# Novartis Clinical Trial ResultsTemplate:

## Sponsor:

Novartis

## Generic Drug Name:

Not applicable

## Trial Indication:

Cognitive impairment associated with  schizophrenia (CIAS)

## Protocol Number:

CAQW051A2205

## Protocol Title

A randomized, double-blind, placebo-controlled, cross-over, single-dose study to evaluate the effects of AQW051 on Cognitive Function in patients with chronic stable schizophrenia including a one week multiple-dose extension to assess the persistence of observed effects and a multiple-dose cross over study in non-smokers only

## Clinical Trial Phase

Phase II

## Phase of Drug Development

Phase II

## Study Start/End Dates

23-Apr-2010 (first patient first visit) to 06-Sep-2011 (last patient last visit)

## Reason for Termination (If applicable)

Not applicable

## Study Design/Methodology

This was a Proof of Concept (PoC) study with two parts:

- Part A: A double-blind, randomized, placebo-controlled, 4-period single dose cross-over part, followed by a seven day multiple dose extension part, in smoking and non-smoking patients with stable chronic schizophrenia.
- Part B: A double-blind, randomized, placebo-controlled, 3-period multiple dose (7 days) cross-over part, in non-smoking patients with stable chronic schizophrenia.

Patients in Part A were randomized to any of the 4 sequences in a 1:1:1:1 fashion. The patients received single oral doses of 2, 15, and 100 mg AQW051, and placebo in the single dose part of the study and multiple oral doses of 2, 15 and 50 mg AQW051 and placebo in the multiple dose extension part of the study;

Patients in Part B were randomized to any of the 3 sequences in a 1:1:1 fashion. The patients received multiple oral doses (7 days) of 2 and 15 mg AQW051, and placebo.

The study consisted of a screening visit (within 28 days of dosing). In Part A four treatment periods with inpatient stays of 2 days each (periods 1 to 3), and 11-12 days (period 4) and in Part B three treatment periods with inpatient stays of 10 days each (periods 1 to 3). Each treatment period was separated by a washout period of 21 days (+/- 2 days). Patients underwent study completion evaluation 21 days (+/- 2 days) after the last drug administration in period 4 (Part A) or period 3 (Part B).

## Centers

Two centers in one country: United States of America

## Publication

None

## Objectives:

### Primary objective:

- To measure the effects of single oral doses of AQW051 versus placebo on cognitive function, as measured by selected CogState tests [Visual learning and Memory (Continuous Paired Associates Learning test (C-PAL)), Reasoning and Problem Solving (Groton maze learning task (GMLT))] in patients with chronic stable schizophrenia.

**Secondary objectives:**

- To measure the effects of single oral doses of AQW051 versus placebo on cognitive function, as measured by additional CogState tests [Attention/vigilance (identification task (IDN)) and Speed of Processing (detection task, (DET))] in patients with chronic stable schizophrenia.
- To measure the effects of single oral doses of AQW051 versus placebo on cognitive function, as measured by selected cognitive tests of MATRICS Consensus Cognitive Battery (MCCB) in patients with chronic stable schizophrenia.
- To assess the effects of multiple oral doses of AQW051 versus placebo on cognitive function, as measured by selected CogState tests (C-PAL, GMLT ) and by selected test of MCCB in patients with chronic stable schizophrenia.
- To measure the correlation of the cognitive domains measured by MCCB versus CogState in patients with chronic stable schizophrenia.
- To measure the pharmacokinetics of single and multiple oral doses of AQW051 in patients with chronic stable schizophrenia.
- To measure tolerability and safety of single doses of AQW051 in patients with chronic stable schizophrenia.

## Test Product (s), Dose(s), and Mode(s) of Administration

### Part A:

Single oral doses of 2, 15, 100 mg AQW051 and matching placebo in the single dose part of the study then switch to multiple oral doses of 2, 15, 50 mg AQW051 and matching placebo in the multiple dose part of the study (Period 4 only). Patients continued to receive the same last dose as received in the single dose part in Period 4 on the following Days 3 to 9. Only patients randomized to the 100 mg AQW051 dose were switched to a lower dose of 50 mg AQW051.

### Part B:

Multiple oral doses (7 days) of 2 mg, 15 mg AQW051 and matching placebo

## Statistical Methods

**Analysis of the primary variable**: The two primary cognitive scales are GMLT and C-PAL from the CogState battery. The primary variable was the area under the effect curve between 4 and 10 h post-dose (AUEC4-10, derived by the linear-trapezoidal rule), as defined on Day 1 for C-PAL and GMLT (CogState battery).

**Statistical hypothesis, model, and method of analysis**

The definition of activity for a given AQW051 dose was based on the observed mean change between AQW051 and placebo in those 2 scales on Day 1 and in their average, expressed in ‘effect size’ (i.e., normalized by the standard deviation of the change from placebo). Specifically, the activity was defined as a moderate effect size of at least 0.33 units on the average of the 2 scales, or as a larger effect size of least 0.58 units in at least 1 of the 2 scales.

The assessment of activity was obtained from a statistical analysis of the AUEC4-10 for GMLT and C-PAL on Day 1, as follows: those variables were separately analyzed by means of a linear mixed effect model adjusted for the period-specific Baseline value for the scale, the treatment group, the period, and the sequence as fixed effects, and for the patient as a random effect. The period-specific Baseline value for the scale was obtained from the average of the period-specific Day -1 values and from the pre-dose value. The mean treatment difference (and its 95% Confidence interval (CI)) between each AQW051 dose group and placebo were obtained from the model. The effect size was obtained by dividing the mean treatment difference (and its 95% CI) by the square root of twice the estimated variance of the residual error. The effect size was computed so that a positive value corresponds to an expected improvement. Activity was assessed from the effect size for GMLT and C-PAL and from their average. AUEC4-10 was chosen as primary variable because it was anticipated that the maximal effect would occur around or after Tmax which was expected between 4 and 6 hours. The mean treatment difference in the primary pharmacokinetic PD variable between each AQW051 dose

group and placebo was obtained from the statistical model. The mean effect size was calculated by dividing the mean treatment difference versus placebo by the square root of twice the estimated variance of the residual error obtained from the model. As this variance is a measurement of the intra-subject variance, this mean effect size defined above can be interpreted as the mean treatment difference versus placebo divided by the (pooled) STD of the treatment difference.

