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Pharmacokinetics, Pharmacodynamics, and Safety of the Highly Selective Dopamine D1/D5 Agonist Tavapadon: Summary of Early Phase Clinical Studies

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CONCLUSIONS

- Tavapadon has exhibited a consistent clinical pharmacology and safety profile across a wide range of doses in phase 1 clinical studies, supporting further investigation as a promising next-generation treatment for PD
- Tavapadon has a long half-life, which may support sustained 24-hour motor control
- Tavapadon is currently being investigated in ongoing phase 3 trials in early-stage PD (TEMPO-1 [NCT04201093] and TEMPO-2 [NCT04223193]), advanced PD (TEMPO-3 [NCT04542499]), and in an open-label extension in early-stage and advanced PD (TEMPO-4 [NCT04760769])

Additional details on TEMPO program

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REFERENCES: 1. Dawson and Dawson. *Sci Transl Med*. 2019;11(520). **2.** de Bie et al. *Lancet Neurol*. 2020;19:452-461. **3.** Napier and Persons. *Eur J Neurosci*. 2019;50:2492-2502. **4.** Riesenberg et al. *Ther Adv Neurol Disord*. 2020;13:1756286420911296. **5.** Sohur et al. *Neurol Ther*. 2018;7:307-319. **6.** NCT04201093. https://www.clinicaltrials.gov/ct2/show/NCT04201093. Accessed March 3, 2022. **7.** NCT04223193. https://www.clinicaltrials.gov/ct2/show/NCT04223193. Accessed March 3, 2022. **8.** NCT04542499. https://www.clinicaltrials.gov/ct2/show/NCT04542499. Accessed March 3, 2022. **9.** NCT04760769. https://www.clinicaltrials.gov/ct2/show/NCT04760769. Accessed March 3, 2022.

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INTRODUCTION

- Current treatment approaches in Parkinson's disease (PD) treat motor symptoms effectively, although overall, treatments are less effective in treating advanced disease, and there is an unmet need for effective and tolerable symptomatic therapies[1]
  - Currently approved D2/D3 selective dopamine receptor agonists often have significant side effects such as impulse control disorders, somnolence, confusion, hallucinations, nausea, fatigue, and hypotension[2-3]
- Tavapadon, a first-in-class, highly selective partial agonist at dopamine D1 and D5 receptors, is in development for the treatment of PD[4,5]
  - By selectively targeting D1/D5 receptors, tavapadon may improve motor symptoms while minimizing adverse events (AEs) generally associated with D2/D3 receptor agonists[4,5]
  - Supported by previous early phase studies, tavapadon is currently being explored in the phase 3 TEMPO program, which will evaluate the efficacy, safety, and tolerability of tavapadon in PD[4-9]

OBJECTIVE

- To describe the pharmacokinetic (PK), pharmacodynamic, and safety data from early phase clinical studies of tavapadon

METHODS

- We reviewed clinical PK, pharmacodynamic, and safety data from several early phase clinical studies conducted in healthy volunteers and patients with PD (**Table 1**)
  - These studies investigated tavapadon in the oral dose range of 0.25 to 25 mg

Table 1. Studies Reviewed in Current Presentation

ClinicalTrials.gov identifier	Phase	Study population	Study description
NCT01981694	1	Healthy volunteers	Safety and tolerability of tavapadon
NCT02224664	1b	Patients with PD	Safety, tolerability, PK, and pharmacodynamics of tavapadon in PD
NCT04295642	1	Patients with PD	Safety, tolerability, and food effect of tavapadon in PD
NCT03121664	1	Healthy volunteers	Effects of itraconazole on PK of tavapadon
NCT02847650	2	Patients with early-stage PD	Efficacy, safety, and tolerability of tavapadon in early-stage PD

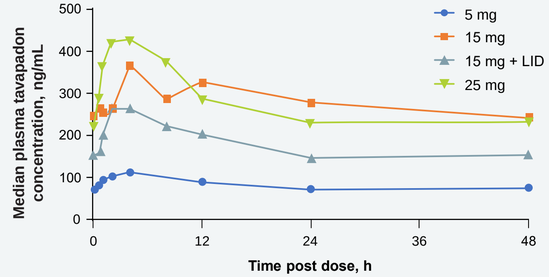
PD, Parkinson's disease; PK, pharmacokinetics.

