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A Placebo-Controlled Trial of AQW051 in Patients with Moderate to Severe Levodopa-Induced Dyskinesia

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Abstract [Word count: 146 (max 150)]**Introduction**

This Phase II, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of the nicotinic acetylcholine receptor $\alpha 7$ agonist, AQW051, in patients with Parkinson's disease and levodopa-induced dyskinesia.

Methods

Patients with idiopathic Parkinson's disease and moderate to severe levodopa-induced dyskinesia were randomized to AQW051 10 mg (n = 24), AQW051 50 mg (n = 24), or placebo (n = 23) once daily for 28 days. Co-primary endpoints were change in Modified Abnormal Involuntary Movement Scale and Unified Parkinson's Disease Rating Scale part III scores. Secondary outcomes included pharmacokinetics.

Results

In total, 67 patients completed the study. AQW051-treated patients experienced no significant improvements in Modified Abnormal Involuntary Movement Scale or Unified Parkinson's Disease Rating Scale part III scores by day 28. AQW051 was well tolerated; the most common adverse events were dyskinesia, fatigue, nausea, and falls.

Conclusions

AQW051 did not significantly reduce dyskinesia or parkinsonian severity.

Introduction

Motor complications such as levodopa (L-dopa)-induced dyskinesia (LID) negatively impact the lives of patients with Parkinson's disease (PD),^{1–3} and there are few sustained, non-invasive treatments for LID that do not reduce the antiparkinsonian benefits of L-dopa. Amantadine is currently the sole medication available and recommended for the management of LID.⁴ However, not all patients respond to or tolerate amantadine, and the prescription of amantadine is restricted by regulatory guidance in some countries (e.g. in Germany⁵).

Nicotine has been shown to protect against or alleviate nigrostriatal damage^{6–11} and improve LID^{12–14} in parkinsonian animal models. The antidyskinetic and neuroprotective effects of nicotine are exerted via multiple nicotinic acetylcholine receptors (nAChRs).^{6,10,12,13,15–17} The antidyskinetic potential of $\alpha 7$ nAChR agonists has now been displayed *in vivo* using the novel, selective partial agonist, (R)-3-(6-p-Tolyl-pyridin-3-yloxy)-1-aza-bicyclo(2.2.2)octane (AQW051).¹⁸ AQW051 significantly reduced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys without compromising the benefits of L-dopa.¹⁹ The objective of the current study was to evaluate the efficacy and safety of AQW051 in patients with moderate to severe PD-LID. As preclinical and clinical evidence suggests that $\alpha 7$ nAChR agonists, including AQW051, can also improve cognition,^{20–32} AQW051 was also evaluated for pro-cognitive effects in a post-hoc exploratory analysis.

Methods

This was a Phase II, multicenter, randomized, double-blind, parallel-group, placebo-controlled multi-dose study in PD-LID. Eligible patients were non-smoking men and women, aged 30–85 years, with idiopathic PD as per the UK Parkinson's Disease Society Brain Bank criteria. Patients were required to have: LID >20% (Unified Parkinson's Disease Rating Scale [UPDRS] item 32 rating ≥ 1) of moderate to severe intensity (UPDRS item 33 rating ≥ 2);³³ LID for ≥ 3 months before randomization; received L-dopa for ≥ 3 years; stable treatment with L-dopa for ≥ 1 month before randomization. Other

concomitant antiparkinsonian medication was allowed if treatment was stable for ≥ 1 month prior to randomization. Treatment with amantadine, antidepressants (except strong cytochrome [CYP]1A2 and CYP3A4 inhibitors), and/or benzodiazepines were permitted provided the dosing regimen was stable for ≥ 1 month before randomization.

Patients were randomized at a ratio of 1:1:1 into one of three treatment groups: AQW051 50 mg, AQW051 10 mg, or placebo. Treatment was administered orally, once daily in the morning after the initial L-dopa dose, for a period of 28 days, with a 2-week follow-up. Assessments were performed every week, once during follow-up, and at the end of study visit.

The protocol and amendments were approved by the Independent Ethics Committee and Institutional Review Board at each study center. This study was conducted according to the ethical principles of the Declaration of Helsinki and was registered on ClinicalTrials.gov (identifier NCT01474421). Informed written consent was obtained from all patients.

Outcomes

The co-primary outcome measures were the Modified Abnormal Involuntary Movement Scale (mAIMS)³⁴ and UPDRS-III items 18–31,³⁵ respectively. Assessments were performed in the morning 1 h post L-dopa dose during ON-time and in the afternoon at a patient-specific time point.

Secondary outcome measures included: UPDRS-IV items 32–33, Lang-Fahn Activities of Daily Living and Dyskinesia Scale (LFADLDS) sum score,³⁶ and a cognitive test battery (CogState)³⁷ for safety analysis and for tracking potential pro-cognitive effects.

Pharmacokinetics

Blood samples (3 mL) were collected into EDTA-containing tubes according to a predefined schedule. Sampling took place pre-dose and on days 1, 8, 16, 21, and 28; 1, 3, 4, 5, 8, and 12 h post-dose on day 28; and before and after the assessments on day 32. Plasma concentrations of AQW051 were

quantified using a validated liquid chromatography tandem mass spectrometry method (HPLC-MS/MS). The lower limit of quantification was 0.050 ng/mL using 0.200 mL of plasma.

Safety

Assessments included adverse events (AEs) and serious AEs (SAEs) reporting, laboratory tests, vital signs, electrocardiograms, and use of the Columbia-Suicidality Severity Rating Scale (C-SSRS).

Statistical analysis

Descriptive statistics were used to summarize AEs, safety, and demographic variables for the safety population (all patients who received ≥ 1 dose of study drug). Analysis of covariance of change from baseline of the per protocol population (all patients with ≥ 1 post-randomization efficacy assessment and no protocol deviations nor withdrawn) was the primary analysis, with relevant baseline values as the covariate and treatment group as a fixed factor. The effect over placebo was estimated for each AQW051 dose using a Dunnett adjustment, and there were no corrections for multiple comparisons between variables.

