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Task-related fMRI responses to a nicotinic acetylcholine receptor partial agonist in schizophrenia: A randomized trial☆

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Abstract

Introduction: AQW051, an α7-nicotinic acetylcholine receptor partial agonist, enhanced cognitive function in rodent models of learning and memory. This study evaluated brain activation during performance of a working memory task (WMT) and an episodic memory task (EMT), and the effect of AQW051 on task-related brain activation and performance in subjects with schizophrenia.

Methods: This was a double-blind, randomized, placebo-controlled, multicenter, 2-period cross-over trial (NCT00825539) in participants with chronic, stable schizophrenia. Participants, stratified according to smoking status, were randomized (1:1:1:1:1:1) to 1 of 6 sequence groups that determined the study drug dose (AQW051 7.5 mg, 50 mg or 100 mg) and order of administration *versus* placebo. The primary outcome was brain activation in *a priori* target regions of interest (ROIs) during performance of the WMT and EMT, measured using functional magnetic resonance imaging. The effect of AQW051 on task-related (EMT and WMT) brain activation and performance was also assessed, as were safety and tolerability.

☆Ethical statementThe study was conducted according to the ethical principles of the Declaration of Helsinki, with informed consent obtained from each participant in writing prior to randomization. The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center.

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Results: Overall, 60 of 68 enrolled participants completed the study (AQW051 then placebo: 7.5 mg $n = 9$; 50 mg $n = 11$; 100 mg $n = 10$. Placebo then AQW051: 7.5 mg $n = 10$; 50 mg $n = 11$; 100 mg $n = 9$). Significant task-related brain activation (5% significance level) was observed with placebo. During the WMT, a medium effect size was observed in the inferior prefrontal cortex with AQW051 100 mg *versus* placebo (0.431; $p = 0.105$). During the EMT encoding phase, a large effect size was observed in the anterior hippocampus (0.795; $p = 0.007$) and a medium effect size in the posterior hippocampus (0.476; $p = 0.079$) with AQW051 7.5 mg. No other medium/large effect sizes were observed with any dose on either task. Effects on brain activation were generally not associated with changes in cognitive performance. AQW051 was well tolerated with an acceptable safety profile.

Conclusions: Overall, no consistent effects of AQW051 on brain regions involved in the performance of a WMT or EMT were observed; however, this study presents a model for evaluating potential response to pharmacological interventions for cognitive impairment in schizophrenia.

Keywords

AQW051; Clinical trial; Functional magnetic resonance imaging; Nicotinic acetylcholine receptor (nAChR); Schizophrenia

1. Introduction

Cognitive performance is a major factor determining functional outcomes and rehabilitation in people with schizophrenia (Gold et al., 2002; Green, 1996). Working and episodic memory are key aspects of cognitive function affected by the disease and several studies have demonstrated involvement of the cholinergic neurotransmitter pathway in these cognitive functions (Furey et al., 2000; Vitiello et al., 1997; Hasselmo and Bower, 1993). Differential expression of nicotinic acetylcholine receptors (nAChRs) is associated with cognitive impairment in schizophrenia (Freedman et al., 1995; Breese et al., 2000; Leonard et al., 2002), and animal studies have demonstrated specific involvement of the α7-nAChR subtype in cognitive tasks involving learning and memory (McLean et al., 2011; Roncarati et al., 2009). The α7-nAChR partial agonist, GTS-21, enhanced working and episodic memory in healthy human subjects (Kitagawa et al., 2003). In addition, α7-nAChR agonists have shown positive effects on memory and other cognitive domains in rodent models (Wallace and Porter, 2011). AQW051, an orally bioavailable α7-nAChR partial agonist, improved cognitive functioning in rodents, with these effects reduced by the α7-nAChR antagonist, methyllycaconitine (Feuerbach et al., 2015). These data suggest that AQW051 has the potential to enhance cognitive function, and provides a rationale for efficacy studies of AQW051 on cognitive dysfunction in people with schizophrenia.

Limited progress has been made in developing suitable and effective therapies that target working and episodic memory in people with schizophrenia (Carter et al., 2011). One of the main obstacles is a lack of relationship between the tools used to measure efficacy within clinical trials (*e.g.*, neuropsychological measures) compared with those from cognitive neuroscience that have been used to refine understanding of cognitive deficits in schizophrenia (*e.g.*, experimental tasks combined with functional magnetic resonance

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imaging [fMRI] or electrophysiological studies) (Carter et al., 2011). Although biomarkers that index the occupancy of specific receptors can be used to objectively measure a treatment response or pathogenic process (Carter et al., 2011; Carter and Barch, 2012), currently there is no quantifiable ligand that could be used as a biomarker to assess the efficacy of an α7-nAChR partial agonist on cognitive function or target engagement in people with schizophrenia. The use of neuroimaging to monitor the actions of therapies for cognitive deficits in schizophrenia could have a substantial impact on drug development by providing a common measure of effectiveness and a quantifiable biomarker (Carter et al., 2011). Analysis by fMRI of the brain regions activated in individuals with schizophrenia during performance of working memory tasks (WMTs) and episodic memory tasks (EMTs) will produce quantifiable data that could be used as a biomarker for therapeutic actions (Barch et al., 2012). As such, the aim of this randomized, placebo-controlled fMRI study was to evaluate task-related activation in key areas of the brain associated with working and episodic memory and assess the effects of AQW051 on brain activation during the performance of a WMT and EMT in participants with schizophrenia.

2. Methods

2.1. Study objectives

The ‘primary’ and ‘secondary’ study objectives, as codified in the ClinicalTrials.gov database (identifier: NCT00825539) prior to the study, were as follows: *primary objective* — to assess brain activation in *a priori* target regions of interest (ROIs) during performance of a WMT and EMT using blood-oxygenation-level dependent (BOLD) responses, measured by fMRI, in participants with schizophrenia; *secondary objective* — to assess effects of a single dose of AQW051 on brain activation in these ROIs and on participant performance during a WMT and EMT. Exploratory objectives included the effect of participant smoking status on BOLD responses. Safety and tolerability were also assessed.

2.2. Participants

The study was performed at seven centers in the USA between April 2009 (first patient dosed) and November 2011. Participants were screened 21 days prior to randomization. Eligible participants were males and females aged 18–60 years with a diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders IV [DSM-IV-TR] criteria (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), 1994)), who were receiving treatment with a stable regimen of one or more second-generation antipsychotics (olanzapine, risperidone, paliperidone, quetiapine, ziprasidone or aripiprazole). Participants were required to be symptomatically stable and not having suffered from an acute exacerbation of their illness within the past 6 months. Female participants of childbearing age and all male participants were obliged to use two acceptable methods of contraception. Regular administration of concomitant drugs (except those listed in the exclusion criteria) was permitted, provided the participant was on a stable treatment regimen for at least 3 months prior to enrollment.

Exclusion criteria included: current treatment with anticholinergic agents, strong inhibitors of cytochrome P450 (CYP) isoforms CYP3A4 (*e.g.*, HIV antivirals, clarithromycin) and

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CYP1A2 (*e.g.*, fluvoxamine and ciprofloxacin), first-generation antipsychotics (*e.g.*, fluphenazine and haloperidol) or clozapine; DSM-IV diagnosis of substance abuse within 1 month prior to study enrollment (except nicotine); history of significant head injury/trauma; or a medical or neurological disorder or treatment for such disorder that could interfere with study medication or assessment.

The study was conducted according to the ethical principles of the Declaration of Helsinki, with informed consent obtained from each participant in writing prior to randomization. The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center.