**Analysis of secondary variables:**

- AUEC4-10 on Day 1 of IDENT and DETECT (CogState battery)
- AUEC4-10 on Day 9 of Period 4 in Part A and Day 7 of each period in Part B (after 7 days of multiple doses), and on day 10 of each period in Part B (3 days after last dose) for C-PAL, GMLT, IDENT and DET (CogState battery) and of all scales of the MCCB battery.
- The change from period-specific Baseline (average of the Day-1 and the Day 1 pre-dose assessments) to each post Baseline time point (Day 1 and Day 2 and, in Period 4, Days 3, 5, 7, 9, and 10) in each scale of the CogState battery in Part A only.
- The change from Period-specific Baseline to Day 1 (and to Day 9 in Period 4 in Part A and Day 7 and Day 10 in Part B) in each scale of the MCCB battery.

**Statistical analysis for efficacy variables after single dose (Days 1-2)**

The AUECs derived for the CogState secondary scales (IDENT and DET) and the MCCB changes from period-specific baseline on Day 1 were similarly analyzed as the co-primary variables.

A repeated measures analysis on Day 1 and Day 2 was also performed for each CogState scale using a linear mixed effect model on the change from period-specific baseline, adjusted for the period-specific baseline value, the time point and its interaction with baseline, the treatment group and its interaction with the time point, the period, and the sequence as fixed effects, and for the patient and the patient-by-period interaction as random effects.

**Statistical analysis for efficacy variables after multiple doses (Days 9-10 of Period 4) in Part A**

The persistence of the treatment effect after multiple doses was estimated in two ways:

The AUEC4-10 on Days 1 and 9 of Period 4 were analyzed, separately for each CogState scale, by means of a linear mixed effect model adjusted for the day, the period-specific baseline value for the scale and its interaction with the day, and the treatment group and its interaction with the day as fixed effects and for the subject as a random intercept effect. The period-specific baseline value for the scale was obtained from the average of the Day -1 values and from the pre-dose Day 1 value of Period 4. The persistence of the treatment effect was estimated, for each dose group, by the mean (95% CI) of the change from Day 1 to Day 9 in a dose group minus that in placebo. Estimate of mean difference on Day 9 between each dose group and placebo were also obtained from the model.

The result of the persistence analysis had to be reviewed cautiously as the AQW051 dose administered from Day 3 in the multiple dose (MD) period of the patients who received 100mg in Period 4 was half of that administered on Day 1. Patients switched from 100 mg single dose to 50 mg multiple doses. In addition, this MD part was done only in Period 4, comparing treatment between subjects, thus has very weak power, unlike the within subject analysis of the single dose crossover.

Descriptive statistics of MCCB scales changes from baseline to Day 9 were provided.

**Statistical analysis for efficacy variables after multiple doses and after follow-up (Days 7 and 10) in Part B**

The AUEC4-10 on Days 1, 7 and 10 were analyzed, separately for each CogState scale, by means of a linear mixed effect model suitable to repeated measures in a cross-over design. The model included fixed terms for the sequence, period, treatment and day, the period-specific baseline value for the scale as covariate and the following interactions: baseline by day, and treatment by day. Inter-patient, inter-period and within-period variability components were estimated using subject and subject by period interaction as random effects. The period-specific baseline value for the scale was obtained from the average of the Day -1 values and from the pre-dose Day 1 value of the specific period. The persistence of the treatment effect was estimated, for each dose group, by the mean (95% CI) of the change from Day 1 to Day 7 and Day 10 in a dose group minus that in placebo. Estimate of mean difference on Day 7 and Day 10 between each dose group and placebo was also obtained from the model.

Descriptive statistics of MCCB scales changes from baseline to Days 7 and 10 were provided.

**Statistical methods for pharmacokinetic analyses**

The AQW051 concentrations in plasma and CSF were summarized per dose group and time point, by means of descriptive statistics including mean, geometric mean, standard deviation (SD), coefficient of variation (CV), min, median, and max.

The AQW051 PK parameters were summarized per dose group separately for Parts A and B, by means of descriptive statistics including mean, geometric mean, SD, CV, min, median, and max. Since Tmax was evaluated by a nonparametric method, only median values and ranges but no means were given for this parameter.

## Study Population: Key Inclusion/Exclusion Criteria

### Inclusion criteria

- Male and female patients aged 18 to 55 years (inclusive)
- Diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV/DSM-IV-TR).
- Patients were to be symptomatically stable for at least three (3) months prior to first dosing and did not suffer from an acute exacerbation of their psychosis.
- Patients were being treated with a stable regimen for at least three (3) months prior to first dosing with one of the following second generation antipsychotics: risperidone, paliperidone, quetiapine, ziprasidone, aripiprazole.
- Patients had a Clinical Global Impression-Severity (CGI-S) score of less or equal to 4.
- Patients had a Calgary Depression Scale (CDS) total score of less than or equal to 10.
- Patients had a Positive and Negative Symptoms Scale (PANSS) total score of less or equal to 70 and PANSS Positive Subscale (sum of all P1-P7) of less than or equal to 18.
- Patients who met the following cognitive performance criteria:
  - Maximum performance level: Performance below 1.0 SD from perfect performance on the Hopkins Verbal Learning Test (HVLT) total (31 or less)
  - Minimum performance level: patient were able to perform and complete the CogState practice session
  - Wechsler Test of Adult Reading (WTAR): 5th grade reading level assessment

### Exclusion criteria

- Current treatment with an anticholinergic or other agent known to adversely interfere with the cholinergic system, as determined by the investigator, and/ or treatment with cholinesterase inhibitor within the last three (3) months prior to randomization.
- Current treatment with conventional antipsychotics (e.g. fluphenazine, haloperidol) or clozapine.
- History of neuroleptic malignant syndrome.
- Patients with a DSM-IV diagnosis of substance abuse (other than nicotine Part A only) within the last month.
- Patients with a DSM-IV diagnosis of alcohol or substance dependence (other than nicotine Part A only) within the last 6 months.
- Patients with a medical or neurological disorder or treatment for such disorder that could have interfered with the study medication of the assessment of the patient.