The pharmacokinetic parameters at steady state: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the curve for 0–24 h (AUC_{0-24h}), and oral clearance (CL/F) were determined using non-compartmental methods and summarized by dose group using descriptive statistics for the PK population (all patients with valid PK data).

Results

Seventy-one patients were randomized to receive AQW051 10 mg ($n = 24$), AQW051 50 mg ($n = 24$), or placebo ($n = 23$); 67 patients completed the study and 63 did so without protocol deviations.

Patient demographics and clinical variables for the safety population are summarized in Table 1.

Efficacy

The study did not meet its primary endpoints, with change in mean sum score for mAIMS and UPDRS-III showing no significant improvements in LID or parkinsonian symptoms following AQW051 treatment at either dose (Table 2).

Cognitive function

In the primary analysis, AQW051 was not associated with statistically significant improvements in cognitive outcomes. However, exploratory repeated measures analysis of the safety population showed that compared with placebo, AQW051 50 mg/day yielded a change corresponding to a standardized effect size of 0.5 ($P = 0.024$) in the CogState memory composite scores and an effect size of 0.4 ($P = 0.073$) was seen for AQW051 10 mg/day. The individual memory tasks included in the memory composite (One-Back Task [ONB] + International Shopping List Task [ISL]) also improved moderately at both AQW051 doses, with improvements in the ISL at AQW051 50 mg/day reaching significance ($P = 0.048$).

Pharmacokinetics

Comparison of pre-dose plasma concentrations of AQW051 indicates steady state was reached within the first week of dosing. At day 28, T_{max} median (range) values were very similar for 10 and 50 mg/day; 5.00 h (2.92–11.9) and 4.99 h (3–8), respectively. Mean (SD) CL/F values were 88.8 (68.4) L/h and 102 (59.2) L/h at 10 and 50 mg/day, respectively. Exposure in terms of AUC_{0-24h} and C_{max} increased 4.3 (160–686 ng*h/mL) and 4.5-fold (8.62–38.7 ng/mL), respectively, with a 5-fold increase of dose from 10 to 50 mg suggesting dose proportionality in systemic exposure across the dose range for AQW051.

Safety

AEs were experienced by 18 patients receiving AQW051 10 mg/day, 15 receiving AQW051 50 mg/day, and 18 receiving placebo. They were mostly mild to moderate, with dyskinesia the most frequently reported AE across all treatment groups (4.2%, 25.0%, and 13.0% of patients in the 10 mg/day, 50 mg/day, and placebo groups, respectively). Nausea (20.8%, 4.2%, and 0%,

respectively), falls (8.3%, 12.5%, and 4.3%, respectively) and fatigue (8.3%, 8.3%, and 8.7%, respectively) were the next most commonly reported AEs overall after dyskinesia.

Two patients receiving AQW051 50 mg/day experienced SAEs (one case each of mild ON-OFF phenomenon and severe neuroborreliosis). These were not considered to be treatment-related by the investigators and no action regarding study medication was taken. In both cases the event had resolved on follow-up. Two patients experienced AEs that the investigators considered treatment-related and resulted in their withdrawal from the study. One patient reported worsening dyskinesia on day 2 after treatment with AQW051 50 mg/day; the dyskinesia was ongoing at the last follow-up on day 21, and no further follow-ups have been reported. The second patient (with an active history of depression) reported mild depression on day 11 of treatment with AQW051 10 mg/day. Her depression had resolved when followed up 12 months later.

Discussion

AQW051 treatment did not significantly improve dyskinesia or parkinsonian symptoms when using the primary endpoint of change in mAIMS or UPDRS-III scores. Our findings contrast with the current understanding of nicotinic receptor function in the basal ganglia, and preclinical efficacy of AQW051 in the LID primate model.¹⁹ This forces us to reconsider the hypothesis of targeting the $\alpha 7$ nicotinic receptors to suppress LID in humans. However, a variety of factors may explain these negative results without invalidating the concept, such as a sub-therapeutic dosing of AQW051 for PD-LID; a lack of sensitivity of mAIMS in measuring treatment-related changes in PD-LID;³⁸ or a low comparability between groups for exposure to amantadine and potential effect on response to AQW051. The significant variability of dyskinesia among patients should not be overlooked as a reason for the study not meeting its primary endpoints, as biphasic dyskinesias were not separately reported in this study and may have different pathological mechanisms and pharmacological responses than peak-dose LIDs.

A possible benefit for AQW051 in cognition was observed following a post-hoc exploratory analysis. Moderate treatment effects were observed on memory tasks of consistent magnitude and several differences to placebo were statistically significant. These exploratory results are supported by the preclinical cognitive-enhancing potential of AQW051 and other nAChR alpha7 agonists,^{20–28} and clinical findings in healthy male subjects²⁹ and patients with schizophrenia.^{30–32} These findings reinforce the concept that neuropsychological and behavioral assessments should be considered as part of future studies evaluating these compounds.

AQW051 was well tolerated and the majority of AEs were mild to moderate in severity. AQW051 did not cause any psychiatric AEs in patients with advanced PD who are known to be at high risk for developing these side effects with various drugs. This observation might echo some positive signals discussed previously, although the limited size of the sample and short duration of follow-up prevent any firm conclusion. The higher incidence of dyskinesia as an AE within the 50 mg AQW051 group was unexpected. This might be related to some disparity between the treatment groups that occurred by chance at randomization. Patients in the 50 mg AQW051 group received higher mean daily doses of L-dopa and were more frequently exposed to amantadine, with the risk of potential unknown pharmacodynamic drug interactions.

In conclusion, AQW051 did not significantly reduce dyskinesia or parkinsonian severity when using the primary endpoints of change in mAIMS and UPDRS. Further effects of this drug need to be explored with more specific trial designs and larger patient populations.