2.3. Study design

The trial was designed in two parts: Part 1 investigated task-related brain activation and the efficacy of single oral doses of AQW051; Part 2 was designed to investigate the safety and tolerability of multiple doses of AQW051. The trial was terminated after review of Part 1 and therefore only Part 1 is discussed herein. Part 1 was a double-blind, randomized, placebo-controlled, multicenter, stratified trial, employing a cross-over design. Participants were randomized to one of six sequence groups, A–F, which determined the study drug dose (AQW051 7.5 mg, 50 mg, or 100 mg) and the order of AQW051 *versus* placebo administration, and stratified according to smoking status before entering a two-period cross-over phase (Fig. 1).

The randomization scheme was generated by Novartis Drug Supply Management, and reviewed and approved by the Novartis Biostatistics Assurance Group. Subjects and investigators were blinded to the treatment allocation using a double-dummy design, whereby AQW051 and placebo capsules appeared identical, and all sequence groups received an equal number of capsules. It was planned that a maximum of 72 participants (24/dose group) would be enrolled to ensure that at least 20 participants per dose group completed Part 1 of the study. An exploratory analysis team (not including study investigators or participants) was unblinded to perform planned interim analyses after 40 participants had completed Part 1, and at the end of Part 1.

Three days prior to randomization, participants underwent task practice sessions; no fMRI data were collected during these sessions. After randomization and on the days of fMRI scanning, participants received either AQW051 or placebo 5 h prior to the start of the fMRI session. A washout period of at least 10 days occurred between each participant's two fMRI sessions. A study completion visit took place within 14–17 days after the second fMRI session and involved a physical examination, pregnancy test (if appropriate), recording of vital signs, recording of adverse events (AEs), clinical chemistry evaluation, and psychiatric symptom assessments.

2.4. fMRI assessments

Test sites used a Siemens 3 T TimTrio scanner with a 12-channel head coil (4 sites), a General Electric 3 T scanner with an 8-channel head coil (2 sites), or a Philips 3 T Achieva scanner with an 8-channel head coil (1 site). All sites followed a set of specific functional imaging protocols that included two 3D high-resolution T1-weighted (MPRAGE) scans

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(repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, inversion time [TI] = 900 ms, 9° flip angle, field of view [FOV] = 256 × 240 mm, 1.0 mm in-plane voxels, 160 slices, 1.2-mm slice thickness, GRAPPA/ASSET/SENSE factor = 2, approximately 5 min acquisition), and gradient-echo BOLD acquisitions using echo planar imaging (TR = 2000 ms, TE = 30 ms, 77° flip angle, FOV = 220 × 220 mm, 3.43 mm in-plane voxels, 28 slices, 4-mm thickness with a 1-mm gap). In addition, pulsed Arterial Spin Labeling (ASL) data were collected at a subset of the sites (the 4 Siemens sites and 1 GE site) to assess possible changes in global blood flow, using a PICORE Q2T sequence (TR = 4000 ms, TE = 13 ms, TI1/TI2 = 600/1600 ms, saturation stop time = 1500 ms, 6/8 phase partial Fourier, 24 slices, same spatial resolution as the BOLD scans, 105 measurements, 7:02 min acquisition). The ASL data were collected with the participant at rest (i.e., no task). The cognitive testing research team member who administered the pre-scan practice also administered the tasks during the scanning sessions.

2.4.1. WMT—The N-Back task (Cohen et al., 1997) was used to assess working memory; both 0-back and 2-back conditions were used in this sequential-letter memory task. Functional MRI data were obtained using a block design, with two runs of 0-back *versus* fixation, and two runs of 2-back *versus* fixation with the order of the 0-back and 2-back runs counter-balanced across participants. Each run consisted of 138 whole brain images (4.6 min) and contained 3 N-back blocks of 54 s, during which a letter was presented every 3 s. Each N-back block was followed by 30 s of fixation. Behavioral measures were calculated under both conditions and included discriminability d′ (*D*-prime; measure of discriminability computed from 'hits' and 'false alarms') and the median reaction times for identifying correct 'hits' (target letters) and 'rejections' (nontarget letters).

2.4.2. EMT—The EMT consisted of two encoding runs each lasting approximately 4.1 min (124 frames) during which the same list of 48 words was presented (in differing order for the two runs). Words were presented for 2000 ms, followed by a fixation cross for either 500, 3000, or 5500 ms (*i.e.*, jittered inter-stimulus intervals). Participants were asked to push a button each time a word appeared on the screen and to try and remember the words for a subsequent memory test. The two encoding phase runs were immediately followed by two retrieval phase runs (4.1 min each) that included 24 of the previously seen encoding phase words on each run interspersed with 24 new words. The same stimulus timing was used in the retrieval phase runs as in the encoding phase runs. In the retrieval runs, participants had to indicate if they had seen the word in either of the two encoding runs (*i.e.*, determine whether the word was 'old' or 'new'). During the two retrieval runs, similar behavioral measures to those assessed during the WMT were calculated: d′ was calculated from correct responses and false alarms, and median reaction times were also calculated for correct 'hits' and 'rejections'.

2.4.3. Functional MRI and ASL data processing—Functional MRI analysis was carried out using the fMRI Expert Analysis Tool (FEAT) in the Functional Software Library (FSL) toolbox (version 4.1.6). Pre-processing steps within FEAT consisted of motion correction to compensate for rigid body motion (using FSL's MCFLIRT) and spatial smoothing using a 6-mm full width at half maximum Gaussian kernel. The analysis of each

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fMRI run used General Linear Modeling (GLM) of the BOLD responses to each task and included pre-whitening (FILM) to account for the temporal autocorrelation of the fMRI time series. The GLM for the WMT consisted of blocks of tasks (0-back or 2-back). The GLM for the encoding runs of the EMT modeled the presentation of each word (event-related design). The GLM for the retrieval runs of the EMT consisted of separate explanatory variables (EVs) for 'hits' (correctly identified words from encoding runs), 'misses' (incorrectly identified words from encoding runs), 'correct rejections' (correctly identified new word) and 'false alarms' (incorrectly identified new word). The retrieval results focused on the 'hits' contrast. All GLMs used convolution with FEAT's default 'gamma' function. Additionally, we included the temporal derivative of the EVs in all models so as to reduce residual noise arising from possible differences in response latency across regions or participants. The FEAT analysis also included the calculation of the affine matrices for registration to MNI152 space. Specifically, the BOLD data were registered to the first MPRAGE from the imaging session using a 6 degree-of-freedom (DOF) registration, and the MPRAGE was registered to MNI152 space using an affine, 12 DOF transformation. Our analysis focused on *a priori* ROIs, with the dependent measure for each ROI computed as the average GLM beta value across all nonzero voxels within that ROI. These betas were computed from the run-specific FEAT output by projecting the ROIs as defined in MNI152 standard space to the space of each run's BOLD data according to the inverse of the transform between the BOLD data and MNI152 space. For the WMT, the ensuing average beta for each ROI for the 0-back task was subtracted from the average beta for the 2-back task to create a differential beta value for each ROI and participant, which was then used as the primary variable in the statistical analysis for the WMT.

Cerebral blood flow (CBF) was computed using the ASL Toolbox ("ASLtbx") from the University of Pennsylvania (Wang et al., 2008). Mean gray matter CBF was quantified using a gray matter mask obtained from the participant's MPRAGE using the segment function of Statistical Parametric Mapping 8 (http://www.fil.ion.ucl.ac.uk/spm/), after affine registration of the MPRAGE to the ASL reference image.

2.5. ROI definition

Brain activation was analyzed using an ROI approach to maximize the power to detect a significant drug effect. We identified ROIs that have shown consistent evidence of task-related changes in brain activation among individuals with schizophrenia in previously published fMRI studies using similar tasks (Anticevic et al., 2013; Barch et al., 2000; Barch and Csernansky, 2007; Glahn et al., 2005; Jessen et al., 2003; Ragland et al., 2009; Thermenos et al., 2007). ROIs were spheres 25 mm in diameter based on the centroid co-ordinates in Table 1. The ROIs for the WMT were the dorsolateral prefrontal cortex (PFC), inferior PFC and the dorsal parietal cortex. For the EMT, the ROIs were the anterior and posterior hippocampus and the anterior and posterior parahippocampal gyrus.

