability

As PMDA ambassador Lori, age 57, shares, "Parkinson's means I don't have 24 hours in my day anymore, I have smaller and smaller windows of function and need to fit my life into those windows."

Evidence shows that treatment in Parkinson's disease is centered on maintaining independence and quality of life, shaped by both motor and non-motor symptoms [1,2].

Heterogeneity and Need for Additional Treatment Options
Parkinson's disease is highly heterogeneous, with variability in symptoms, progression, and treatment response.

"What works for someone else in my PD support group doesn't always work for me. When you've met one person with Parkinson's, you've met one person with Parkinson's, my doc always says."
-Todd, age 59, living with Parkinson's

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Patients frequently require individualized and evolving treatment regimens. Research highlights the broad variability in clinical presentation and treatment response, reinforcing the need for multiple therapeutic options [2].

Pill Burden and Daily Impact
Treatment burden remains a major contributor to reduced quality of life.

"We have pill trays. We have everything written out. It has to be very structured. The day is built around when he takes his medication, because if it's late or missed, it's a problem. He can freeze, he can fall. Everything revolves around that schedule." – Deb, age 62, Parkinson's care partner

Levodopa-based regimens often require frequent dosing due to short half-life and variable absorption. This contributes to adherence challenges and fluctuating symptom control. Evidence suggests that non-continuous dopaminergic stimulation contributes to motor complications and reduced treatment reliability over time [1,5]. Therapies that reduce dosing frequency or provide more stable receptor stimulation may improve adherence and daily functioning.

Motor Fluctuations and Predictability
Motor fluctuations are a key driver of disability and reduced quality of life.

"When my meds stop working, I describe myself as a walking Frankenstein. It is hard to even get out of bed." – Jennifer, age 45, person living with Parkinson's

Fluctuations affect a substantial proportion of patients as disease progresses and are associated with impaired daily functioning and decreased quality of life [5]. Importantly, patients emphasize that predictability of response is as important as total ON time. Therapies that provide more consistent symptom control can help people stay independent and take part in their daily lives.

Neuropsychiatric Risks
Current FDA-approved dopamine agonists are associated with neuropsychiatric adverse effects.

"The first medicine I was on was supposed to help with my tremor and my depression but the side effect was terrible. I got addicted to online shopping."
-Judy, age 85, living with Parkinson's

Impulse control disorders and related behavioral complications remain well-documented risks of dopaminergic therapies, with meaningful impact on patients and families [6]. These risks frequently limit use in clinical practice. A therapy with improved tolerability could expand treatment options for patients who are unable or unwilling to use existing therapies.

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Care Partner and Societal Impact
Parkinson's disease places a heavy burden on care partners, families of those diagnosed, and the broader community.

"The whole experience is horrible for both of us. I have to fight every step of the way to get the services he needs, not to mention make time to do everything for my own health."
-Corrie, age 67, Parkinson's care partner and spouse

Recent studies demonstrate that PD significantly impacts caregiver burden, healthcare utilization, and societal costs, driven by functional decline and neuropsychiatric complications [7,8]. Therapies that improve symptom control, reduce fluctuations, and simplify treatment may help delay loss of independence and reduce caregiver burden.

Considerations for ICER's Assessment
To ensure a comprehensive evaluation of tavapadon, we encourage ICER to:

- Prioritize patient-centered outcomes reflecting function, independence, and predictability of symptom control
- Factor in lived experience, including how treatments are started, adjusted, and changed over time, as well as combination therapy
- Account for pill burden, including dosing frequency, timing, and impact on routines
- Capture clinical trade-offs related to neuropsychiatric risks, including their influence on patient and provider decision-making
- Recognize the impact on family units, including care coordination and loss of independence
- Reflect how PD progresses differently for each person, including how symptoms and treatment needs change over time

Conclusion
There remains a significant unmet need in Parkinson's disease for therapies that improve quality of life, functional independence, and treatment experience. As PMDA ambassador Lori puts it, "I need to focus on living my life, not constantly chasing my symptoms."