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References

1. Fabbrini G, Brothie JM, Grandas F, Nomoto M, Goetz CG. Levodopa-induced dyskinesias. *Mov Disord* 2007;22:1379–1389.
2. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001;16:448–458.
3. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord* 2005;20:224–230.
4. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord* 2011;26(Suppl 3):S42–S80.
5. ratiopharm GmbH. Amantadin-ratiopharm® 100 mg Filmtabletten [in German]. Ulm, ratiopharm, 2010.
6. Huang LZ, Parameswaran N, Bordia T, Michael MJ, Quik M. Nicotine is neuroprotective when administered before but not after nigrostriatal damage in rats and monkeys. *J Neurochem* 2009;109:826–837.
7. Parain K, Marchand V, Dumery B, Hirsch E. Nicotine, but not cotinine, partially protects dopaminergic neurons against MPTP-induced degeneration in mice. *Brain Res* 2001;890:347–350.
8. Quik M, Chen L, Parameswaran N, Xie X, Langston JW, McCallum SE. Chronic oral nicotine normalizes dopaminergic function and synaptic plasticity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned primates. *J Neurosci* 2006;26:4681–4689.

9. Quik M, Parameswaran N, McCallum SE, et al. Chronic oral nicotine treatment protects against striatal degeneration in MPTP-treated primates. *J Neurochem* 2006;98:1866–1875.
10. Ryan RE, Ross SA, Drago J, Loiacono RE. Dose-related neuroprotective effects of chronic nicotine in 6-hydroxydopamine treated rats, and loss of neuroprotection in alpha4 nicotinic receptor subunit knockout mice. *Br J Pharmacol* 2001;132:1650–1656.
11. Visanji NP, O'Neill MJ, Duty S. Nicotine, but neither the alpha4beta2 ligand RJR2403 nor an alpha7 nAChR subtype selective agonist, protects against a partial 6-hydroxydopamine lesion of the rat median forebrain bundle. *Neuropharmacology* 2006;51:506–516.
12. Bordia T, Campos C, Huang L, Quik M. Continuous and intermittent nicotine treatment reduces L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias in a rat model of Parkinson's disease. *J Pharmacol Exp Ther* 2008;327:239–247.
13. Huang LZ, Campos C, Ly J, Ivy Carroll F, Quik M. Nicotinic receptor agonists decrease L-dopa-induced dyskinesias most effectively in partially lesioned parkinsonian rats. *Neuropharmacology* 2011;60:861–868.
14. Quik M, Cox H, Parameswaran N, O'Leary K, Langston JW, Di Monte D. Nicotine reduces levodopa-induced dyskinesias in lesioned monkeys. *Ann Neurol* 2007;62:588–596.
15. Stuckenholz V, Bacher M, Balzer-Geldsetzer M, et al. The alpha7 nAChR agonist PNU-282987 reduces inflammation and MPTP-induced nigral dopaminergic cell loss in mice. *J Parkinsons Dis* 2013;3:161–172.
16. Suzuki S, Kawamata J, Matsushita T, et al. 3-[(2,4-Dimethoxy)benzylidene]-anabaseine dihydrochloride protects against 6-hydroxydopamine-induced parkinsonian neurodegeneration through alpha7 nicotinic acetylcholine receptor stimulation in rats. *J Neurosci Res* 2013;91:462–471.

17. Zhang D, Mallela A, Sohn D, et al. Nicotinic receptor agonists reduce L-DOPA-induced dyskinesias in a monkey model of Parkinson's disease. *J Pharmacol Exp Ther* 2013;347:225–234.
18. Hurth K, Gomez-Mancilla B, Hoyer D, et al. Identification of AQW051, an $\alpha 7$ nicotinic acetylcholine receptor partial agonist for the treatment of cognitive impairment associated with schizophrenia. Abstract MEDI 222 at the Division of Medicinal Chemistry, 247th American Chemical Society (ACS) National Meeting, Dallas, Texas, USA, March 16–20, 2014.
19. Di Paolo T, Gregoire L, Feuerbach D, Elbast W, Weiss M, Gomez-Mancilla B. AQW051, a novel and selective nicotinic acetylcholine receptor $\alpha 7$ partial agonist, reduces L-Dopa-induced dyskinesias and extends the duration of L-Dopa effects in parkinsonian monkeys. *Parkinsonism Relat Disord* 2014;20:1119–1123.
20. Feuerbach D, Pezous N, Weiss M, Shakeri-Nejad K, Lingenhoebl K, Hoyer D, Hurth K, Bilbe G, Pryce CR, McAllister K, Chaperon F, Kucher K, Johns D, Blaettler T, Lopez Lopez C. AQW051, a novel, potent and selective $\alpha 7$ nicotinic ACh receptor partial agonist: pharmacological characterization and phase I evaluation. *Br J Pharmacol*. 2015;172:1292–304.
21. de Fiebre CM, Meyer EM, Henry JC, Muraskin SI, Kem WR, Papke RL. Characterization of a series of anabaseine-derived compounds reveals that the 3-(4)-dimethylaminocinnamylidene derivative is a selective agonist at neuronal nicotinic $\alpha 7/125I$ - α -bungarotoxin receptor subtypes. *Mol Pharmacol* 1995;47:164–171.
22. Feuerbach D, Nozulak J, Lingenhoebl K, McAllister K, Hoyer D. JN403, in vitro characterization of a novel nicotinic acetylcholine receptor $\alpha 7$ selective agonist. *Neurosci Lett* 2007;416:61–65.