2.6. Pharmacokinetic analysis

Blood samples were collected by direct venipuncture or an indwelling cannula inserted into a forearm vein at 4, 5, 6 and 7 h post-dose. AQW051 in blood and plasma was measured using a validated liquid chromatography tandem mass spectrometry method (lower limit of

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quantification: 0.15 ng/mL and 0.30 ng/mL, respectively). C_{max} was determined using non-compartmental methods (WinNonlin).

2.7. Safety analysis

All AEs and serious AEs (SAEs) were collected, with the severity and relationship to study drug recorded. Regular monitoring of hematology, blood chemistry and urine was performed at each study site, in addition to regular assessment of vital signs, electrocardiograms, physical condition and body weight.

2.8. Statistical analysis

Randomization of participants was stratified by smoking status to allow assessment of the potential differential effects of nicotinic agonists as a function of smoking. Smokers were defined by urine cotinine levels ≥500 ng/mL.

2.8.1. Sample size determination—We assumed that blood flow changes that might ultimately translate into improved performance would occur in some or all of a set of predefined ROIs. Seven ROIs were defined as primary (Table 1). As impaired behavior was associated with reduced activation in previous studies, we assumed that a beneficial effect would manifest itself as increased activation in response to either of the highest AQW051 doses (50 mg and 100 mg). Sample size was determined using simulations assuming that an effect of AQW051 *versus* placebo would be observed with either AQW051 50 mg or 100 mg. These simulations showed that the overall type I error (*i.e.*, the probability to erroneously detect a significant increase in BOLD response by AQW051 *versus* placebo in any of the seven primary ROIs for either AQW051 50 mg or 100 mg) was equal to 0.20. In order to control for this large false-positive rate, the following composite criterion was developed *a priori* and used to define 'acceptable activity' in response to a given dose of AQW051: either a medium effect size (*i.e.*, of at least 0.4; defined below) in at least two of the three ROIs for the WMT or two of the four ROIs for the EMT, or a large effect size (*i.e.*, of at least 0.7) in at least one of the seven ROIs during either memory task.

2.8.2. Primary analysis—The basis for all analyses was the change in brain activity as manifested by the BOLD signal during the specific tasks. The BOLD response variables were analyzed separately for each ROI, by means of a mixed effect model adjusted for stratum (smoking status), sequence, treatment and period as fixed effects, with participant as a random effect. The mean pair-wise treatment differences (between each AQW051 dose and placebo) in BOLD response and their two-sided 95% confidence intervals (CI) were estimated from the model. In order to further interpret the clinical relevance of a notable mean difference *versus* placebo, its normalized difference (effect size: the mean difference in least squares mean in BOLD response divided by the pooled standard deviation [SD] of the BOLD response [sum of intra- and inter-participant variability also obtained from the model]) was calculated. We present two-sided *p*-values for medium and large effects without adjustment for multiplicity.

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2.8.3. Other analyses—The influence of smoking was assessed using the same mixed model modified by adding the treatment-by-smoking status interaction term. Within-stratum estimates were obtained from this model. The behavioral measures were similarly analyzed.

The safety analyses were descriptive statistics by treatment and based on the safety set, which included all randomized participants who received at least one dose of study drug.

2.9. Phantom scanning and quality assurance

Prior to participating in the study, each site had to demonstrate the stability of BOLD time series collected on their scanner using a protocol and set of metrics developed by the Functional Bioinformatics Research Network (fBIRN) (Friedman and Glover, 2006). Sites collected two 200-frame acquisitions (on at least two different days) of an agar quality control phantom using the same BOLD protocol as the human imaging, which was processed using fBIRN tools to measure the signal-to-fluctuation noise ratio (SFNR; *i.e.*, temporal signal-tonoise ratio) and percent fluctuation. A SFNR of >245 was required for a site to qualify for participation in the study and the SFNR had to remain >245 throughout the study (agar phantom scans were repeated monthly). Percent fluctuation was always ≤0.10% except for the Philips site, for which it ranged consistently between 0.14 and 0.17%. Additionally, sites were required to submit a volunteer participant scan, which was reviewed and checked for fMRI activation in regions of expected robust activity prior to acceptance to participate in the study.

3. Results

3.1. Participant disposition, characteristics and demographics

Overall, 68 participants were enrolled, with 60 participants reaching study completion (Fig. 1). One participant entered the study twice; safety data from both periods of enrollment for this participant were included in the analyses. However, fMRI data from only the second enrollment were included as no data were available from the first enrollment. Baseline demographic data are shown in Table 2.

3.2. Task activation in a priori ROIs

3.2.1. Activation in response to AQW051 according to the composite criterion—Above we described our *a priori* composite criterion to define ‘acceptable activity’ in response to a given dose of AQW051 (either a medium effect size of at least 0.4 in at least two of the three ROIs for the WMT or two of the four ROIs for the EMT, or a large effect size of at least 0.7 in at least one of the seven ROIs during either memory task). As will be presented in more detail below, according to this criterion, ‘acceptable activity’ in response to AQW051 was demonstrated in the total population at the 7.5-mg dose, but not at the 50-mg or 100-mg dose. When assessed by smoking status, AQW051 7.5 mg demonstrated ‘acceptable activity’ in both smokers and nonsmokers. ‘Acceptable activity’ was also seen in response to AQW051 100 mg in nonsmokers, but not smokers.

3.2.2. Activation in a priori ROIs during the WMT—During the WMT, significant increases (5% significance level) in BOLD signal between 0-back and 2-back conditions

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were detected under placebo conditions in all of the *a priori* ROIs (Supplemental Fig. 1). A medium (≥0.4), though nonsignificant, effect size was observed in the inferior PFC in response to AQW051 100 mg *versus* placebo in the overall population (effect size, 0.431; $p = 0.105$; Table 3, Fig. 2A).

In nonsmokers, a significant large (≥0.7) effect size (0.925, $p = 0.004$) was observed in the inferior PFC in response to AQW051 100 mg *versus* placebo and a medium, but nonsignificant, effect size was seen in the same region in response to AQW051 50 mg *versus* placebo (0.512, $p = 0.088$; Table 3). In contrast, no medium or large effect sizes for individual ROIs were observed in smokers in response to any dose of AQW051 (*versus* placebo) (Table 3).

3.2.3. Activation in a priori ROIs during the EMT—During the EMT, an fMRI activation signal (5% significance level) was detected under placebo conditions in the posterior hippocampus and the posterior parahippocampal gyrus during both the encoding and retrieval phases of the EMT (Supplementary Fig. 1). During the encoding phase, a significant large effect size (0.795, $p = 0.007$) was observed in the anterior hippocampus and a medium, but nonsignificant, effect size (0.476, $p = 0.079$) was observed in the posterior hippocampus in response to AQW051 7.5 mg *versus* placebo in the overall population (Table 3). No medium/large individual ROI effect sizes were observed on individual ROIs in response to either 50-mg or 100-mg doses of AQW051 in the overall study population.

Analysis of task-related brain activation by smoking status indicated a large effect size in the anterior hippocampus in nonsmokers (0.830, $p = 0.022$) and smokers (0.727, $p = 0.075$) in response to AQW051 7.5 mg *versus* placebo during the encoding phase of the EMT, which reached significance in nonsmokers (Table 3). In addition, nonsmokers also showed a large effect size in response to AQW051 7.5 mg *versus* placebo in the posterior hippocampus (0.744, $p = 0.030$; Table 3). No medium/large effect sizes were observed on individual ROIs in response to the 50-mg or 100-mg doses of AQW051 according to smoking status.

