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<td><strong>Keywords:</strong> Parkinson’s disease, levodopa (L-dopa), nicotinic acetylcholine receptor agonist (nAChR) α7, AQW051, dyskinesias</td>
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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 α7 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), 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. 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 Germany).

Nicotine has been shown to protect against or alleviate nigrostriatal damage and improve LID in parkinsonian animal models. The antidyskinetic and neuroprotective effects of nicotine are exerted via multiple nicotinic acetylcholine receptors (nAChRs). The antidyskinetic potential of α7 nAChR agonists has now been displayed in vivo using the novel, selective partial agonist, (R)-3-(6-ρ-Tolyl-pyridin-3-yloxy)-1-aza-bicyclo(2.2.2)octane (AQW051). AQW051 significantly reduced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys without compromising the benefits of L-dopa. 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 α7 nAChR agonists, including AQW051, can also improve cognition, 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); 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)\textsuperscript{34} and UPDRS-III items 18–31,\textsuperscript{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 Dysfunction Scale (LFADLDS) sum score,\textsuperscript{36} and a cognitive test battery (CogState)\textsuperscript{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 ($C_{\text{max}}$), time to maximum plasma concentration ($T_{\text{max}}$), 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, $T_{\text{max}}$ 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 $\text{AUC}_{0-24\text{h}}$ and $C_{\text{max}}$ 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. This forces us to reconsider the hypothesis of targeting the alpha7 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, 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, and clinical findings in healthy male subjects and patients with schizophrenia. 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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is a full-time employee of CogState Ltd. Judith Jaeger was a full-time employee at CogState Ltd at the
time of the study. She is now President and Principal Scientist at CognitionMetrics, LLC. Annamaria
Jakab and Judit Sovago are employees of Novartis Pharma AG. Baltazar Gomez-Mancilla, Dominik
Feuerbach, Izabela Rozenberg, and Markus Weiss are employees of, and hold shares in, Novartis
Pharma AG; Markus Weiss is also a Novartis patent holder. Donald Johns was a full-time employee of
Novartis at the time of the study. He is now a full-time employee of, and holds shares in, Biogen.
Michał Gostkowski and Lin Zhang have declared no financial interests for the previous 12 months.
References


5. ratiopharm GmbH. Amantadin-ratiopharm® 100 mg Filmtabletten [in German]. Ulm, ratiopharm, 2010.


TABLE 1. Baseline patient characteristics and baseline CogState composite scores

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

*a Beck Depression Inventory, mild: 10–18; moderate: 19–29.

**PD-MCI determined by reanalyzing baseline cognitive scores according to the Movement Disorder Society Task Force Guidelines.*

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

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

\( ^a \) Dunnett adjustment.

\( ^b \) Improvement 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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Running title: AQW051 in levodopa-induced dyskinesia (character count: 37 inc spaces; limit = 45 letters inc spaces)

Key words: Parkinson’s disease; levodopa (L-dopa); nicotinic acetylcholine receptor agonist (nAChR) α7; AQW051; dyskinesias

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served on advisory boards and received honoraria from Novartis. Franck Durif has served on advisory boards for Novartis. Thérèse Di Paolo has a collaborative research contract with Novartis Pharma AG for investigating new compounds in vivo, and is also a co-author on patents with Novartis Pharma AG. Hans-Ulrich Hockey is an employee of Biometrics Matters Ltd (BML) and served as a contracted statistical consultant to Novartis Pharma AG when working on this article. Paul Maruff is a full-time employee of CogState Ltd, and Judith Jaeger was a full-time employee of CogState Ltd at the time of the study. Annamaria Jakab and Judit Sovago are employees of Novartis Pharma AG. Baltazar Gomez-Mancilla, Dominik Feuerbach, Izabela Rozenberg, and Markus Weiss are employees of, and hold shares in, Novartis Pharma AG; Markus Weiss is also a Novartis patent holder. Donald Johns was a full-time employee of Novartis at the time of the study. Alberto Espay, Lin Zhang, Jean-Philippe Azulay, Michal Gostkowski, Christine Tranchant, Pascal Derkinderen, Andrew Feigin, and Jean-Luc Houeto have declared no financial conflicts of interest related to research covered in this article.
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 α7 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), 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. 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 Germany).

Nicotine has been shown to protect against or alleviate nigrostriatal damage and improve LID in parkinsonian animal models. The antidyskinetic and neuroprotective effects of nicotine are exerted via multiple nicotinic acetylcholine receptors (nAChRs). The antidyskinetic potential of α7 nAChR agonists has now been displayed in vivo using the novel, selective partial agonist, (R)-3-(6-ρ-Tolyl-pyridin-3-yloxy)-1-aza-bicyclo(2.2.2)octane (AQW051). AQW051 significantly reduced dyskinesia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys without compromising the benefits of L-dopa. 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 α7 nAChR agonists, including AQW051, can also improve cognition, 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); 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) and UPDRS-III items 18–31, 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, and a cognitive test battery (CogState) 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\text{max}), time to maximum plasma concentration (T\text{max}), area under the curve for 0–24 h (AUC\text{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, $T_{\text{max}}$ 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 $\text{AUC}_{0–24\text{h}}$ and $C_{\text{max}}$ 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. This forces us to reconsider the hypothesis of targeting the alpha7 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; 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, and clinical findings in healthy male subjects and patients with schizophrenia. 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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