23. Feuerbach D, Lingenhoebl K, Olpe HR, et al. The selective nicotinic acetylcholine receptor alpha7 agonist JN403 is active in animal models of cognition, sensory gating, epilepsy and pain. *Neuropharmacology* 2009;56:254–263.
24. Hajos M, Hurst RS, Hoffmann WE, et al. The selective alpha7 nicotinic acetylcholine receptor agonist PNU-282987 [N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride] enhances GABAergic synaptic activity in brain slices and restores auditory gating deficits in anesthetized rats. *J Pharmacol Exp Ther* 2005;312:1213–1222.
25. Bitner R, Anderson D, Drescher K, et al. Preclinical characterization of a selective alpha-7 neuronal nicotinic acetylcholine receptor agonist ABT-126: a novel therapeutic agent for the treatment of cognitive impairment in Alzheimer's disease and schizophrenia. *Alzheimers Dement* 2013;9:P817–P818.
26. Hauser TA, Kucinski A, Jordan KG, et al. TC-5619: an alpha7 neuronal nicotinic receptor-selective agonist that demonstrates efficacy in animal models of the positive and negative symptoms and cognitive dysfunction of schizophrenia. *Biochem Pharmacol* 2009;78:803–812.
27. Mazurov AA, Kombo DC, Hauser TA, et al. Discovery of (2S,3R)-N-[2-(pyridin-3-ylmethyl)-1-azabicyclo[2.2.2]oct-3-yl]benzo[b]furan-2-carboxamide (TC-5619), a selective alpha7 nicotinic acetylcholine receptor agonist, for the treatment of cognitive disorders. *J Med Chem* 2012;55:9793–9809.
27. Prickaerts J, van Goethem NP, Chesworth R, et al. EVP-6124, a novel and selective alpha7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of alpha7 nicotinic acetylcholine receptors. *Neuropharmacology* 2012;62:1099–1110.

29. Kitagawa H, Takenouchi T, Azuma R, et al. Safety, pharmacokinetics, and effects on cognitive function of multiple doses of GTS-21 in healthy, male volunteers. *Neuropsychopharmacology* 2003;28:542–551.
30. Olincy A, Harris JG, Johnson LL, et al. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. *Arch Gen Psychiatry* 2006;63:630–638.
31. Lieberman JA, Dunbar G, Segreti AC, et al. A randomized exploratory trial of an alpha-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. *Neuropsychopharmacology* 2013;38:968–975.
32. Preskorn SH, Gawryl M, Dgetluck N, Palfreyman M, Bauer LO, Hilt DC. Normalizing effects of EVP-6124, an alpha-7 nicotinic partial agonist, on event-related potentials and cognition: a proof of concept, randomized trial in patients with schizophrenia. *J Psychiatr Pract* 2014;20:12–24.
33. Fahn S, Elton R, Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M. Eds. *Recent developments in Parkinson's disease*. Florham Park, NJ, Macmillan Healthcare Information, 1987; 153–164.
34. Guy W. *Assessment Manual for Psychopharmacology: Revised* (DHEW publication no. ADM 76-338). Rockville, MD, US Department of Health, Education and Welfare; Public Health Service; Alcohol, Drug Abuse and Mental Health Administration; NIMH Psychopharmacology Research Branch; Division of Extramural Research Programs, 1976.
35. Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Mov Disord* 1994;9:2–12.

36. Parkinson Study Group. Evaluation of dyskinesias in a pilot, randomized, placebo-controlled trial of remacemide in advanced Parkinson disease. *Arch Neurol* 2001;58:1660–1668.
37. Falletti MG, Maruff P, Collie A, Darby DG. Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. *J Clin Exp Neuropsychol* 2006;28:1095–1112.
38. Goetz CG, Stebbins GT, Chung KA, et al. Which dyskinesia scale best detects treatment response? *Mov Disord* 2013;28:341–346.
39. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012;27:349–356.

TABLE 1. Baseline patient characteristics and baseline CogState composite scores

Characteristic	AQW051		Placebo (n = 23)
	10 mg (n = 24)	50 mg (n = 24)	
Age, years			
Mean (SD)	64.2 (8.30)	65.5 (10.26)	63.3 (10.01)
Sex, n (%)			
Male	11 (45.8)	15 (62.5)	13 (56.5)
Female	13 (54.2)	9 (37.5)	10 (43.5)
L-dopa equivalent dose, mg/day			
Mean (SD)	681.7 (389.49)	919.6 (523.0)	767.4 (368.0)
Amantadine taken, n (%)			
Yes	4 (16.7)	9 (37.5)	8 (34.8)
Mild to moderate depression, n (%) ^a	12 (50)	11 (46)	11 (48)
mAIMS score			
Mean (SD)	9.38 (3.61)	11.44 (4.59)	11.76 (5.08)
UPDRS-III score			
Mean (SD)	17.65 (8.18)	14.92 (7.28)	18.46 (11.14)
LFADLDS score			
Mean (SD)	9.2 (3.50)	9.7 (3.33)	10.8 (3.46)
PD-MCI, n (%) ^b			
Yes	15 (62.5)	15 (62.5)	16 (69.6)
CogState composite scores			
	n = 23	n = 21	n = 21
Psychomotor/attentional	0.038	-0.053	0.011
Executive function	0.154	0.010	-0.196
Memory	0.192	-0.111	-0.103

^aBeck Depression Inventory, mild: 10–18; moderate: 19–29.

^bPD-MCI determined by reanalyzing baseline cognitive scores according to the Movement Disorder Society Task Force Guidelines.³⁹

Psychomotor/attentional composite (Detection Task + Identification Task), executive function composite (Groton Maze Learning Test + Controlled Oral Word Association Test), memory composite (One-Back Task + International Shopping List Task).

SD, standard deviation; mAIMS, modified Abnormal Involuntary Movements Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; LFADLDS, Lang-Fahn Activities of Daily Living Dyskinesia Scale; PD-MCI, Parkinson's Disease with mild cognitive impairment.