RESULTS

PHARMACOKINETICS

- In a phase 1, randomized study (NCT01981694) assessing a single dose of tavapadon in idiopathic PD, PK was characterized by rapid absorption and an average terminal elimination half-life of approximately 24 hours after oral administration of tavapadon, supporting once-daily dosing
- In a phase 1, open-label study (NCT02224664) investigating repeated, once-daily doses of tavapadon in patients with PD, median plasma concentrations appeared to be dose proportional (**Figure 1**)

Figure 1. Median plasma tavapadon concentrations on day 22 following multiple daily dose administrations.



LID, levodopa-induced dyskinesia; QD, once daily. Oral daily doses were titrated up to 5 mg QD (5 mg), 15 mg QD (15 mg), and 25 mg QD (25 mg), respectively. In the '15 mg + LID' cohort, oral daily doses were titrated up to 15 mg QD in patients with LID.

FOOD EFFECT

- In a phase 1, open-label food effect study (NCT04295642) of tavapadon in patients with PD, high-fat meals prior to dosing did not have clinically relevant impact on the rate or extent of absorption in patients with PD (**Table 2**)
  - These food effect results were consistent with the previous study in healthy participants (NCT01981694)

Table 2. Statistical Evaluation of Food Effect on C_{max} and AUC_{tau} of Tavapadon

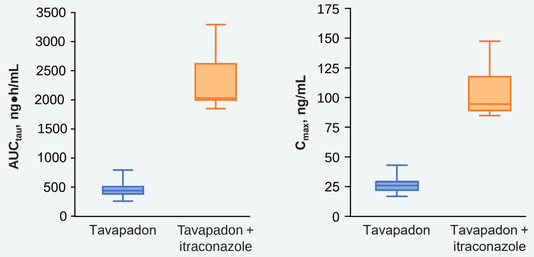
Parameter	Treatment	n	Geometric LS mean	Ratio, %	90% CI
AUC_{tau},[a] ng•h/mL	Fed	9	5230	112	103, 122
	Fasted	9	4670	—	—
C_{max}, ng/mL	Fed	9	291	110	104, 118
	Fasted	9	264	—	—

[a]AUC_{tau} is the area under the concentration-time profile from time 0 to time tau, the dosing interval, where tau = 24 hours (once-daily dosing). AUC, area under the curve; CI, confidence interval; C_{max}, maximum observed concentration; LS, least squares.

METABOLISM

- Tavapadon's clearance is primarily via metabolism by cytochrome P450 (CYP450) 3A4 (CYP3A4)
- In a phase 1, open-label study (NCT03121664) assessing the effects of multiple-dose administration of the potent CYP3A4 inhibitor itraconazole on the steady-state PK of tavapadon in healthy volunteers, coadministration with itraconazole resulted in a 4- and 5-fold increase in peak and overall exposure, respectively (**Figure 2**)

Figure 2. Effect of CYP3A4 inhibition by itraconazole on tavapadon exposure.



[a]AUC_{tau} is area under the concentration-time profile from time 0 to time tau, the dosing interval, where tau = 24 hours. [b]C_{max} is the maximum observed concentration. AUC, area under the curve.