During the retrieval phase of the EMT, no medium or large effect sizes were observed in the *a priori* ROIs in response to AQW051 in either the overall population, or according to smoking status (Table 3, Fig. 2C).

3.3. Global blood flow by ASL

Mean global blood flow under placebo conditions was 48.0 mL/100 g/min and was not significantly different in response to AQW051 (7.5 mg: 48.8 mL/100 g/min; 50 mg: 50.0 mL/100 g/min; 100 mg: 47.9 mL/100 g/min), or according to smoking status.

3.4. Behavioral measures

Under placebo conditions, d′ indicated good task performance during both the WMT and EMT in the overall study population (Table 4). The d′ measures under placebo conditions were similar between smokers and nonsmokers.

No significant differences in d′ were observed in response to either AQW051 7.5 or 50 mg compared with placebo during the 0-back or 2-back phases of the WMT in the overall study

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population, or according to smoking status (Table 4). However, a significant decline in d′ was demonstrated in response to AQW051 100 mg compared with placebo during the 0-back phase ($p = 0.024$) and 2-back phase ($p = 0.018$) of the WMT in the overall study population (Table 4). When stratified by smoking status, a significant decline in d′ was only observed in smokers (0-back, $p < 0.001$; 2-back, $p < 0.001$; Table 4).

No significant change in mean reaction time for hits was observed in response to AQW051 7.5 mg or 50 mg compared with placebo during the 0-back phase or 2-back phase of the WMT in the overall study population, or when analyzed by smoking status (Table 4). However, a significant increase in the mean reaction time for hits was demonstrated by participants during the 0-back phase of the WMT in response to AQW051 100 mg compared with placebo in the overall study population ($p = 0.050$) and smokers ($p = 0.050$, Table 4). No significant effect of AQW051 100 mg on mean reaction time for hits was observed during the 2-back phase of the WMT.

Assessment of mean reaction time for correct rejections during the 0-back phase of the WMT showed no significant change in response to AQW051 compared with placebo in the overall study population, or when analyzed by smoking status. Although similar findings were observed during the 2-back phase of the WMT in response to AQW051 7.5 mg and 100 mg, a significant decrease (improvement) in response to AQW051 50 mg compared with placebo was observed in the overall study population ($p = 0.016$; Table 4), but this decrease did not reach significance when assessed by smoking status.

There were no significant effects of AQW051 compared with placebo on d′, reaction time for hits or reaction time for correct rejections during the EMT in the overall study population, or according to smoking status.

3.5. Pharmacokinetics

The mean (SD) C_{max} following single-dose administration of AQW051 was 2.19 (0.74) ng/mL, 16.5 (4.79) ng/mL and 33.6 (11.1) ng/mL with the 7.5-mg, 50-mg and 100-mg dose, respectively; similar findings were obtained when participants were stratified according to either smoking status (data not shown) or antipsychotic drug used (Table 5).

3.6. Safety evaluation

Numerically higher incidences of AEs were reported in response to placebo compared with AQW051 7.5 mg (47.4% *vs* 36.4%) and AQW051 100 mg (50.0% *vs* 45.0%), whereas a numerically higher incidence of AEs was reported in response to AQW051 50 mg compared with placebo (43.5% *vs* 34.8%; Table 6). None of the between-group differences in the incidence of AEs were statistically significant. The most commonly reported AEs according to primary system organ class were gastrointestinal disorders (dry mouth, nausea or diarrhea), central nervous system (CNS) disorders (headache, dizziness or sedation), and psychiatric disorders (insomnia or restlessness) (Table 6). Three participants discontinued the study due to AEs. Discontinuation due to mild AEs occurred in two instances, neither of which was considered to be due to study treatment (claustrophobia, most likely from the MRI assessment, and numbness in right arm, most likely due to blood sampling). One SAE was reported during the study (worsening of underlying disease), which led to participant

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discontinuation; however, this was not considered to be due to study treatment. There were no deaths during the study.

4. Discussion

This randomized, double-blind, placebo-controlled fMRI study was conducted to evaluate task-related activation in key areas of the brain during the performance of a WMT and an EMT, and the effect of a single dose (7.5 mg, 50 mg or 100 mg) of AQW051, a nAChR partial agonist, in participants with schizophrenia. The ROIs selected in the current analysis had shown consistent evidence of task-related changes in brain activation among individuals with schizophrenia in previously published fMRI studies using similar tasks (Anticevic et al., 2013; Barch et al., 2000; Barch and Csernansky, 2007; Glahn et al., 2005; Jessen et al., 2003; Ragland et al., 2009; Thermenos et al., 2007). We observed significant task-related activation under placebo conditions for both the WMT and the encoding and retrieval phases of the EMT in participants with schizophrenia. According to pre-defined composite criterion, ‘acceptable activity’ was observed in response to AQW051 7.5 mg in the overall population, and in both smokers and nonsmokers when the study population was assessed by smoking status. ‘Acceptable activity’ was also observed in response to AQW051 100 mg in nonsmokers, but not smokers.

For the WMT, no significant medium or large effect sizes were observed in any of the *a priori* ROIs in the overall population in response to AQW051 compared with placebo; however, a medium, but nonsignificant effect size was observed in the inferior PFC with AQW051 100 mg. When stratified by smoking status, a significant large effect size was observed in the inferior PFC of nonsmokers in response to the highest dose of AQW051 (100 mg) compared with placebo, and a medium (but nonsignificant) effect in nonsmokers in the same region at the 50-mg dose. However, no effect was observed in smokers. This may be related to the effect of smoking on nAChRs, making them less sensitive to modulation by AQW051. Although, as described below, activation increases were seen in smokers during the EMT.

A significant large effect size was observed in the anterior hippocampus during the encoding phase of the EMT in response to AQW051 7.5 mg *versus* placebo in the overall population and in nonsmokers. A large effect size was observed in the anterior hippocampus in smokers, but this did not reach significance. A medium, but nonsignificant, effect size was also detected in the posterior hippocampus during the encoding phase of the EMT in response to AQW051 7.5 mg in the overall population; a significant large effect size was detected in this region in nonsmokers, but no medium or large effect sizes were observed in the posterior hippocampus smokers. Medium or large effect sizes were not observed during the encoding phase of the EMT with any other dose, or during the retrieval phase of the EMT. The fact that the effects were found for the encoding phase, and not for the retrieval phase, may suggest that any benefits of AQW051 were mediated by encoding, rather than retrieval-related processes. However, the absence of effects on behavior suggests that further research is needed to ascertain whether such findings can be replicated and whether they relate to behavior in a larger sample receiving multiple doses of AQW051.

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The performance of participants on the WMT and EMT, as measured by the d′ parameter, was generally similar between smokers and non-smokers. A significant decrease in d′ was observed during the WMT in response to AQW051 100 mg, which was only significant for smokers. An increase (worsening) in reaction time for hits during the WMT was observed in response to AQW051 100 mg in smokers; again this effect was not observed in nonsmokers. These findings suggest that further stimulation of nAChR by AQW051, in addition to stimulation of the receptor from smoking, may not be beneficial to working memory. This is consistent with the observation that any increases in functional brain activation in response to AQW051 during the WMT were seen only in nonsmokers, as described above. Again, further research replicating these findings in a larger sample will be needed to help tease apart the relative impacts on brain activation *versus* behavior and the moderating effects of smoking status. An overall decrease (improvement) in reaction time for correct rejections during the WMT 2-back phase was observed in response to AQW051 50 mg compared with placebo. However, no other significant behavioral effects were observed with the other doses of AQW051, or during the EMT, or when data were stratified by smoking status.