We appreciate ICER's commitment to incorporating stakeholder perspectives and encourage continued emphasis on the lived experience of Parkinson's disease in this evaluation.

Sincerely,

Andrea Merriam, CEO
PMD Alliance
On behalf of the entire PMD Alliance community

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References

1. Poewe W, et al. Parkinson disease. Nat Rev Dis Primers. 2025.
2. Hayes MT. Parkinson's disease and parkinsonism. Am J Med. 2024.
3. Jones-Tabah J, et al. The signaling and pharmacology of the dopamine D1 receptor. Front Cell Neurosci. 2022.
4. Hauser RA, et al. Dopamine receptor pharmacology and emerging therapies in Parkinson's disease. Mov Disord. 2023.
5. Espay AJ, et al. Revisiting motor fluctuations in Parkinson disease. Lancet Neurol. 2024.
6. Weintraub D, et al. Impulse control disorders in Parkinson's disease. Mov Disord. 2023.
7. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA. 2024.
8. Yang W, et al. Economic burden and future projections for Parkinson's disease. npj Parkinsons Dis. 2023.

To: ICER Scoping Committee

Re: Proposed Scoping Document for Tavapadon in Parkinson's Disease

Date: March 24, 2026

To the ICER Scoping Committee,

Should Population 1 be stratified by age? Or, can it be defined as simply "early PD in patients <60 years old?" While a cutoff of 60 years old may seem arbitrary, I would argue that the age of the patient (< 60 years, vs >60 years) is a significant consideration that drives my decision making when choosing initial therapy.

In patients >60 years old, levodopa is the undisputed gold standard for initial treatment, and I would imagine that the clinical hurdle for tavapadon to show superiority or non-inferiority to L-dopa would be very high.

The clinical decision is more nuanced for patients <60 years old, however. It is in this population that I more carefully consider the tradeoffs of sufficiently treating motor symptoms, risk of dyskinesia, ease of dosing (TID vs once-a-day for the ER formulations), ICD/neuropsychiatric side effects, etc. I'm not sure if your analysis allows you to stratify the population, or if Population 1 should be narrowed to <60 years old, but I can say that as a clinician who sees patients with PD everyday and will read this report, I am much more interested in how tavapadon compares to levodopa in a 45 year old or 55 year old patient with early PD, rather than in a 65 year old or 75 year old patient.

I don't have any comments re: the Population 2 intervention or comparators.

Thanks for letting me provide feedback. I'm happy to discuss further. I want to note that I have performed a small amount of independent consulting for Abbvie in the past.

Sincerely,

Jason Crowell, MD, MPA
Movement Disorder Specialist
Louisville, KY

Public Comment on ICER Draft Scope: Tavapadon for Parkinson's Disease

Submitted by [redacted], Professor Emerita, New York University; Research Advocate, Parkinson's Foundation.

Note: This statement has been prepared independent of my role as a Research Advocate for the Parkinson's Foundation and reflects my personal views as a person living with Parkinson's disease and as a research scientist.

I. Personal Narrative: Levodopa-Phobia as a Barrier to Diagnosis

Nearly seventeen years ago, I began experiencing symptoms that would ultimately be recognized as early Parkinson's disease (PD). My tremor was disorganized and atypical in its initial presentation, making confident clinical diagnosis challenging. I sought evaluation from a well-regarded general neurologist who pursued the diagnostic question diligently, ordering a wide range of complex and, at times, invasive tests to characterize what could be causing my symptoms.