- Any clinically significant suicidal ideation (Type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the last month) or previous history of suicide behavior which could have prevented the successful and safe completion of the study as assessed by the investigator
- Patients with a history of significant head injury/trauma, as defined by: Loss of consciousness (LOC) for more than 1 hour, recurring seizures resulting from the head injury, clear cognitive sequelae of the injury, cognitive rehabilitation following the injury
- Use of concomitant medication that were strong inhibitors of CYP3A4 and CYP1A2
- PART B only Smokers (use of tobacco products in the previous 3 months)

## Participant Flow Table

**Patient disposition – n (%) of patients - Part A**

| | Sequence 1 N=8 | Sequence 2 N=9 | Sequence 3 N=8 | Sequence 4 N=8 | Total N=33 |
|---|---|---|---|---|---|
| Patients | | | | | |
| Completed | 7 (87.5%) | 7 (77.8%) | 7 (87.5%) | 6 (75.0%) | 27 (81.8%) |
| Discontinued | 1 (12.5%) | 2 (22.2%) | 1 (12.5%) | 2 (25.0%) | 6 (18.2%) |
| Main cause of discontinuation | | | | | |
| Lost to follow-up | 0 | 1 (11.1%) | 1 (12.5%) | 0 | 2 (6.1%) |
| Protocol deviation | 1 (12.5%) | 0 | 0 | 0 | 1 (3.0%) |
| Patient withdrew consent | 0 | 1 (11.1%) | 0 | 2 (25.0%) | 3 (9.1%) |

Sequence 1: Placebo, AQW051 100 mg, AQW051 15 mg, AQW051 2 mg (SD)/2 mg (MD)

Sequence 2: AQW051 2 mg, Placebo, AQW051 100 mg, AQW051 15 mg (SD)/15 mg (MD)

Sequence 3: AQW051 15 mg, AQW051 2 mg, Placebo, AQW051 100 mg (SD)/50 mg (MD)

Sequence 4: AQW051 100 mg, AQW051 15 mg, AQW051 2 mg, Placebo (SD)/Placebo (MD)

### Patient disposition – n (%) of patients - Part B

| | Sequence 5 N=8 | Sequence 6 N=8 | Sequence 7 N=8 | Total N=24 |
|---|---|---|---|---|
| Patients | | | | |
| Completed | 6 (75.0%) | 6 (75.0%) | 5 (62.5%) | 17 (70.8%) |
| Discontinued | 2 (25.0%) | 2 (25.0%) | 3 (37.5%) | 7 (29.2%) |
| Main cause of discontinuation | | | | |
| Adverse Event(s) | 0 | 0 | 1 (12.5%) | 1 (4.2%) |
| Lost to follow-up | 0 | 0 | 1 (12.5%) | 1 (4.2%) |
| Patient withdrew consent | 2 (25.0%) | 2 (25.0%) | 1 (12.5%) | 5 (20.8%) |

Sequence 5: Placebo, AQW051 15 mg, AQW051 2 mg

Sequence 6: AQW051 2 mg, Placebo, AQW051 15 mg

Sequence 7: AQW051 15 mg, AQW051 2 mg, Placebo

## Baseline Characteristics

### Demographic summary - Part A (Safety analysis set)

| | | Sequence 1 N=8 | Sequence 2 N=9 | Sequence 3 N=8 | Sequence 4 N=8 | Total N=33 |
|---|---|---|---|---|---|---|
| Age (years) | Mean (SD) | 43.8 (11.32) | 39.6 (10.90) | 40.6 (7.09) | 41.5 (8.94) | 41.3 (9.42) |
| | Median | 46.5 | 44.0 | 41.5 | 45.0 | 44.0 |
| | Range | 22 - 55 | 19 - 54 | 26 - 49 | 26 - 52 | 19 - 55 |
| Gender – n (%) | Male | 6 (75%) | 7 (78%) | 4 (50%) | 6 (75%) | 23 (70%) |
| | Female | 2 (25%) | 2 (22%) | 4 (50%) | 2 (25%) | 10 (30%) |
| Predominant race - n(%) | Caucasian | 3 (38%) | 0 | 1 (13%) | 0 | 4 (12%) |
| | Black | 5 (63%) | 9 (100%) | 7 (88%) | 8 (100%) | 29 (88%) |
| Ethnicity – n (%) | Hispanic/Latino | 1 (13%) | 0 | 0 | 0 | 1 (3%) |
| | Other | 7 (88%) | 9 (100%) | 8 (100%) | 8 (100%) | 32 (97%) |
| Height (cm) | Mean (SD) | 172.3 (6.36) | 173.8 (9.13) | 171.8 (8.73) | 173.4 (7.33) | 172.8 (7.67) |