Mean global blood flow, as measured by ASL, in participants at rest, showed no significant differences in response to AQW051, or between smokers and nonsmokers. This indicates that global blood flow was not modulated by a single dose of AQW051. Calculated C_{max} levels were in good agreement with single dose peak levels observed in patients with schizophrenia (unpublished data), and confirm the absence of a marked effect of smoking on the pharmacokinetics of AQW051.

Overall, this study provided limited evidence to support the hypothesized positive effects of nAChR agonists on memory in people with schizophrenia. Strengths of this study included the assurance of the quality of the fMRI scans due to the stringent protocol. However, there were also limitations, including the small number of participants randomized to each sequence group. In addition, these analyses were not powered to detect treatment differences in individual ROIs. Therefore, although these analyses provided very modest evidence for drug effects, no conclusions can be drawn regarding the effects of AQW051 on specific regions of the brain.

Other studies evaluating the effects of nAChR agonists on cognition have shown mixed results. In healthy male volunteers, the α7-nAChR partial agonist GTS-21/DMXB-A enhanced attention, working memory and episodic memory (Kitagawa et al., 2003). In a Phase II study in participants with clinically stable schizophrenia, administration of GTS-21/DMXB-A caused a significant increase in the working memory domain score of the MATRICS Consensus Cognitive Battery (MCCB), although overall results across all MCCB domains did not show a positive effect on cognition (Freedman et al., 2008). More recently, results from a randomized, placebo-controlled study investigating the effects of the α7-nAChR agonist, RG3487, in participants with schizophrenia showed that RG3487 did not improve cognition, as assessed by the MCCB (Umbricht et al., 2014). By contrast, a proof-of-concept study of the α7-nAChR partial agonist, EVP-6124, showed positive effects on performance in cognitive tests assessing nonverbal learning, memory and executive function in participants with schizophrenia, and larger Phase II studies are planned to further assess the potential pro-cognitive effects of this drug (Preskorn et al., 2014).

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Safety evaluations in this study suggest that AQW051 was well tolerated and showed a favorable safety profile, with incidences of AEs not significantly different following any of the AQW051 doses *versus* placebo. The most common AEs were gastrointestinal disorders, CNS disorders, and psychiatric disorders, which were consistent with AEs reported in other studies of nAChR agonists (Freedman et al., 2008).

5. Conclusion

In our study, we did not observe a consistent effect of AQW051 across the brain regions pre-determined to be involved in the performance of a WMT or EMT. According to the composite criterion, 'acceptable activity' was observed across smoking status in response to AQW051 at a dose of 7.5 mg and in nonsmokers only in response to AQW051 100 mg; however, this criterion was based on the assumption that activity would manifest at the highest two AQW051 doses. No significant effects were observed on working memory-related brain activation; however, minor changes in cognitive performance of WMT were observed. Conversely, there was evidence for an effect on brain activation following treatment with 7.5 mg AQW051 during the EMT; however, this was not accompanied by a change in cognitive performance. Further research is needed to evaluate the fMRI findings observed on the EMT evaluation specifically for the 7.5-mg dose of AQW051. If these findings are confirmed, they may suggest that a lower dose of AQW051 is more appropriate to evaluate in further studies. Overall, this study presents a model for evaluating potential biomarkers of cognitive effects in response to novel pharmacological interventions for cognitive impairment in schizophrenia using fMRI BOLD activity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Financial disclosure/conflict of interest

DMB serves as a consultant to Pfizer, Amgen, Roche, Takeda and P1Vital. SRM has served on advisory boards for AbbVie, Forum, Roche, Otsuka, Actavis, Takeda, Lundbeck and Boehringer Ingelheim. He has received research support from Forum and Amgen. MPH has no relevant conflicts of interest to declare. LFJ has received research grant support from Genentech, Amgen, Sunovion and Auspex. He has served on a Data Monitoring Committee for Janssen, on an advisory board for Roche, and as a consultant for Clintara, LLC. RWB has served on advisory boards for AbbVie, Amgen, EnVivo (now Forum), Roche and Takeda. He has served as a consultant for AbbVie, BMS, EnVivo (now Forum) and Omeros. He has served on a Data and Safety Monitoring Board for Pfizer. LSC has no relevant conflicts of interest to declare. WC has received research support from Novartis, EnVivo, Sunovion, and Boeringer Ingelheim. MW, RPM, NP, DF, CLL, RBB and BGM are employees of Novartis Pharma AG, Basel, Switzerland. DRJ was an employee of Novartis Pharma AG, Basel, Switzerland during the design and initiation of the study.

Abbreviations:

AE	Adverse event

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ant.	Anterior
ASL	Arterial Spin Labeling
BOLD	Blood-oxygenation-level dependent
CBF	Cerebral blood flow
CI	Confidence interval
CYP	Cytochrome P450
DOF	Degree of freedom
EMT	Episodic memory task
EV	Explanatory variables
fBIRN	Functional Bioinformatics Research Network
FEAT	fMRI Expert Analysis Tool
fMRI	Functional magnetic resonance imaging
FSL	Functional Software Library
GLM	General Linear Modeling
Hippo.	Hippocampus
MCCB	MATRICS Consensus Cognitive Battery
nAChR	Nicotinic acetylcholine receptor
Parahippo.	Parahippocampal
Pariet.	Parietal
PFC	Prefrontal cortex
post.	posterior
ROI	Region of interest
SAE	Serious adverse event
SD	Standard deviation
SFNR	Signal-to-fluctuation noise ratio
WMT	Working memory task

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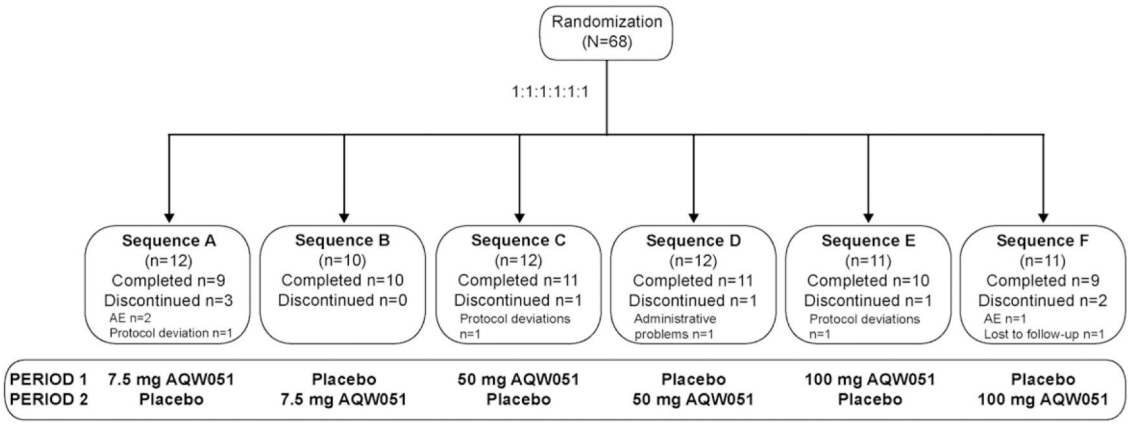

Fig. 1.

Study design and participant flow. Of the eight participants who discontinued the study, three discontinued due to adverse events (claustrophobia, numb right arm, worsening of underlying disease), three discontinued due to protocol deviations, one discontinued due to administrative issues and one participant was lost to follow-up and subsequently withdrawn.