As a person with PhD-level research training and solid familiarity with the clinical literature on PD, informed in part by my dad's PD diagnosis several years before my own, I suggested to the general neurologist that a therapeutic trial of levodopa might itself be diagnostically informative, given that levodopa-responsiveness is a hallmark feature of idiopathic PD. He had been wavering between a diagnosis of PD with atypical early presentation and the possibility of a "psychogenic" movement disorder. My proposal to trial levodopa produced a dramatic response: the neurologist was horrified. My suggestion was dismissed, not on clinical grounds that were ever articulated, but out of what I can only describe as an aversion to trialing levodopa for diagnostic purposes. I later met a person with PD who was being treated by this same neurologist; he was clearly receiving such low doses of levodopa that his symptoms were poorly controlled. It appeared that the neurologist maintained a common but ultimately falsified belief that levodopa only works for a limited amount of time, so *don't start taking levodopa too early* and *don't take too much of it until you desperately need it!*

This encounter crystallized for me something I have since come to understand as well-documented in the peer-reviewed literature: levodopa-phobia does not merely delay or complicate treatment in people with established PD. It can obstruct diagnosis. When a clinician is unwilling to consider a levodopa trial as a diagnostic tool, despite that trial being one of the most time-honored approaches in movement disorder medicine, the patient bears the cost of that fear in the form of delayed diagnosis, unnecessary testing, and prolonged uncertainty.

Within mere weeks following my disturbing encounter with the general neurologist, my disorganized tremors evolved into a classic pill-rolling resting tremor. Now, there was no doubt in my mind about my diagnosis: I interviewed a half dozen movement disorder specialists and chose one who shared a career in clinical research and knew well the cognitive demands of my

work, a woman who immediately started me on carbidopa/levodopa. Once medicated, I was able to function quite well, after nearly six months of unexplained and bizarre symptoms that had left me debilitated and in near despair. PD was now something that I could “live with.”

II. Levodopa-Phobia: A Documented, Persistent, and Consequential Problem

The term "levodopa-phobia" was formally introduced into the peer-reviewed literature in 2005 by Kurlan, who described it as "a new iatrogenic cause of disability in Parkinson disease": physicians’ avoidance of prescribing levodopa that left patients undertreated and functionally impaired [1]. Nearly two decades later, the phenomenon remains well-documented and clinically consequential.

In 2018, Titova and colleagues published a comprehensive review identifying multiple subtypes of levodopa-phobia: those driven by physicians unwilling to prescribe, patients influenced by available literature or social media, and carers who resist treatment on behalf of their loved ones [2]. The clinical consequences include motor deterioration, muscle contractures, social isolation, and -- crucially and devastatingly for some-- the emergence of impulse control disorders (ICDs) attributable to reliance on dopamine agonists in patients who would have been better served by levodopa.

The fear underlying levodopa-phobia is largely rooted in concerns about levodopa-induced dyskinesias and, to a lesser degree, the now-discredited theoretical concern that levodopa may be toxic to dopaminergic neurons. As early as 2011, Vlaar and colleagues argued compellingly that most of these concerns are invalid, and that levodopa remains the most effective and best-tolerated PD medication, concluding that "a 'phobia' for levodopa…is unacceptable according to current evidence" [3]. Nonnekes et al further demonstrated that levodopa-phobia contributes to what they term "pseudoresistance" in the form of patients who appear not to respond to levodopa, not because of true resistance but because they have never been adequately dosed [4].

Critically, while levodopa-phobia may be somewhat attenuated in the United States and United Kingdom following landmark studies such as the LEAP trial [7] and PD MED [10], it continues robustly in international settings. Bruno and colleagues documented significant geographic variation in levodopa prescribing patterns within the US itself, with states having fewer neurologists showing lower proportions of levodopa prescriptions [6]. A 2025 survey of movement disorder specialists in Polish tertiary centers confirms that levodopa-phobia continues to influence prescribing patterns even among specialists [9].

The evidence base for delaying levodopa has, if anything, weakened over time. A 2024 meta-analysis by Ramanzini and colleagues, encompassing seven randomized controlled trials and 1,149 patients, found that delaying levodopa does not prevent motor complications or dyskinesias, and that motor fluctuations were less frequent in the early-start group [8]. These findings reinforce what the LEAP trial demonstrated in 2019: there is no meaningful clinical

benefit to delaying treatment with levodopa. Rather, potentially active harm is associated with levodopa delay [7].