| | | Sequence 1 N=8 | Sequence 2 N=9 | Sequence 3 N=8 | Sequence 4 N=8 | Total N=33 |
|---|---|---|---|---|---|---|
| | Median | 171.5 | 173.0 | 174.0 | 173.0 | 173.0 |
| | Range | 163 - 180 | 165 - 193 | 159 - 183 | 165 - 184 | 159 - 193 |
| Weight (kg) | Mean (SD) | 93.90 (16.120) | 91.07 (13.166) | 93.65 (25.133) | 85.68 (24.791) | 91.07 (19.589) |
| | Median | 91.00 | 95.40 | 89.80 | 81.55 | 90.50 |
| | Range | 62.6 - 115.9 | 63.8 - 104.8 | 54.8 - 133.8 | 58.9 - 128.3 | 54.8 - 133.8 |
| BMI ($kg/m^2$) | Mean (SD) | 31.843 (6.6304) | 30.276 (4.9005) | 31.633 (8.2660) | 28.061 (5.7097) | 30.448 (6.3221) |
| | Median | 30.867 | 31.257 | 29.616 | 27.069 | 29.645 |
| | Range | 21.41 - 43.62 | 22.60 - 37.58 | 21.68 - 49.15 | 21.63 - 37.90 | 21.41 - 49.15 |
| Formal education (years) | Mean (SD) | 11.8 (1.67) | 11.3 (1.41) | 11.8 (1.58) | 11.4 (0.92) | 11.5 (1.37) |
| | Median | 12.0 | 12.0 | 11.5 | 12.0 | 12.0 |
| | Range | 8 - 14 | 10 - 14 | 10 - 14 | 10 - 12 | 8 - 14 |
| Smoking history | Non smoker | 2 (25%) | 3 (33%) | 2 (25%) | 2 (25%) | 9 (27%) |
| | Smoker | 6 (75%) | 6 (67%) | 6 (75%) | 6 (75%) | 24 (73%) |
| Duration of the disease (years) | Mean (SD) | 21.9 (11.66) | 11.2 (6.94) | 15.8 (6.54) | 15.5 (11.94) | 15.9 (9.87) |
| | Median | 22.0 | 10.0 | 17.0 | 10.5 | 14.0 |
| | Range | 5 - 35 | 3 - 25 | 6 - 24 | 5 - 36 | 3 - 36 |

Sequence 1: Placebo, AQW051 100 mg, AQW051 15 mg, AQW051 2 mg (SD)/2 mg (MD)

Sequence 2: AQW051 2 mg, Placebo, AQW051 100 mg, AQW051 15 mg (SD)/15 mg (MD)

Sequence 3: AQW051 15 mg, AQW051 2 mg, Placebo, AQW051 100 mg (SD)/50 mg (MD)

Sequence 4: AQW051 100 mg, AQW051 15 mg, AQW051 2 mg, Placebo (SD)/Placebo (MD)

BMI = body mass index

**Demographic summary - Part B (Safety analysis set)**

| | Sequence 5 N=8 | Sequence 6 N=8 | Sequence 7 N=8 | Total N=24 |
|---|---|---|---|---|

| | | Sequence 5<br>N=8 | Sequence 6<br>N=8 | Sequence 7<br>N=8 | Total<br>N=24 |
|---|---|---|---|---|---|
| Age (years) | Mean (SD) | 43.3 (11.46) | 41.3 (9.48) | 41.8 (7.55) | 42.1 (9.25) |
| | Median | 44.5 | 40.5 | 42.5 | 41.5 |
| | Range | 22 - 55 | 26 - 54 | 31 - 54 | 22 - 55 |
| Gender – n (%) | Male | 5 (63%) | 7 (88%) | 5 (63%) | 17 (71%) |
| | Female | 3 (38%) | 1 (13%) | 3 (38%) | 7 (29%) |
| Predominant race - n(%) | Black | 8 (100%) | 7 (88%) | 8 (100%) | 23 (96%) |
| | Caucasian | | 1 (13%) | | 1 (4%) |
| Ethnicity – n (%) | Other | 8 (100%) | 8 (100%) | 8 (100%) | 24 (100%) |
| Height (cm) | Mean (SD) | 174.0 (12.04) | 174.9 (6.81) | 172.6 (14.36) | 173.8 (11.04) |
| | Median | 178.0 | 173.5 | 169.5 | 173.5 |
| | Range | 152 - 188 | 164 - 185 | 152 - 193 | 152 - 193 |
| Weight (kg) | Mean (SD) | 98.65 (15.775) | 94.94 (12.753) | 100.79 (21.195) | 98.13 (16.372) |
| | Median | 92.85 | 94.40 | 102.50 | 94.90 |
| | Range | 75.5 - 127.0 | 79.3 - 113.0 | 72.2 - 133.1 | 72.2 - 133.1 |
| BMI ($kg/m^2$) | Mean (SD) | 32.557 (3.7191) | 31.043 (3.6871) | 34.281 (9.2141) | 32.627 (6.0011) |
| | Median | 32.923 | 31.447 | 30.312 | 31.622 |
| | Range | 25.92 - 39.20 | 24.88 - 35.92 | 26.52 - 51.64 | 24.88 - 51.64 |
| Formal education (years) | Mean (SD) | 11.5 (1.51) | 12.0 (1.85) | 12.0 (1.69) | 11.8 (1.63) |
| | Median | 11.5 | 12.0 | 12.0 | 12.0 |
| | Range | 10 - 14 | 8 - 14 | 9 - 15 | 8 - 15 |
| Smoking history | Non smoker | 8 (100%) | 8 (100%) | 8 (100%) | 24 (100%) |
| Duration of the disease (years) | Mean (SD) | 14.4 (9.69) | 12.6 (6.95) | 20.1 (7.94) | 15.7 (8.55) |
| | Median | 14.0 | 13.0 | 22.0 | 18.0 |
| | Range | 4 - 31 | 4 - 22 | 4 - 29 | 4 - 31 |