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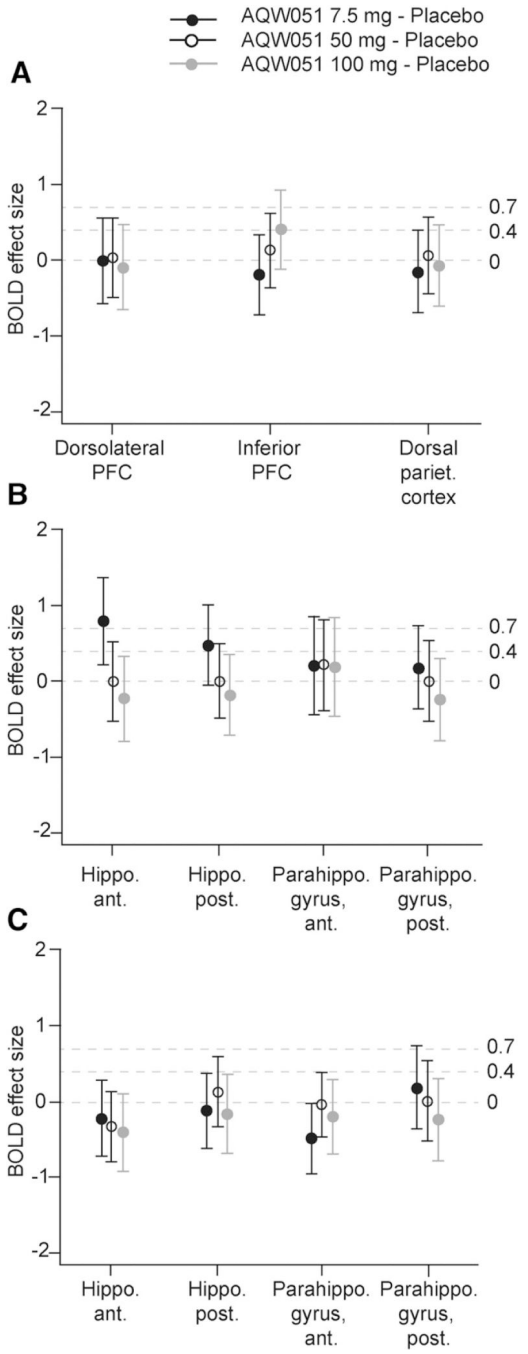

Fig. 2.

Mean effect size (95% CI) of task-related brain activation in the *a priori* ROIs in response to AQW051 administration *versus* placebo in the overall study population (pharmacodynamic analysis set). Brain regions assessed during A) change from 0- to 2-back in the WMT, B) EMT encoding phase, and C) EMT retrieval phase. Effect sizes of 0.4 and 0.7 are noted *via* dashed lines. The pharmacodynamic analysis set included all randomized participants that received at least one dose of study drug with available pharmacodynamic data. BOLD: blood-oxygenation-level dependent; Dorsal pariet. cortex: dorsal parietal cortex; EMT:

episodic memory task; Hippo. ant.: hippocampus, anterior; Hippo. post.: hippocampus, posterior; Parahippo. gyrus, ant.: parahippocampal gyrus, anterior; Parahippo. gyrus, post.: Parahippocampal gyrus, posterior; PFC: prefrontal cortex; ROIs: regions of interest; WMT: working memory task.

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Table 1

Primary *a priori* defined regions of interest.

			Talairach coordinates of centroid		
Task	**Region of interest**	**Brodmann area**	**X**	**Y**	**Z**
Working memory	Dorsolateral PFC	46/9	+40	+34	+29
			−36	+31	+13
	Inferior PFC	44/6	+43	+2	+31
			−44	+6	+32
	Dorsal parietal cortex	7/40	(±) 34	−51	+40
Episodic memory	Hippocampus, anterior		(±) 28.5	−15	−21
	Hippocampus, posterior		(±) 25.5	−42	0
	Parahippocampal gyrus, anterior	36/37	(±) 18	+6	−34
	Parahippocampal gyrus, posterior	36/37	(±) 30	−40	−16

The regions of interest were spheres of 25 mm diameter centered on the Talairach coordinates.

PFC: prefrontal cortex.

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Table 2

Baseline participant demographic data.

		Low-dose cohort AQW051 7.5 mg			Medium-dose cohort AQW051 50 mg			High-dose cohort AQW051 100 mg			
		A *n* = 12	**B *n* = 10**	**Overall *n* = 22**	**C *n* = 12**	**D *n* = 12**	**Overall *n* = 24**	**E *n* = 11**	**F *n* = 11**	**Overall *n* = 22**	**Total *n* = 68**
Age (years)	Mean (SD)	39.3 (11.06)	46.8 (8.57)	42.7 (10.49)	40.3 (7.24)	39.8 (11.49)	40.1 (9.39)	42.7 (10.90)	41.0 (12.56)	41.9 (11.51)	41.5 (10.37)
Weight (kg)	Mean (SD)	92.2 (21.20)	87.1 (15.79)	89.9 (18.68)	93.3 (23.45)	91.5 (20.81)	92.4 (21.70)	93.2 (22.10)	94.4 (15.17)	93.8 (18.51)	92.1 (19.52)
Gender, *n* (%)	Female	3 (25.0)	2 (20.0)	5 (22.7)	4 (33.3)	3 (25.0)	7 (29.2)	2 (18.2)	3 (27.3)	5 (22.7)	17 (25.0)
Race, *n* (%)	Caucasian	4 (33.3)	3 (30.0)	7 (31.8)	6 (50.0)	10 (83.3)	16 (66.7)	7 (63.6)	2 (18.2)	9 (40.9)	32 (47.1)
	Black	7 (58.3)	5 (50.0)	12 (54.5)	6 (50.0)	2 (16.7)	8 (33.3)	4 (36.4)	8 (72.7)	12 (54.5)	32 (47.1)
	Asian	1 (8.3)	2 (20.0)	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.4)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	1 (4.5)	1 (1.5)
Smoking status, *n* (%)	Smokers	5 (41.7)	5 (50.0)	10 (45.5)	5 (41.7)	5 (41.7)	10 (41.7)	5 (45.5)	4 (36.4)	9 (40.9)	29 (42.6)
Antipsychotic drug use (*n*)[a]	All			19			22			20	
	Risperidone-Paliperidone			8			3			9	
	Olanzapine			4			6			4	
	Aripiprazole			3			4			4	
	Quetiapine			0			3			3	
	Ziprasidone			1			5			0	

Sequence groups are labeled A–F. n: number of participants; SD: standard deviation.

[a]61 patients received antipsychotic drugs; 4 participants received ≥2 different antipsychotic drugs and are not included within the values for individual drugs.

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Table 3

Effect sizes of fMRI activation on drug vs placebo in *a priori* ROIs for each memory task.