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TABLE 2. Analysis of mean change from baseline to day 28 in outcome measures of parkinsonian symptoms and dyskinesia for the per protocol population

	AQW051		Placebo
	10 mg (n = 23)	50 mg (n = 19)	(n = 21)
mAIMS			
LS mean change (SE)	-3.22 (0.85)	-1.92 (0.92)	-3.14 (0.89)
Difference vs placebo (SE)	-0.07 (1.24)	1.22 (1.28)	
95% CI ^a	-2.89, 2.75	-1.67, 4.12	
<i>P</i> value ^a	0.997	0.534	
UPDRS-III			
LS mean change (SE)	-1.32 (1.28)	-0.44 (1.41)	-1.92 (1.33)
Difference vs placebo (SE)	0.60 (1.85)	1.48 (1.95)	
95% CI ^a	-3.60, 4.79	-2.39, 5.89	
<i>P</i> value ^a	0.928	0.667	
UPDRS-IV (items 32–33)			
LS mean change (SE)	-0.95 (0.28)	-1.01 (0.31)	-1.14 (0.29)
Difference vs placebo (SE)	0.18 (0.41)	0.12 (0.43)	
95% CI ^a	-0.74, 1.10	-0.84, 1.09	
<i>P</i> value ^a	0.867	0.940	
LFADLDS			
LS mean change (SE)	-0.96 (0.57)	-1.73 (0.62)	-0.85 (0.60)
Difference vs placebo (SE)	-0.11 (0.83)	-0.88 (0.87)	
95% CI ^a	-1.98, 1.77	-2.84, 1.08	
<i>P</i> value ^a	0.987	0.494	

^aDunnett adjustment.

^bImprovement on task is indicated by a positive change from baseline.

mAIMS, Modified Abnormal Involuntary Movement Scale; LS mean, least squares mean; SE, standard error; UPDRS, Unified Parkinson's Disease Rating Scale; LFADLDS, Lang-Fahn Activities of Daily Living and Dyskinesia Scale.

A Placebo-Controlled Trial of AQW051 in Patients with Moderate to Severe Levodopa-Induced Dyskinesia

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Abstract [Word count: 146 (max 150)]**Introduction**

This Phase II, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of the nicotinic acetylcholine receptor $\alpha 7$ agonist, AQW051, in patients with Parkinson's disease and levodopa-induced dyskinesia.

Methods

Patients with idiopathic Parkinson's disease and moderate to severe levodopa-induced dyskinesia were randomized to AQW051 10 mg (n = 24), AQW051 50 mg (n = 24), or placebo (n = 23) once daily for 28 days. Co-primary endpoints were change in Modified Abnormal Involuntary Movement Scale and Unified Parkinson's Disease Rating Scale part III scores. Secondary outcomes included pharmacokinetics.

Results

In total, 67 patients completed the study. AQW051-treated patients experienced no significant improvements in Modified Abnormal Involuntary Movement Scale or Unified Parkinson's Disease Rating Scale part III scores by day 28. AQW051 was well tolerated; the most common adverse events were dyskinesia, fatigue, nausea, and falls.

Conclusions

AQW051 did not significantly reduce dyskinesia or parkinsonian severity.

Introduction

Motor complications such as levodopa (L-dopa)-induced dyskinesia (LID) negatively impact the lives of patients with Parkinson's disease (PD),^{1–3} and there are few sustained, non-invasive treatments for LID that do not reduce the antiparkinsonian benefits of L-dopa. Amantadine is currently the sole medication available and recommended for the management of LID.⁴ However, not all patients respond to or tolerate amantadine, and the prescription of amantadine is restricted by regulatory guidance in some countries (e.g. in Germany⁵).

Nicotine has been shown to protect against or alleviate nigrostriatal damage^{6–11} and improve LID^{12–14} in parkinsonian animal models. The antidyskinetic and neuroprotective effects of nicotine are exerted via multiple nicotinic acetylcholine receptors (nAChRs).^{6,10,12,13,15–17} The antidyskinetic potential of $\alpha 7$ nAChR agonists has now been displayed *in vivo* using the novel, selective partial agonist, (R)-3-(6-p-Tolyl-pyridin-3-yloxy)-1-aza-bicyclo(2.2.2)octane (AQW051).¹⁸ AQW051 significantly reduced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys without compromising the benefits of L-dopa.¹⁹ The objective of the current study was to evaluate the efficacy and safety of AQW051 in patients with moderate to severe PD-LID. As preclinical and clinical evidence suggests that $\alpha 7$ nAChR agonists, including AQW051, can also improve cognition,^{20–32} AQW051 was also evaluated for pro-cognitive effects in a post-hoc exploratory analysis.

Methods

This was a Phase II, multicenter, randomized, double-blind, parallel-group, placebo-controlled multi-dose study in PD-LID. Eligible patients were non-smoking men and women, aged 30–85 years, with idiopathic PD as per the UK Parkinson's Disease Society Brain Bank criteria. Patients were required to have: LID >20% (Unified Parkinson's Disease Rating Scale [UPDRS] item 32 rating ≥ 1) of moderate to severe intensity (UPDRS item 33 rating ≥ 2);³³ LID for ≥ 3 months before randomization; received L-dopa for ≥ 3 years; stable treatment with L-dopa for ≥ 1 month before randomization. Other

concomitant antiparkinsonian medication was allowed if treatment was stable for ≥ 1 month prior to randomization. Treatment with amantadine, antidepressants (except strong cytochrome [CYP]1A2 and CYP3A4 inhibitors), and/or benzodiazepines were permitted provided the dosing regimen was stable for ≥ 1 month before randomization.

Patients were randomized at a ratio of 1:1:1 into one of three treatment groups: AQW051 50 mg, AQW051 10 mg, or placebo. Treatment was administered orally, once daily in the morning after the initial L-dopa dose, for a period of 28 days, with a 2-week follow-up. Assessments were performed every week, once during follow-up, and at the end of study visit.

The protocol and amendments were approved by the Independent Ethics Committee and Institutional Review Board at each study center. This study was conducted according to the ethical principles of the Declaration of Helsinki and was registered on ClinicalTrials.gov (identifier NCT01474421). Informed written consent was obtained from all patients.