Sequence 5: Placebo, AQW051 15 mg, AQW051 2 mg

Sequence 6: AQW051 2 mg, Placebo, AQW051 15 mg

Sequence 7: AQW051 15 mg, AQW051 2 mg, Placebo

BMI = body mass index

## Summaryof Efficacy

## Primary Outcome Results

### Inference for AUC4-10 for each CogState domain on Day 1- Part A (PD analysis set)

| | | | Comparison *vs.* Placebo | | | | |
|---|---|---|---|---|---|---|---|
| | | | Mean difference | | | Effect size | |
| **CogState domain** | **Treatment** | **Mean** | **Estimate** | **(95% CI)** | **P-value** | **Estimate** | **(95% CI)** |
| CPAL - Total number of errors | Placebo | 492.9 | | | | | |
| | AQW051 2 mg | 410.4 | -82.5 | (-159.0, -5.9) | 0.0353 | 0.384 | (0.027, 0.741) |
| | AQW051 15 mg | 422.6 | -70.3 | (-147.1, 6.5) | 0.0720 | 0.327 | (-0.030, 0.685) |
| | AQW051 100 mg | 433.0 | -59.9 | (-136.6, 16.8) | 0.1235 | 0.279 | (-0.078, 0.636) |
| GMLT - Total number of errors | Placebo | 363.2 | | | | | |
| | AQW051 2 mg | 392.8 | 29.6 | (-19.0, 78.2) | 0.2300 | -0.216 | (-0.570, 0.138) |
| | AQW051 15 mg | 391.5 | 28.3 | (-20.4, 77.1) | 0.2522 | -0.206 | (-0.561, 0.149) |
| | AQW051 100 mg | 379.7 | 16.5 | (-32.1, 65.1) | 0.5029 | -0.120 | (-0.474, 0.234) |
| Average CPAL and GMLT - Total number of errors | Placebo | 433.4 | | | | | |
| | AQW051 2 mg | 403.3 | -30.2 | (-83.9, 23.6) | 0.2675 | 0.198 | (-0.155, 0.551) |
| | AQW051 15 mg | 410.2 | -23.2 | (-77.1, 30.7) | 0.3934 | 0.152 | (-0.201, 0.506) |
| | AQW051 100 mg | 404.6 | -28.9 | (-82.7, 24.9) | 0.2887 | 0.190 | (-0.164, 0.543) |

CPAL AUEC: Total number of errors (count*hr); GMLT AUEC: Total number of errors (count*hr);

Average CPAL and GMLT AUEC: Total number of errors (count*hr);

A positive effect size denotes an improvement on active versus placebo

**Inference for AUC4-10 for each CogState domain - Part B**

| | | | Comparison *vs.* Placebo | | | | |
|---|---|---|---|---|---|---|---|
| | | | Mean difference | | | Effect size | |
| **CogState domain** | **Treatment** | **Mean** | **Estimate** | **(95% CI)** | **P-value** | **Estimate** | **(95% CI)** |
| CPAL - Total number of errors | Placebo | 422.8 | | | | | |
| | AQW051 2 mg | 547.1 | 124.3 | (54.8, 193.8) | 0.0009 | -0.776 | (-1.210, -0.343) |
| | AQW051 15 mg | 396.8 | -26.0 | (-94.2, 42.3) | 0.4455 | 0.162 | (-0.264, 0.589) |
| GMLT - Total number of errors | Placebo | 394.4 | | | | | |
| | AQW051 2 mg | 419.2 | 24.8 | (-29.7, 79.4) | 0.3663 | -0.193 | (-0.616, 0.231) |
| | AQW051 15 mg | 390.4 | -3.9 | (-57.8, 50.0) | 0.8850 | 0.030 | (-0.388, 0.448) |
| Average CPAL and GMLT - Total number of errors | Placebo | 408.1 | | | | | |
| | AQW051 2 mg | 483.3 | 75.3 | (27.3, 123.2) | 0.0030 | -0.681 | (-1.114, -0.247) |
| | AQW051 15 mg | 393.6 | -14.4 | (-61.6, 32.8) | 0.5386 | 0.131 | (-0.296, 0.558) |

CPAL AUEC: Total number of errors (count*hr); GMLT AUEC: Total number of errors (count*hr);

Average CPAL and GMLT AUEC: Total number of errors (count*hr)

A positive effect size denotes an improvement on active versus placebo

## Secondary Outcome Result(s)

**Effect of single oral doses of AQW051 versus placebo on cognitive function (Attention/vigilance (IDN) and Speed of processing (DET)] in patients with chronic schizophrenia**

**Single dose in Part A (Day 1)**

**Inference for AUC4-10 for each CogState domain on Day 1- Part A (PD analysis set)**

| | | | Comparison *vs.* Placebo | | | | |
|---|---|---|---|---|---|---|---|
| | | | Mean difference | | | Effect size | |
| **CogState domain** | **Treatment** | **Mean** | **Estimate** | **(95% CI)** | ***P-value*** | **Estimate** | **(95% CI)** |
| DET - Speed of performance (log10 milliseconds) | Placebo | 15.6 | | | | | |
| | AQW051 2 mg | 15.6 | -0.0 | (-0.2, 0.2) | 0.9805 | 0.004 | (-0.353, 0.362) |
| | AQW051 15 mg | 15.5 | -0.0 | (-0.2, 0.2) | 0.7218 | 0.064 | (-0.291, 0.419) |
| | AQW051 100 mg | 15.6 | 0.0 | (-0.2, 0.2) | 0.9014 | -0.022 | (-0.376, 0.332) |
| IDN - Speed of performance (log10 milliseconds) | Placebo | 16.6 | | | | | |
| | AQW051 2 mg | 16.5 | -0.0 | (-0.2, 0.2) | 0.7822 | 0.050 | (-0.306, 0.406) |
| | AQW051 15 mg | 16.6 | -0.0 | (-0.2, 0.2) | 0.8811 | 0.027 | (-0.327, 0.381) |
| | AQW051 100 mg | 16.6 | 0.0 | (-0.1, 0.2) | 0.6330 | -0.085 | (-0.438, 0.268) |