	ROI	Low-dose cohort AQW051 7.5 mg		Medium-dose cohort AQW051 50 mg		High-dose cohort AQW051 100 mg	
		Effect size	**95% CI**	**Effect size**	**95% CI**	**Effect size**	**95% CI**
All participants							
WMT	Dorsolateral PFC	0.010	(−0.558, 0.579)	0.059	(−0.473, 0.590)	−0.064	(−0.628, 0.500)
	Inferior PFC	−0.165	(−0.693, 0.363)	0.163	(−0.330, 0.656)	*0.431*	*(−0.093, 0.955) p = 0.105*
	Dorsal parietal cortex	−0.121	(−0.664, 0.422)	0.085	(−0.422, 0.592)	−0.047	(−0.585, 0.492)
EMT (E)	Hippocampus, anterior	**0.795**	**(0.228, 1.362) *p* = 0.007**	−0.001	(−0.523, 0.521)	−0.228	(−0.793, 0.337)
	Hippocampus, posterior	*0.476*	*(−0.057, 1.010) p = 0.079*	0.004	(−0.485, 0.493)	−0.178	(−0.709, 0.354)
	Parahippocampal gyrus, anterior	0.214	(−0.432, 0.860)	0.217	(−0.389, 0.822)	0.187	(−0.461, 0.836)
	Parahippocampal gyrus, posterior	0.186	(−0.363, 0.734)	0.044	(−0.461, 0.548)	−0.240	(−0.786, 0.307)
EMT (R)	Hippocampus, anterior	−0.211	(−0.703, 0.282)	−0.326	(−0.785, 0.134)	−0.396	(−0.910, 0.118)
	Hippocampus, posterior	−0.117	(−0.618, 0.384)	0.140	(−0.328, 0.607)	−0.151	(−0.674, 0.373)
	Parahippocampal gyrus, anterior	−0.477	(−0.941, −0.012)	−0.030	(−0.463, 0.402)	−0.197	(−0.683, 0.289)
	Parahippocampal gyrus, posterior	−0.068	(−0.609, 0.474)	−0.081	(−0.587, 0.425)	−0.240	(−0.804, 0.324)
‘Acceptable activity’ criterion met?[a]		Yes		-		-	
Nonsmokers							
WMT	Dorsolateral PFC	0.043	(−0.659, 0.745)	0.325	(−0.329, 0.979)	0.212	(−0.471, 0.896)
	Inferior PFC	−0.199	(−0.836, 0.437)	*0.512*	*(−0.078, 1.103) p = 0.088*	0.925	**(0.308, 1.542) *p* = 0.004**
	Dorsal parietal cortex	−0.309	(−0.982, 0.364)	0.301	(−0.325, 0.927)	0.204	(−0.450, 0.858)
EMT (E)	Hippocampus, anterior	**0.830**	**(0.126, 1.533) *p* = 0.022**	0.112	(−0.544, 0.767)	−0.313	(−0.998, 0.372)
	Hippocampus, posterior	**0.744**	**(0.077, 1.411) *p* = 0.030**	−0.006	(−0.626, 0.615)	−0.207	(−0.856, 0.441)
	Parahippocampal gyrus, anterior	0.077	(−0.720, 0.873)	0.257	(−0.488, 1.002)	0.263	(−0.516, 1.042)
	Parahippocampal gyrus, posterior	0.319	(−0.368, 1.007)	0.080	(−0.560, 0.721)	−0.406	(−1.075, 0.262)
EMT (R)	Hippocampus, anterior	−0.398	(−1.035, 0.239)	−0.273	(−0.865, 0.319)	−0.314	(−0.960, 0.332)
	Hippocampus, posterior	−0.104	(−0.744, 0.536)	0.018	(−0.577, 0.613)	−0.051	(−0.700, 0.599)
	Parahippocampal gyrus, anterior	−0.620	(−1.224, −0.015)	0.124	(−0.437, 0.684)	−0.165	(−0.777, 0.447)
	Parahippocampal gyrus, posterior	0.038	(−0.646, 0.721)	0.055	(−0.581, 0.691)	−0.022	(−0.716, 0.672)
‘Acceptable activity’ criterion met?[a]		Yes		–		Yes	
smokers							

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	ROI	Low-dose cohort AQW051 7.5 mg		Medium-dose cohort AQW051 50 mg		High-dose cohort AQW051 100 mg	
		Effect size	**95% CI**	**Effect size**	**95% CI**	**Effect size**	**95% CI**
WMT	Dorsolateral PFC	−0.031	(−0.799, 0.736)	−0.307	(−1.054, 0.440)	−0.465	(−1.250, 0.320)
	Inferior PFC	−0.131	(−0.829, 0.568)	−0.312	(−0.989, 0.364)	−0.263	(−0.983, 0.457)
	Dorsal parietal cortex	0.111	(−0.626, 0.848)	−0.211	(−0.927, 0.505)	−0.405	(−1.161, 0.352)
EMT (E)	Hippocampus, anterior	**0.727**	**(−0.076, 1.530) *p* = 0.075**	−0.152	(−0.901, 0.597)	−0.097	(−0.924, 0.731)
	Hippocampus, posterior	0.103	(−0.663, 0.868)	0.015	(−0.695, 0.725)	−0.137	(−0.929, 0.655)
	Parahippocampal gyrus, anterior	0.376	(−0.488, 1.240)	0.157	(−0.689, 1.004)	0.074	(−0.836, 0.984)
	Parahippocampal gyrus, posterior	−0.002	(−0.798, 0.785)	−0.006	(−0.738, 0.726)	0.016	(−0.796, 0.828)
EMT (R)	Hippocampus, anterior	0.021	(−0.679, 0.720)	−0.390	(−1.068, 0.288)	−0.512	(−1.276, 0.253)
	Hippocampus, posterior	−0.130	(−0.833, 0.573)	0.298	(−0.383, 0.980)	−0.290	(−1.059, 0.478)
	Parahippocampal gyrus, anterior	−0.299	(−0.964, 0.366)	−0.236	(−0.879, 0.407)	−0.247	(−0.978, 0.484)
	Parahippocampal gyrus, posterior	−0.198	(−0.946, 0.551)	−0.270	(−0.997, 0.458)	−0.555	(−1.366, 0.257)
‘Acceptable activity’ criterion met?[a]		Yes		–		–	

CI: confidence interval; EMT: episodic memory task; E: encoding; MRI: magnetic resonance imaging; PFC: pre-frontal cortex; R: retrieval; ROIs: regions of interest; WMT: working memory task.

[a]‘Acceptable activity’ criterion: medium effect ≥0.4 in two or more ROIs for either EMT (E) or WMT; large effect ≥0.7 in one or more ROIs. Effect sizes ≥0.7 are shown in bold; those between 0.4 and 0.7 are italicized. *P*-values are provided for effect sizes ≥0.4.

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Table 4

Analysis of behavioral WMT and EMT (retrieval phase) variables (mean of the median individual values).

		Placebo	Low-dose cohort AQW051 7.5 mg	Medium-dose cohort AQW051 50 mg	High-dose cohort AQW051 100 mg
Behavioral measure	**Task**	**Mean (95% CI)**	**Mean change (95% CI) from placebo**		
All participants					
d′	WMT 0-back	3.475 (3.314, 3.636)	−0.124 (−0.519, 0.272)	0.346 (−0.024, 0.717)	**−0.453 (−0.843, −0.062)**[a]
	WMT 2-back	2.220 (1.925, 2.516)	−0.349 (−0.842, 0.144)	−0.042 (−0.501, 0.416)	**−0.598 (−1.088, −0.107)**[a]
	EMT (retrieval)	1.510 (1.228, 1.792)	0.001 (−0.339, 0.342)	0.033 (−0.284, 0.349)	−0.240 (−0.599, 0.119)
Time to hit (ms)	WMT 0-back	636.8 (606.7, 666.9)	12.2 (−23.4, 47.8)	−23.7 (−56.8, 9.3)	**35.5 (0.0, 71.0)**[a]
	WMT 2-back	826.2 (767.6, 884.7)	32.4 (−61.7, 126.6)	−70.2 (−155.9, 15.5)	24.0 (−67.8, 115.8)
	EMT (retrieval)	1018.2 (967.3, 1069.0)	43.0 (−20.1, 106.2)	−53.9 (−111.0, 3.3)	35.5 (−29.4, 100.4)
Time to rejection (ms)	WMT 0-back	630.6 (592.3, 668.9)	11.2 (−41.3, 63.7)	−45.0 (−93.8, 3.8)	22.8 (−29.5, 75.1)
	WMT 2-back	817.1 (770.2, 864.0)	−19.3 (−82.2, 43.6)	**−72.7 (−131.1, −14.2)**[a]	36.2 (−28.1, 100.6)
	EMT (retrieval)	957.6 (910.5, 1004.6)	−16.2 (−73.3, 40.9)	−52.6 (−105.6, 0.4)	50.6 (−9.6, 110.7)
Nonsmokers					
d′	WMT 0-back	3.490 (3.290, 3.691)	−0.080 (−0.553, 0.393)	0.364 (−0.078, 0.807)	−0.033 (−0.495, 0.429)
	WMT 2-back	2.184 (1.803, 2.565)	−0.459 (−1.069, 0.151)	0.080 (−0.484, 0.645)	−0.144 (−0.733, 0.446)
	EMT (retrieval)	1.502 (1.129, 1.876)	0.079 (−0.374, 0.532)	−0.056 (−0.473, 0.361)	−0.251 (−0.706, 0.205)
Time to hit (ms)	WMT 0-back	624.3 (585.3, 663.2)	17.7 (−30.0, 65.4)	−36.9 (−80.8, 7.0)	22.1 (−23.7, 68.0)
	WMT 2-back	821.6 (745.9, 897.2)	−11.0 (−133.1, 111.1)	−100.2 (−208.2, 7.8)	−42.9 (−155.7, 69.8)
	EMT (retrieval)	990.8 (923.4, 1058.1)	64.6 (−21.2, 150.5)	−59.6 (−135.3, 16.1)	49.7 (−33.1, 132.4)
Time to rejection (ms)	WMT 0-back	617.0 (567.5, 666.4)	35.9 (−34.3, 106.2)	−38.5 (−103.3, 26.3)	13.6 (−54.1, 81.2)
	WMT 2-back	805.8 (745.1, 866.5)	−66.8 (−149.4, 15.9)	−73.0 (−149.1, 3.2)	27.0 (−52.5, 106.5)
	EMT (retrieval)	942.8 (880.7, 1004.9)	−43.8 (−119.0, 31.4)	−57.8 (−127.0, 11.4)	69.1 (−6.6, 144.7)
smokers					
d′	WMT 0-back	3.497 (3.254, 3.739)	−0.179 (−0.692, 0.334)	0.314 (−0.189, 0.817)	**−1.006 (−1.525, −0.488)**[a]
	WMT 2-back	2.317 (1.865, 2.770)	−0.214 (−0.888, 0.460)	−0.225 (−0.873, 0.423)	**−1.267 (−1.969, −0.564)**[a]
	EMT (retrieval)	1.516 (1.083, 1.948)	−0.095 (−0.598, 0.408)	0.151 (−0.329, 0.631)	−0.223 (−0.791, 0.345)
Time to hit (ms)	WMT 0-back	647.0 (601.2, 692.7)	5.2 (−47.8, 58.2)	−5.9 (−56.5, 44.6)	**55.9 (0.1, 111.8)**[a]