Outcomes

The co-primary outcome measures were the Modified Abnormal Involuntary Movement Scale (mAIMS)³⁴ and UPDRS-III items 18–31,³⁵ respectively. Assessments were performed in the morning 1 h post L-dopa dose during ON-time and in the afternoon at a patient-specific time point.

Secondary outcome measures included: UPDRS-IV items 32–33, Lang-Fahn Activities of Daily Living and Dyskinesia Scale (LFADLDS) sum score,³⁶ and a cognitive test battery (CogState)³⁷ for safety analysis and for tracking potential pro-cognitive effects.

Pharmacokinetics

Blood samples (3 mL) were collected into EDTA-containing tubes according to a predefined schedule. Sampling took place pre-dose and on days 1, 8, 16, 21, and 28; 1, 3, 4, 5, 8, and 12 h post-dose on day 28; and before and after the assessments on day 32. Plasma concentrations of AQW051 were

quantified using a validated liquid chromatography tandem mass spectrometry method (HPLC-MS/MS). The lower limit of quantification was 0.050 ng/mL using 0.200 mL of plasma.

Safety

Assessments included adverse events (AEs) and serious AEs (SAEs) reporting, laboratory tests, vital signs, electrocardiograms, and use of the Columbia-Suicidality Severity Rating Scale (C-SSRS).

Statistical analysis

Descriptive statistics were used to summarize AEs, safety, and demographic variables for the safety population (all patients who received ≥ 1 dose of study drug). Analysis of covariance of change from baseline of the per protocol population (all patients with ≥ 1 post-randomization efficacy assessment and no protocol deviations nor withdrawn) was the primary analysis, with relevant baseline values as the covariate and treatment group as a fixed factor. The effect over placebo was estimated for each AQW051 dose using a Dunnett adjustment, and there were no corrections for multiple comparisons between variables.

The pharmacokinetic parameters at steady state: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the curve for 0–24 h (AUC_{0-24h}), and oral clearance (CL/F) were determined using non-compartmental methods and summarized by dose group using descriptive statistics for the PK population (all patients with valid PK data).

Results

Seventy-one patients were randomized to receive AQW051 10 mg ($n = 24$), AQW051 50 mg ($n = 24$), or placebo ($n = 23$); 67 patients completed the study and 63 did so without protocol deviations.

Patient demographics and clinical variables for the safety population are summarized in Table 1.

Efficacy

The study did not meet its primary endpoints, with change in mean sum score for mAIMS and UPDRS-III showing no significant improvements in LID or parkinsonian symptoms following AQW051 treatment at either dose (Table 2).

Cognitive function

In the primary analysis, AQW051 was not associated with statistically significant improvements in cognitive outcomes. However, exploratory repeated measures analysis of the safety population showed that compared with placebo, AQW051 50 mg/day yielded a change corresponding to a standardized effect size of 0.5 ($P = 0.024$) in the CogState memory composite scores and an effect size of 0.4 ($P = 0.073$) was seen for AQW051 10 mg/day. The individual memory tasks included in the memory composite (One-Back Task [ONB] + International Shopping List Task [ISL]) also improved moderately at both AQW051 doses, with improvements in the ISL at AQW051 50 mg/day reaching significance ($P = 0.048$).

Pharmacokinetics

Comparison of pre-dose plasma concentrations of AQW051 indicates steady state was reached within the first week of dosing. At day 28, T_{max} median (range) values were very similar for 10 and 50 mg/day; 5.00 h (2.92–11.9) and 4.99 h (3–8), respectively. Mean (SD) CL/F values were 88.8 (68.4) L/h and 102 (59.2) L/h at 10 and 50 mg/day, respectively. Exposure in terms of AUC_{0-24h} and C_{max} increased 4.3 (160–686 ng*h/mL) and 4.5-fold (8.62–38.7 ng/mL), respectively, with a 5-fold increase of dose from 10 to 50 mg suggesting dose proportionality in systemic exposure across the dose range for AQW051.

Safety

AEs were experienced by 18 patients receiving AQW051 10 mg/day, 15 receiving AQW051 50 mg/day, and 18 receiving placebo. They were mostly mild to moderate, with dyskinesia the most frequently reported AE across all treatment groups (4.2%, 25.0%, and 13.0% of patients in the 10 mg/day, 50 mg/day, and placebo groups, respectively). Nausea (20.8%, 4.2%, and 0%,

respectively), falls (8.3%, 12.5%, and 4.3%, respectively) and fatigue (8.3%, 8.3%, and 8.7%, respectively) were the next most commonly reported AEs overall after dyskinesia.

Two patients receiving AQW051 50 mg/day experienced SAEs (one case each of mild ON-OFF phenomenon and severe neuroborreliosis). These were not considered to be treatment-related by the investigators and no action regarding study medication was taken. In both cases the event had resolved on follow-up. Two patients experienced AEs that the investigators considered treatment-related and resulted in their withdrawal from the study. One patient reported worsening dyskinesia on day 2 after treatment with AQW051 50 mg/day; the dyskinesia was ongoing at the last follow-up on day 21, and no further follow-ups have been reported. The second patient (with an active history of depression) reported mild depression on day 11 of treatment with AQW051 10 mg/day. Her depression had resolved when followed up 12 months later.

Discussion

AQW051 treatment did not significantly improve dyskinesia or parkinsonian symptoms when using the primary endpoint of change in mAIMS or UPDRS-III scores. Our findings contrast with the current understanding of nicotinic receptor function in the basal ganglia, and preclinical efficacy of AQW051 in the LID primate model.¹⁹ This forces us to reconsider the hypothesis of targeting the $\alpha 7$ nicotinic receptors to suppress LID in humans. However, a variety of factors may explain these negative results without invalidating the concept, such as a sub-therapeutic dosing of AQW051 for PD-LID; a lack of sensitivity of mAIMS in measuring treatment-related changes in PD-LID;³⁸ or a low comparability between groups for exposure to amantadine and potential effect on response to AQW051. The significant variability of dyskinesia among patients should not be overlooked as a reason for the study not meeting its primary endpoints, as biphasic dyskinesias were not separately reported in this study and may have different pathological mechanisms and pharmacological responses than peak-dose LIDs.