A positive effect size denotes an improvement on active versus placebo

### Single dose in Part B of study (Day 1)

### Inference for AUC4-10 for each CogState domain - Part B

| | | | Comparison *vs.* Placebo | | | | |
|---|---|---|---|---|---|---|---|
| | | | Mean difference | | | Effect size | |
| **CogState domain** | **Treatment** | **Mean** | **Estimate** | **(95% CI)** | ***P-value*** | **Estimate** | **(95% CI)** |
| DET - Speed of performance (log10 milliseconds) | Placebo | 15.5 | | | | | |
| | AQW051 2 mg | 15.8 | 0.3 | (-0.2, 0.8) | 0.2141 | -0.271 | (-0.704, 0.163) |
| | AQW051 15 mg | 15.5 | 0.0 | (-0.4, 0.5) | 0.8418 | -0.042 | (-0.470, 0.385) |
| IDN - Speed of performance (log10 milliseconds) | Placebo | 16.4 | | | | | |
| | AQW051 2 mg | 16.5 | 0.1 | (-0.4, 0.7) | 0.6534 | -0.097 | (-0.530, 0.337) |
| | AQW051 15 mg | 16.3 | 0.0 | (-0.5, 0.5) | 0.9595 | 0.011 | (-0.416, 0.438) |

IDN AUEC: Speed of performance (log10 milliseconds*hr); DET AUEC: Speed of performance (log10 milliseconds*hr)

A positive effect size denotes an improvement on active versus placebo

### Effect of single dose of AQW051 versus placebo on Cognitive function measured by MCCB

### Single dose in Part A (Day 1)

### Inference for change from baseline for each MCCB domain - Part A (PD analysis set)

| | | | Comparison vs Placebo | | | |
|---|---|---|---|---|---|---|
| | | | Mean difference | | Effect size | |
| **MCCB domain** | **Treatment** | **Mean** | **Estimate (95% CI)** | **P-value** | **Estimate (95% CI)** | |
| NAB Mazes | PLACEBO | -0.2 | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | AQW051 2MG | 2.4 | 2.6 (-0.7, 6.0) | 0.1184 | 0.284 (-0.074,0.642) |
| | AQW051 15MG | 3.1 | 3.3 (-0.0, 6.7) | 0.0504 | 0.358 (-0.001, 0.716) |
| | AQW051 100MG | 1.4 | 1.6 (-1.7, 5.0) | 0.3349 | 0.175 (-0.184, 0.534) |
| BVMT-Revised | PLACEBO | 1.8 | | | |
| | AQW051 2MG | 2.2 | 0.4 (-3.8, 4.7) | 0.8328 | 0.038 (-0.321, 0.397) |
| | AQW051 15MG | 1.8 | -0.0 (-4.3, 4.2) | 0.9961 | -0.001 (-0.360, 0.359) |
| | AQW051 100MG | 0.2 | -1.6 (-5.9, 2.6) | 0.4485 | -0.137 (-0.497, 0.222) |
| Category Fluency - Animals | Placebo | 2.1 | | | |
| | AQW051 2MG | 2.3 | 0.2 (-2.7, 3.1) | 0.8752 | 0.028 (-0.330, 0.387) |
| | AQW051 15MG | 3.4 | 1.3 (-1.6, 4.3) | 0.3592 | 0.167 (-0.193, 0.526) |
| | AQW051 100MG | 1.5 | -0.5 (-3.4, 2.4) | 0.7120 | -0.067 (-0.426, 0.292) |
| CPT-IP | PLACEBO | -0.3 | | | |
| | AQW051 2MG | 1.4 | 1.7 (-1.4, 4.8) | 0.2732 | 0.202 (-0.162, 0.566) |
| | AQW051 15MG | 1.3 | 1.6 (-1.5, 4.7) | 0.3122 | 0.187 (-0.179, 0.554) |
| | AQW051 100MG | 0.3 | 0.6 (-2.6, 3.7) | 0.7150 | 0.067 (-0.299, 0.433) |

**Single dose in Part B of study (Day 1)**

**Inference for change from baseline for each MCCB domain - Part B (PD analysis set)**

| MCCB domain | Treatment | Mean | Comparison vs Placebo Mean difference Estimate (95% CI) | P-value | Effect size Estimate (95% CI) P-value |
|---|---|---|---|---|---|
| NAB Mazes | PLACEBO | 4.0 | | | |
| | AQW051 2MG | 2.6 | -1.4 (-5.7, 2.9) | 0.5004 | -0.146 (-0.583, 0.291) |
| | AQW051 15MG | 1.0 | -3.0 (-7.3, 1.2) | 0.1523 | -0.309 (-0.739, 0.121) |
| BVMT- | PLACEBO | 2.4 | | | |

| | | | | | |
|---|---|---|---|---|---|
| Revised | | | | | |
| | AQW051 2MG | 2.7 | 0.3 (-5.6, 6.2) | 0.9180 | 0.022 (-0.408, 0.452) |
| | AQW051 15MG | -1.9 | -4.3 (-10.2, 1.5) | 0.1377 | -0.318 (-0.742, 0.106) |
| Category Fluency - animals | PLACEBO | 0.4 | | | |
| | AQW051 2MG | 2.2 | 1.8 (-2.4, 6.1) | 0.3918 | 0.183 (-0.241, 0.606) |
| | AQW051 15MG | 2.4 | 2.0 (-2.2, 6.3) | 0.3391 | 0.202 (-0.218, 0.622) |
| CPT-IP | PLACEBO | 1.6 | | | |
| | AQW051 2MG | 2.0 | 0.3 (-2.9, 3.6) | 0.8324 | 0.045 (-0.378, 0.468) |
| | AQW051 15MG | 0.7 | -0.9 (-4.1, 2.3) | 0.5818 | -0.116 (-0.533, 0.302) |