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		Placebo	Low-dose cohort AQW051 7.5 mg	Medium-dose cohort AQW051 50 mg	High-dose cohort AQW051 100 mg
Behavioral measure	**Task**	**Mean (95% CI)**	**Mean change (95% CI) from placebo**		
	WMT 2-back	817.1 (727.3, 906.8)	82.8 (−46.4, 211.9)	−29.4 (−153.5, 94.7)	124.6 (−10.3, 259.4)
	EMT (retrieval)	1047.8 (970.4, 1125.3)	18.3 (−73.0, 109.6)	−46.1 (−133.3, 41.0)	13.5 (−89.5, 116.5)
Time to rejection (ms)	WMT 0-back	645.0 (586.6, 703.4)	−20.0 (−97.8, 57.7)	−53.7 (−128.2, 20.8)	36.5 (−45.0, 118.0)
	WMT 2-back	823.9 (752.3, 895.5)	39.6 (−51.9, 131.2)	−72.0 (−159.6, 15.6)	52.8 (−49.8, 155.4)
	EMT (retrieval)	972.9 (901.0, 1044.8)	18.3 (−65.3, 101.8)	−45.7 (−125.5, 34.0)	21.5 (−72.8, 115.8)

CI: confidence interval; EMT: episodic memory task; WMT: working memory task.

[a]Represents significance at 0.05 level.

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Table 5

C_{max} (ng/mL) following single-dose administration of AQW051 according to antipsychotic treatment received.

		AQW051 7.5 mg	AQW051 50 mg	AQW051 100 mg
Risperidone–paliperidone	N	8	3	9
	Mean (SD)	2.5 (0.7)	13.8 (2.3)	39.0 (10.1)
	Median	2.4	13.8	40.8
	Range	1.5–3.8	11.5–16.1	27.2–56.3
Olanzapine	N	4	6	4
	Mean (SD)	2.0 (0.8)	17.6 (4.6)	30.1 (12.6)
	Median	1.8	16.2	29.4
	Range	1.4–3.1	13.5–25.4	18.3–43.4
Aripiprazole	N	3	4	4
	Mean (SD)	2.5 (0.7)	16.2 (7.6)	30.8 (9.1)
	Median	2.4	19.1	30.4
	Range	1.9–3.2	5.1–21.6	21.8–40.7
Quetiapine	N	–	3	3
	Mean (SD)		19.7 (1.6)	26.0 (12.5)
	Median		19.6	32.1
	Range		18.2–21.3	11.7–34.3
Ziprasidone	N	1	5	–
	Mean (SD)	2.3	14.9 (5.4)	
	Median	2.3	14.8	
	Range	–	9.3–22.4	
All	N	19	22	20
	Mean (SD)	2.2 (0.7)	16.5 (4.8)	33.6 (11.1)
	Median	2.2	16.8	34.8
	Range	0.8–3.8	5.1–25.4	11.7–56.3

61 participants received antipsychotic drugs during the study period; of these, 4 participants were excluded from the description by antipsychotics because they had at least 2 different types of antipsychotics.

SD: Standard deviation.

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Table 6

Incidence of AEs by primary system organ class (safety set).

	Low-dose cohort			Medium-dose cohort			High-dose cohort		
	7.5 mg *n* = 22 *n* (%)	**Placebo *n* = 19 *n* (%)**	**Overall *n* = 22 *n* (%)**	**50 mg *n* = 23 *n* (%)**	**Placebo *n* = 23 *n* (%)**	**Overall *n* = 24[a] *n* (%)**	**100 mg *n* = 20 *n* (%)**	**Placebo *n* = 22 *n* (%)**	**Overall *n* = 22 *n* (%)**
Participants with AE(s)	8 (36.4)	9 (47.4)	15 (68.2)	10 (43.5)	8 (34.8)	13 (54.2)	9 (45.0)	11 (50.0)	13 (59.1)
System organ class									
Gastrointestinal disorders	4 (18.2)	3 (15.8)	7 (31.8)	5 (21.7)	1 (4.3)	6 (25.0)	2 (10.0)	3 (13.6)	5 (22.7)
Nervous system disorders	3 (13.6)	2 (10.5)	4 (18.2)	5 (21.7)	5 (21.7)	7 (29.2)	1 (5.0)	7 (31.8)	7 (31.8)
Psychiatric disorders	2 (9.1)	2 (10.5)	4 (18.2)	3 (13.0)	3 (13.0)	5 (20.8)	2 (10.0)	2 (9.1)	4 (18.2)
Musculoskeletal and connective tissue disorders	2 (9.1)	1 (5.3)	3 (13.6)	0 (0.0)	2 (8.7)	2 (8.3)	1 (5.0)	1 (4.5)	2 (9.1)
Respiratory, thoracic and mediastinal disorders	2 (9.1)	0 (0.0)	2 (9.1)	1 (4.3)	2 (8.7)	3 (12.5)	1 (5.0)	0 (0.0)	1 (4.5)
Eye disorders	0 (0.0)	2 (10.5)	2 (9.1)	2 (8.7)	0 (0.0)	2 (8.3)	1 (5.0)	0 (0.0)	1 (4.5)
Injury, poisoning and procedural complications	0 (0.0)	1 (5.3)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (4.5)	2 (9.1)
Cardiac disorders	0 (0.0)	1 (5.3)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (4.5)	1 (4.5)
Renal and urinary disorders	0 (0.0)	1 (5.3)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Arranged in descending order of total frequency and including all AEs occurring in ≥5% of participants in any sequence group.

AE: adverse event; *n*: number of participants.

[a]One participant entered the study twice; safety data from both periods of enrollment for this participant were included in the study analyses.