A possible benefit for AQW051 in cognition was observed following a post-hoc exploratory analysis. Moderate treatment effects were observed on memory tasks of consistent magnitude and several differences to placebo were statistically significant. These exploratory results are supported by the preclinical cognitive-enhancing potential of AQW051 and other nAChR alpha7 agonists,^{20–28} and clinical findings in healthy male subjects²⁹ and patients with schizophrenia.^{30–32} These findings reinforce the concept that neuropsychological and behavioral assessments should be considered as part of future studies evaluating these compounds.

AQW051 was well tolerated and the majority of AEs were mild to moderate in severity. AQW051 did not cause any psychiatric AEs in patients with advanced PD who are known to be at high risk for developing these side effects with various drugs. This observation might echo some positive signals discussed previously, although the limited size of the sample and short duration of follow-up prevent any firm conclusion. The higher incidence of dyskinesia as an AE within the 50 mg AQW051 group was unexpected. This might be related to some disparity between the treatment groups that occurred by chance at randomization. Patients in the 50 mg AQW051 group received higher mean daily doses of L-dopa and were more frequently exposed to amantadine, with the risk of potential unknown pharmacodynamic drug interactions.

In conclusion, AQW051 did not significantly reduce dyskinesia or parkinsonian severity when using the primary endpoints of change in mAIMS and UPDRS. Further effects of this drug need to be explored with more specific trial designs and larger patient populations.

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References

1. Fabbrini G, Brotchie JM, Grandas F, Nomoto M, Goetz CG. Levodopa-induced dyskinesias. *Mov Disord* 2007;22:1379–1389.
2. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001;16:448–458.
3. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. *Mov Disord* 2005;20:224–230.
4. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord* 2011;26(Suppl 3):S42–S80.
5. ratiopharm GmbH. Amantadin-ratiopharm® 100 mg Filmtabletten [in German]. Ulm, ratiopharm, 2010.
6. Huang LZ, Parameswaran N, Bordia T, Michael MJ, Quik M. Nicotine is neuroprotective when administered before but not after nigrostriatal damage in rats and monkeys. *J Neurochem* 2009;109:826–837.
7. Parain K, Marchand V, Dumery B, Hirsch E. Nicotine, but not cotinine, partially protects dopaminergic neurons against MPTP-induced degeneration in mice. *Brain Res* 2001;890:347–350.
8. Quik M, Chen L, Parameswaran N, Xie X, Langston JW, McCallum SE. Chronic oral nicotine normalizes dopaminergic function and synaptic plasticity in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned primates. *J Neurosci* 2006;26:4681–4689.

9. Quik M, Parameswaran N, McCallum SE, et al. Chronic oral nicotine treatment protects against striatal degeneration in MPTP-treated primates. *J Neurochem* 2006;98:1866–1875.
10. Ryan RE, Ross SA, Drago J, Loiacono RE. Dose-related neuroprotective effects of chronic nicotine in 6-hydroxydopamine treated rats, and loss of neuroprotection in alpha4 nicotinic receptor subunit knockout mice. *Br J Pharmacol* 2001;132:1650–1656.
11. Visanji NP, O'Neill MJ, Duty S. Nicotine, but neither the alpha4beta2 ligand RJR2403 nor an alpha7 nAChR subtype selective agonist, protects against a partial 6-hydroxydopamine lesion of the rat median forebrain bundle. *Neuropharmacology* 2006;51:506–516.
12. Bordia T, Campos C, Huang L, Quik M. Continuous and intermittent nicotine treatment reduces L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias in a rat model of Parkinson's disease. *J Pharmacol Exp Ther* 2008;327:239–247.
13. Huang LZ, Campos C, Ly J, Ivy Carroll F, Quik M. Nicotinic receptor agonists decrease L-dopa-induced dyskinesias most effectively in partially lesioned parkinsonian rats. *Neuropharmacology* 2011;60:861–868.
14. Quik M, Cox H, Parameswaran N, O'Leary K, Langston JW, Di Monte D. Nicotine reduces levodopa-induced dyskinesias in lesioned monkeys. *Ann Neurol* 2007;62:588–596.
15. Stuckenholtz V, Bacher M, Balzer-Geldsetzer M, et al. The alpha7 nAChR agonist PNU-282987 reduces inflammation and MPTP-induced nigral dopaminergic cell loss in mice. *J Parkinsons Dis* 2013;3:161–172.
16. Suzuki S, Kawamata J, Matsushita T, et al. 3-[(2,4-Dimethoxy)benzylidene]-anabaseine dihydrochloride protects against 6-hydroxydopamine-induced parkinsonian neurodegeneration through alpha7 nicotinic acetylcholine receptor stimulation in rats. *J Neurosci Res* 2013;91:462–471.