**Multiple dose part:**

**Effect of multiple oral doses of AQW051 versus placebo on cognitive function (C-PAL, GMLT) in Part A (Day 9; Period 4) and Part B (Day 7 and Day 10) patients with chronic schizophrenia**

**Part A (Day 9; Period 4)**

**Inference for AUEC4-10 for each CogState domain on Day 9- Part A (PD analysis set)**

| | | Least squares mean | | | Comparison vs Placebo | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Day 9 - Day 1 | | Day 9 | |
| CogState domain | Treatment | Day 1 | Day 9 | Day 9 - Day 1 | Estimate (95% CI) | P-value | Estimate (95% CI) | P-value |
| CPAL | PLACEBO | 501.5 | 357.3 | -144.3 | | | | |
| | AQW051 2MG | 483.5 | 371.4 | -112.2 | 32.1 (-163.7,227.9) | 0.738 | 14.1 (-199.2,227.4) | 0.894 |
| | AQW051 15MG | 356.3 | 425.6 | 69.3 | 213.6 (22.9,404.2) | 0.030 | 68.4 (-138.3,275.0 | 0.508 |
| | AQW051 100 MG | 366.7 | 241.1 | -125.5 | 18.8 (-171.5,209.0) | 0.841 | -116.1 (-323.3,91.1) | 0.264 |
| GMLT | PLACEBO | 329.2 | 357.5 | 28.3 | | | | |
| | AQW051 2MG | 385.7 | 355.6 | -30.1 | -58.4 (-237.8,120.9) | 0.459 | -2.0 (-121.6,117.7) | 0.974 |
| | AQW051 15MG | 435.0 | 329.3 | -105.71 | 134.0 (-312.2,44.2) | 0.118 | -28.2 (-152.2,95.7) | 0.648 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | AQW051 100 MG | 356.9 | 310.5 | -46.34 | -74.6 (-246.1,96.9) | 0.332 | -47.0 (-161.7,67.7) | 0.412 |
| Average CPAL and GMLT | PLACEBO | 447.8 | 349.6 | -98.13 | | | | |
| | AQW051 2MG | 436.1 | 369.0 | -67.16 | 31.0 (-122.9,184.9) | 0.682 | 19.4 (-145.9,184.6) | 0.814 |
| | AQW051 15MG | 396.9 | 413.2 | 16.26 | 114.4 (-33.7,262.5) | 0.124 | 63.6 (-94.8,222.0) | 0.422 |
| | AQW051 100 MG | 364.9 | 277.0 | -87.87 | 10.3 (-138.5,159.0) | 0.888 | -72.6 (-232.3,87.0) | 0.363 |

CPAL AUEC: Total number of errors (count*hr); GMLT AUEC: Total number of errors (count*hr);

Average CPAL and GMLT AUEC: Total number of errors (count*hr)

## Part B (Day 7 and Day 10)

### Inference for AUEC4-10 for each CogState domain - Day 1, 7 and 10 - Part B (PD analysis set)-Page 1 of 3

| | | | | | Least squares mean | | |
|---|---|---|---|---|---|---|---|
| **CogState domain** | **Treatment** | **Day 1** | **Day 7** | **Day 10** | **Day 7 – Day 1** | **Day 10 – Day 1** | **Day 10 – Day 7** |
| CPAL | PLACEBO | 425.6 | 395.4 | 363.7 | -30.3 | -61.9 | -31.7 |
| | AQW051 2MG | 546.1 | 430.5 | 403.0 | -115.6 | -143.1 | -27.6 |
| | AQW051 15MG | 401.4 | 410.8 | 369.7 | 9.425 | -31.7 | -41.1 |
| GMLT | PLACEBO | 389.9 | 372.2 | 397.8 | -17.8 | 7.8 | 25.6 |
| | AQW051 2MG | 416.1 | 392.4 | 386.1 | -23.7 | -30.0 | -6.3 |
| | AQW051 15MG | 391.8 | 347.7 | 347.4 | -44.1 | -44.4 | -0.3 |
| Average CPAL and GMLT | PLACEBO | 407.7 | 383.5 | 380.0 | -24.2 | -27.7 | -3.5 |
| | AQW051 2MG | 480.2 | 409.6 | 392.8 | -70.6 | -87.3 | -16.8 |
| | AQW051 15MG | 396.9 | 379.3 | 358.8 | -17.7 | -38.1 | -20.5 |

CPAL AUEC: Total number of errors (count*hr); GMLT AUEC: Total number of errors (count*hr);

Average CPAL and GMLT AUEC: Total number of errors (count*hr)

**Inference for AUEC4-10 for each CogState domain - Day 1, 7 and 10 - Part B (PD analysis set) - Page 2 of 3**

| | | Comparison vs Placebo | | | |
|---|---|---|---|---|---|
| | | Day 7- Day 1 | | Day 10 – Day 1 | |
| **CogState domain** | **Treatment** | **Estimate (95% CI)** | **P-value** | **Estimate (95% CI)** | **P-valu** |
| CPAL | PLACEBO | | | | |
| | AQW051 2MG | -85.3 (-171.0,0.4) | 0.051 | -81.2 (-166.8,4.5) | 0.063 |
| | AQW051 15MG | 39.7 (-45.2,124.6) | 0.357 | 30.2 (-54.7,115.1) | 0.482 |
| GMLT | PLACEBO | | | | |
| | AQW051 2MG | -5.9 (-74.8,63.0) | 0.866 | -37.8 (-106.7,31.1) | 0.280 |
| | AQW051 15MG | -26.3 (-94.7,42.1) | 0.448 | -52.2 (-120.6,16.2) | 0.133 |
| Average CPAL and GMLT | PLACEBO | | | | |
| | AQW051 2MG | -46.4 (-111.0,18.3) | 0.158 | -59.6 (-124.3,5.0) | 0.070 |
| | AQW051 15MG | 6.5 (-57.6,70.7) | 0.840 | -10.4 (-74.6,53.7) | 0.748 |