- In the same study, the major circulating hydroxylated metabolite (PF-06752844) exposure decreased by 36% following coadministration with itraconazole
- Due to low recovery of tavapadon in urine (≤0.2%) and its extensive hepatic metabolism, planned studies will evaluate PK and safety in patients with severe renal impairment and patients with mild and moderate hepatic impairment

PHARMACODYNAMICS

In a phase 2,[a] flexible-dose, randomized, placebo-controlled **study in patients with early-stage PD**, **patients demonstrated a significant mean** (standard error [SE]) **change** from baseline to week 15 **in** the primary study efficacy endpoint of Movement Disorder Society–Unified Parkinson's Disease Rating Scale **(MDS-UPDRS) Part III score of -9.0 (1.54) compared with -4.3 (1.65) for placebo**, **corresponding to** a least-squares mean (SE) **improvement over placebo of 4.8 (2.26) for tavapadon**[4]

[a]Enrollment was terminated early for reasons unrelated to the trial.

SAFETY

- There were no notable abnormalities in laboratory or electrocardiogram parameters across early phase studies, with nausea and headache observed as the most frequent AEs
  - A dose-dependent increase in the frequency of nausea and headache was observed across all trials; the appearance of nausea, orthostatic blood pressure changes, and fatigue are often related to the speed of titration and may be mitigated by a slower titration method
  - Analysis of multidose cohorts in Phase 1 trials in healthy volunteers and patients with PD (including patients treated at doses up to 25 mg QD of tavapadon) did not suggest that tavapadon prolonged the QT interval corrected for heart rate
  - In a phase 2, flexible-dose, randomized, placebo-controlled study in patients with early-stage PD, nausea was noted as the most common nonserious AE in patients treated with tavapadon (**Table 4**)[4]; hallucination was not an observed AE with tavapadon
    - In the same study, there were no apparent differences between tavapadon and placebo cohorts in impulse control disorders (ICDs), and sleepiness; orthostatic hypotension–related AEs and significant echocardiogram changes were not observed with tavapadon compared with placebo

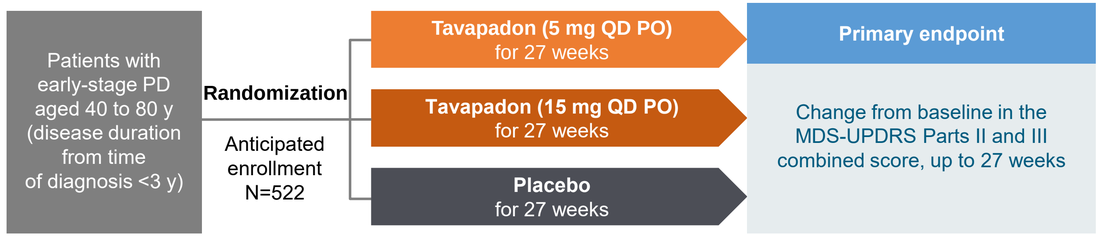
Table 4. Most-Common AEs[a] in a Phase 2, Placebo-Controlled Study (NCT02847650)[4]

AE, n (%)	Placebo (n=28)	Tavapadon (n=29)
Nausea	2 (7)	9 (31)
Headache	2 (7)	7 (24)
Dry mouth	0	5 (17)
Somnolence	1 (4)	4 (14)
Tremor	2 (7)	4 (14)
Urinary tract infection	0	3 (10)
Decreased appetite	0	3 (10)
Arthralgia	0	3 (10)
Hot flush	0	3 (10)
Back pain	1 (4)	3 (10)
Fatigue	3 (11)	3 (10)

[a]All-cause AEs occurring in ≥10% of patients in either group. AE, adverse event.