17. Zhang D, Mallela A, Sohn D, et al. Nicotinic receptor agonists reduce L-DOPA-induced dyskinesias in a monkey model of Parkinson's disease. *J Pharmacol Exp Ther* 2013;347:225–234.
18. Hurth K, Gomez-Mancilla B, Hoyer D, et al. Identification of AQW051, an $\alpha 7$ nicotinic acetylcholine receptor partial agonist for the treatment of cognitive impairment associated with schizophrenia. Abstract MEDI 222 at the Division of Medicinal Chemistry, 247th American Chemical Society (ACS) National Meeting, Dallas, Texas, USA, March 16–20, 2014.
19. Di Paolo T, Gregoire L, Feuerbach D, Elbast W, Weiss M, Gomez-Mancilla B. AQW051, a novel and selective nicotinic acetylcholine receptor $\alpha 7$ partial agonist, reduces L-Dopa-induced dyskinesias and extends the duration of L-Dopa effects in parkinsonian monkeys. *Parkinsonism Relat Disord* 2014;20:1119–1123.
20. Feuerbach D, Pezous N, Weiss M, Shakeri-Nejad K, Lingenhoebl K, Hoyer D, Hurth K, Bilbe G, Pryce CR, McAllister K, Chaperon F, Kucher K, Johns D, Blaettler T, Lopez Lopez C. AQW051, a novel, potent and selective $\alpha 7$ nicotinic ACh receptor partial agonist: pharmacological characterization and phase I evaluation. *Br J Pharmacol*. 2015;172:1292–304.
21. de Fiebre CM, Meyer EM, Henry JC, Muraskin SI, Kem WR, Papke RL. Characterization of a series of anabaseine-derived compounds reveals that the 3-(4)-dimethylaminocinnamylidene derivative is a selective agonist at neuronal nicotinic $\alpha 7/125I$ - α -bungarotoxin receptor subtypes. *Mol Pharmacol* 1995;47:164–171.
22. Feuerbach D, Nozulak J, Lingenhoebl K, McAllister K, Hoyer D. JN403, in vitro characterization of a novel nicotinic acetylcholine receptor $\alpha 7$ selective agonist. *Neurosci Lett* 2007;416:61–65.

23. Feuerbach D, Lingenhoebl K, Olpe HR, et al. The selective nicotinic acetylcholine receptor $\alpha 7$ agonist JN403 is active in animal models of cognition, sensory gating, epilepsy and pain. *Neuropharmacology* 2009;56:254–263.
24. Hajos M, Hurst RS, Hoffmann WE, et al. The selective $\alpha 7$ nicotinic acetylcholine receptor agonist PNU-282987 [N-[(3R)-1-Azabicyclo[2.2.2]oct-3-yl]-4-chlorobenzamide hydrochloride] enhances GABAergic synaptic activity in brain slices and restores auditory gating deficits in anesthetized rats. *J Pharmacol Exp Ther* 2005;312:1213–1222.
25. Bitner R, Anderson D, Drescher K, et al. Preclinical characterization of a selective $\alpha 7$ neuronal nicotinic acetylcholine receptor agonist ABT-126: a novel therapeutic agent for the treatment of cognitive impairment in Alzheimer's disease and schizophrenia. *Alzheimers Dement* 2013;9:P817–P818.
26. Hauser TA, Kucinski A, Jordan KG, et al. TC-5619: an $\alpha 7$ neuronal nicotinic receptor-selective agonist that demonstrates efficacy in animal models of the positive and negative symptoms and cognitive dysfunction of schizophrenia. *Biochem Pharmacol* 2009;78:803–812.
27. Mazurov AA, Kombo DC, Hauser TA, et al. Discovery of (2S,3R)-N-[2-(pyridin-3-ylmethyl)-1-azabicyclo[2.2.2]oct-3-yl]benzo[b]furan-2-carboxamide (TC-5619), a selective $\alpha 7$ nicotinic acetylcholine receptor agonist, for the treatment of cognitive disorders. *J Med Chem* 2012;55:9793–9809.
27. Prickaerts J, van Goethem NP, Chesworth R, et al. EVP-6124, a novel and selective $\alpha 7$ nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of $\alpha 7$ nicotinic acetylcholine receptors. *Neuropharmacology* 2012;62:1099–1110.

29. Kitagawa H, Takenouchi T, Azuma R, et al. Safety, pharmacokinetics, and effects on cognitive function of multiple doses of GTS-21 in healthy, male volunteers. *Neuropsychopharmacology* 2003;28:542–551.
30. Olincy A, Harris JG, Johnson LL, et al. Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. *Arch Gen Psychiatry* 2006;63:630–638.
31. Lieberman JA, Dunbar G, Segreti AC, et al. A randomized exploratory trial of an alpha-7 nicotinic receptor agonist (TC-5619) for cognitive enhancement in schizophrenia. *Neuropsychopharmacology* 2013;38:968–975.
32. Preskorn SH, Gawryl M, Dgetluck N, Palfreyman M, Bauer LO, Hilt DC. Normalizing effects of EVP-6124, an alpha-7 nicotinic partial agonist, on event-related potentials and cognition: a proof of concept, randomized trial in patients with schizophrenia. *J Psychiatr Pract* 2014;20:12–24.
33. Fahn S, Elton R, Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M. Eds. *Recent developments in Parkinson's disease*. Florham Park, NJ, Macmillan Healthcare Information, 1987; 153–164.
34. Guy W. *Assessment Manual for Psychopharmacology: Revised* (DHEW publication no. ADM 76-338). Rockville, MD, US Department of Health, Education and Welfare; Public Health Service; Alcohol, Drug Abuse and Mental Health Administration; NIMH Psychopharmacology Research Branch; Division of Extramural Research Programs, 1976.
35. Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y. Levodopa-induced dyskinesias in Parkinson's disease phenomenology and pathophysiology. *Mov Disord* 1994;9:2–12.

36. Parkinson Study Group. Evaluation of dyskinesias in a pilot, randomized, placebo-controlled trial of remacemide in advanced Parkinson disease. *Arch Neurol* 2001;58:1660–1668.
37. Falletti MG, Maruff P, Collie A, Darby DG. Practice effects associated with the repeated assessment of cognitive function using the CogState battery at 10-minute, one week and one month test-retest intervals. *J Clin Exp Neuropsychol* 2006;28:1095–1112.
38. Goetz CG, Stebbins GT, Chung KA, et al. Which dyskinesia scale best detects treatment response? *Mov Disord* 2013;28:341–346.
39. Litvan I, Goldman JG, Troster AI, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. *Mov Disord* 2012;27:349–356.

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