III. Tavapadon in Early PD: Concerns About Re-Igniting Levodopa-Phobia

My concern about Tavapadon's use as an adjunct therapy in people with advanced PD experiencing Off periods is limited. There, the therapeutic question is relatively well-defined, and Tavapadon's mechanism (i.e., selective dopamine D1/D5 receptor agonism with once-daily dosing) may offer meaningful convenience and Off-period reduction for patients who need it.

My primary concern is the early PD indication. Positioning Tavapadon as a first-line or early-stage alternative to levodopa carries a serious risk: it provides clinicians already inclined toward levodopa-avoidance with a new drug and a new justification to delay or substitute away from levodopa. This risk is compounded by the absence of a direct, within-trial, head-to-head comparison of Tavapadon versus carbidopa/levodopa versus placebo. Inferences drawn from comparing outcomes across different trials are much weaker methodologically. This problematic inference is insufficient to support a clinical positioning decision with this magnitude of downstream consequences.

A financial equity dimension falls under that ICER's scoping process: Generic carbidopa/levodopa is among the most affordable medications in PD treatment. Tavapadon is a patented, brand-name drug. If it is positioned as an early-stage substitute for levodopa, despite absence of evidence of superiority (or even methodologically sound evidence of equivalence) in patient-centered outcomes, patients, payers, and health systems will bear the financial burden of that substitution, with concentrated disadvantage for patients with limited means or inadequate insurance coverage.

I urge ICER, in its scoping phase, to ensure that: (1) the evidence review explicitly addresses whether Tavapadon’s early-PD trial data constitute adequate grounds for comparison with levodopa, given the absence of a direct head-to-head RCT; (2) patient-centered outcomes, including quality of life, functional independence, ability to work, and non-motor symptom burden, be weighted alongside motor outcomes; (3) the comparative cost-effectiveness analysis accounts for the affordability of generic carbidopa/levodopa as the relevant comparator; (4) the scope explicitly considers how market positioning may interact with existing patterns of levodopa-phobia, particularly in settings outside the US where those patterns remain strong; and (5) lived experience testimony is interpreted in the context of the diagnostic journey, not only for established disease management, recognizing that levodopa-phobia can delay and complicate diagnosis, not only treatment.

ICER's work on Tavapadon represents an important opportunity to get the evidence framing right. I am committed to contributing further as this process moves forward.

References

[1] Kurlan R. "Levodopa phobia": a new iatrogenic cause of disability in Parkinson disease. *Neurology.* 2005;64(5):923–924. doi:10.1212/01.WNL.0000152880.77812.5B. PMID: 15753443.

[2] Titova N, Levin O, Katunina E, Chaudhuri KR. 'Levodopa Phobia': a review of a not uncommon and consequential phenomenon. *NPJ Parkinsons Dis.* 2018;4:31. doi:10.1038/s41531-018-0067-z. PMID: 30302392.

[3] Vlaar A, Hovestadt A, van Laar T, Bloem BR. The treatment of early Parkinson's disease: levodopa rehabilitated. *Pract Neurol.* 2011;11(3):145–152. doi:10.1136/practneurol-2011-000011. PMID: 21551108.

[4] Nonnekes J, Timmer MHM, de Vries NM, Rascol O, Helmich RC, Bloem BR. Unmasking levodopa resistance in Parkinson's disease. *Mov Disord.* 2016;31(11):1602–1609. doi:10.1002/mds.26712. PMID: 27430479.

[5] Rota S, Boura I, Batzu L, Titova N, Jenner P, Falup-Pecurariu C, Chaudhuri KR. 'Dopamine agonist Phobia' in Parkinson's disease: when does it matter? Implications for non-motor symptoms and personalized medicine. *Expert Rev Neurother.* 2020;20(9):953–965. doi:10.1080/14737175.2020.1806059. PMID: 32755243.

[6] Bruno MK, Watanabe G, Ishikawa K, Chen JJ, Gao F, Nakagawa K, Taira D. Geographic Variation in Prescription Patterns of Parkinson's Disease Medications. *Mov Disord.* 2022;37(3):646–648. doi:10.1002/mds.28880. PMID: 34859504.