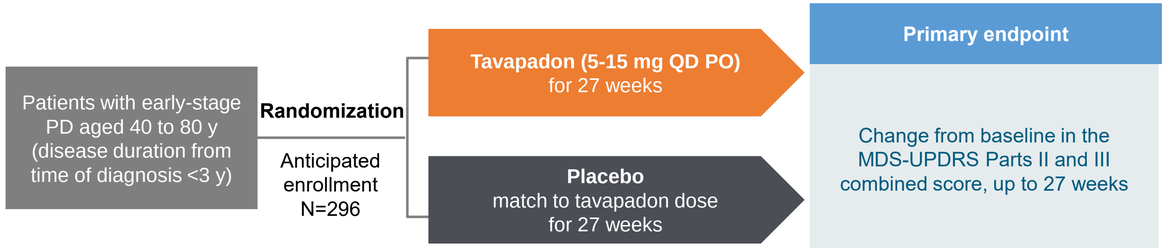
TEMPO Program for Tavapadon in PD

The Phase 3 TEMPO-1[1] Study Will Assess the Safety, Efficacy, and PK of Fixed-Dose Tavapadon Monotherapy in Early-Stage PD (NCT04201093)



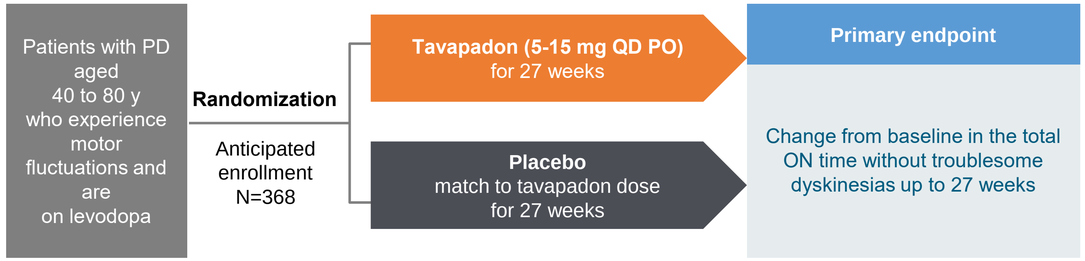
Secondary endpoints will include patient and clinical impression (eg, PGIC, CGI-S, and CGI-I) and safety measures (eg, ESS, QUIP-RS, C-SSRS, and TEAEs)

The Phase 3 TEMPO-2[2] Study Will Assess the Safety, Efficacy, and PK of Flexible-Dose[a] Tavapadon Monotherapy in Early-Stage PD (NCT04223193)



Secondary endpoints will include patient and clinical impression (eg, PGIC, CGI-S, and CGI-I) and safety measures (eg, ESS, QUIP-RS, C-SSRS, and TEAEs)

The Phase 3 TEMPO-3[3] Study Will Assess the Efficacy of Flexible-Dose Tavapadon as Adjunct Therapy in Advanced PD (NCT04542499)



Secondary endpoints will include change from baseline in total daily ON time and OFF time and change from baseline in the MDS-UPDRS Parts I, II, and III individual scores

Phase 3 TEMPO-4[4] Study Will Assess the Long-term Safety and Efficacy of Flexible-Dose Tavapadon in PD (NCT04760769)

CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity of Illness; C-SSRS, Columbia-Suicide Severity Rating Scale; ESS, Epworth Sleepiness Scale; EQ-5D-5L, EuroQol 5-Dimension 5-Level; MDS-UPDRS, Movement Disorder Society–Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; PGIC, Patient Global Impression of Change; PK, pharmacokinetics; PO, oral; PRO, patient-reported outcome; QD, once daily; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale; TEAE, treatment-emergent adverse event; VAS, visual analog scale.

[a]Patients received dose titrated up to 15 mg QD PO, based on individual patient tolerability.

1. NCT04201093. https://www.clinicaltrials.gov/ct2/show/NCT04201093. Accessed March 22, 2022. **2.** NCT04223193. https://www.clinicaltrials.gov/ct2/show/NCT04223193. Accessed March 22, 2022. **3.** NCT04542499. https://www.clinicaltrials.gov/ct2/show/NCT04542499. Accessed March 22, 2022. **4.** NCT04760769. https://www.clinicaltrials.gov/ct2/show/NCT04760769. Accessed March 22, 2022.

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