[7] Verschuur CVM, Suwijn SR, Boel JA, et al.; LEAP Study Group. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. *N Engl J Med.* 2019;380(4):315–324. doi:10.1056/NEJMoa1809983. PMID: 30673543.

[8] Ramanzini LG, Frare JM, Camargo LFM, Silveira JOF, Jankovic J. Does Delaying Levodopa Prevent Motor Complications in Parkinson's Disease? A Meta-Analysis. *Mov Disord Clin Pract.* 2024;11(10):1195–1202. doi:10.1002/mdc3.14198. PMID: 39189097.

[9] Kasprzak J, Dulski J, Przytuła F, et al. Levodopa and dopamine agonist phobia in Parkinson's Disease — does it really matter? A survey on treatment patterns in Polish tertiary centres. *Neurol Neurochir Pol.* 2025;59(1):62–69. doi:10.5603/pjnns.103168. PMID: 40007330.

[10] PD Med Collaborative Group; Gray R, Ives N, Rick C, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson’s disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet.* 2014;384(9949):1196–1205. doi:10.1016/S0140-6736(14)60683-8. PMID: 24928805.

To the ICER Review Committee,

I am a 60-year-old business owner currently living with Stage 1.5 Parkinson's Disease. As a commercial real estate broker, my professional livelihood depends entirely on my executive function, multitasking ability, and mental clarity. I am writing to urge ICER to prioritize "Cognitive Sharpness" and "Functional Productivity" as primary value metrics in your assessment of Tavapadon.

The current standard of care—specifically Levodopa and D2/D3 agonists—often forces a choice between motor control and mental clarity. I frequently experience a sensation of being "underwater"—a debilitating brain fog that hinders my ability to manage complex property portfolios and high-stakes negotiations. Furthermore, the sedative side effects and the risk of impulse control disorders associated with D3-heavy medications are a direct threat to my business and financial stability.

The D1/D5 selective mechanism of Tavapadon represents a critical unmet need for high-functioning professionals. For those of us who must remain "above water" to support our families and businesses, a treatment that targets the prefrontal cortex to improve executive function is not just a lifestyle preference—it is a medical necessity for economic survival. I ask that you recognize the profound value of a non-sedating, pro-cognitive therapy in your final report.

Respectfully,

[redacted]

[redacted]

IECR Inputs March 24, 2026

Dear ICER Review Team,

I am writing to provide public comment on the Draft Scope for the upcoming review of Tavapadon for Parkinson's Disease. My name is [redacted], and I am a patient living with Parkinson's Disease. I also serve as an Ambassador, Research Advocate, and Board Member for the Southwest Chapter of the Parkinson's Foundation.

I recently participated in the 54-week clinical trial for Tavapadon at the Cleveland Clinic in Las Vegas. My experience with this treatment was transformative. During the high-dose phase of the trial, my motor symptoms—including gait, posture, and energy levels—improved dramatically within just 2-3 weeks. For the first time since my diagnosis, I felt like a young man again. I no longer experienced "off" times or the need for daily naps, and my quality of life reached an excellent level that was noticeable to both my family and friends.

However, the contrast after the trial concluded has been stark. After returning the medication following AbbVie's NDA application, I spent two months without Tavapadon, during which time all of my symptoms returned with full force. While I am now on Carbidopa/Levodopa, it does not come close to the efficacy I experienced with Tavapadon. My walking pace is slower (24-minute miles compared to 21-minute miles on Tavapadon), my stamina is reduced, and I must now manage "off" times that were non-existent during the trial.

Regarding the scope of your review, I want to emphasize the critical need for affordability. While my current generic medication costs less than $10 per month, I have seen research prices for Tavapadon cited as high as $9,000 per month. For a drug that offers such a significant improvement in the ability to function and maintain independence, it is vital that the final pricing allows for equitable access.

Thank you for the opportunity to share my lived experience. I hope that the perspectives of trial participants like me are fully considered as you evaluate the clinical and economic value of this promising therapy.

Sincerely,

[redacted]

Parkinson's Foundation Ambassador & Research Advocate