CPAL AUEC: Total number of errors (count*hr); GMLT AUEC: Total number of errors (count*hr);

Average CPAL and GMLT AUEC: Total number of errors (count*hr)

**Inference for AUEC4-10 for each CogState domain - Day 1, 7 and 10 - Part B (PD analysis set) - Page 3 of 3**

| | | Comparison vs Placebo | | | |
|---|---|---|---|---|---|
| | | Day 7 | | Day 10 | |
| **CogState domain** | **Treatment** | **Estimate (95% CI)** | **P-value** | **Estimate (95% CI)** | **P-value** |
| CPAL | PLACEBO | | | | |
| | AQW051 2MG | 35.2 (-39.8,110.1) | 0.353 | 39.3 (-35.7,114.3) | 0.300 |

| | | | | | |
|---|---|---|---|---|---|
| | AQW051 15MG | 15.5 (-58. 2,89.1) | 0.678 | 6.0 (-67.7,79.6) | 0.872 |
| GMLT | PLACEBO | | | | |
| | AQW051 2MG | 20.2 (-32.6,73.0) | 0.450 | -11.7 (-64.5,41.1) | 0.663 |
| | AQW051 15MG | -24.5 (-76.6,27.7) | 0.355 | -50.4 (-102.5,1.8) | 0.058 |
| Average CPAL and GMLT | PLACEBO | | | | |
| | AQW051 2MG | 26.1 (-26.278.3) | 0.325 | 12.8 (-39.5,65.1) | 0.628 |
| | AQW051 15MG | -4.3 (-55.8,47.3) | 0.870 | -21.3 (-72.8,30.3) | 0.416 |

CPAL AUEC: Total number of errors (count*hr); GMLT AUEC: Total number of errors (count*hr);

Average CPAL and GMLT AUEC: Total number of errors (count*hr)

## Effect of multiple doses of AQW051 versus placebo on Cognitive function measured by MCCB

## Part A (Day 9; Period 4)

### Summary for change from baseline for each MCCB domain (MD period)-Day 9, Period 4 - Part A (PD analysis set)

| MCCB domain | Treatment | Statistic | Baseline | Score | Change from baseline |
|---|---|---|---|---|---|
| NAB Mazes | PLACEBO | n | 6 | 6 | 6 |
| | | Mean (SD) | 41.2 (15.13) | 46.0 (6.10) | 4.8 (10.91) |
| | AQW051 2MG | n | 7 | 7 | 7 |
| | | Mean (SD) | 47.6 (11.70) | 47.0 (11.12) | -0.6 (6.05) |
| | AQW051 15MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 48.8 (12.67) | 49.9 (12.19) | 1.1 (6.45) |
| | AQW051 100MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 54.3 (12.20) | 52.6 (12.48) | -1.6 (8.62) |
| BVMT-Revised | PLACEBO | n | 6 | 6 | 6 |
| | | Mean (SD) | 42.5 (9.97) | 34.7 (14.56) | -7.8 (9.87) |
| | AQW051 2MG | n | 7 | 7 | 7 |
| | | Mean (SD) | 40.1 | 34.0 | -6.1 |

| | | | | | |
|---|---|---|---|---|---|
| | | | 14.46 | 7.77 | 12.54 |
| | AQW051 15MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 34.3 | 30.3 | -4.0 |
| | | | 10.93 | 6.73 | 11.49 |
| | AQW051 100MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 41.3 (13.42) | 37.0 (13.47) | -4.3 (7.69) |
| Category Fluency - Animals | PLACEBO | n | 6 | 6 | 6 |
| | | Mean (SD) | 44.5 (10.73) | 43.3 (12.06) | -1.2 (4.17) |
| | AQW051 2MG | n | 7 | 7 | 7 |
| | | Mean (SD) | 41.4 (10.97) | 42.0 (11.20) | 0.6 (6.19) |
| | AQW051 15MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 42.1 (8.51) | 42.5 (6.65) | 0.4 (6.82) |
| | AQW051 100MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 42.8 (7.09) | 47.0 (10.93) | 4.3 (6.88) |
| CPT-IP | PLACEBO | n | 6 | 6 | 6 |
| | | Mean (SD) | 44.7 (12.19) | 38.0 (13.87) | -6.7 (4.59) |
| | AQW051 2MG | n | 7 | 7 | 7 |
| | | Mean (SD) | 37.3 (9.89) | 40.4 (11.80) | 3.1 (6.26) |
| | AQW051 15MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 31.4 (11.99) | 29.6 (15.86) | -1.8 (7.70) |
| | AQW051 100MG | n | 8 | 8 | 8 |
| | | Mean (SD) | 37.1 (9.78) | 34.3 (16.69) | -3.9 (11.73) |

In the multiple dose period, patients randomized to the 100mg AQW051 dose switched to the 50mg AQW051 dose.

## Part B (Day 7 and Day 10)

### Summary for change from baseline for each MCCB domain - Day 7 and Day 10- Part B (PD analysis set)

| MCCB domain | Period Day | Treatment | Statistic | Baseline | Score | Change from baseline |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| NAB Mazes | 7 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 43.6 (8.11) | 46.0 (6.41) | 2.5 (5.76) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 45.0 (8.12) | 48.8 (7.76) | 3.8 (9.10) |
| | | AQW051 15MG | n | 22 | 22 | 22 |
| | | | Mean (SD) | 44.0 (7.11) | 45.7 (7.59) | 1.8 (7.02) |
| | 10 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 43.6 (8.11) | 49.9 (9.48) | 6.3 (6.87) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 45.0 (8.12) | 50.3 (8.17) | 5.2 (8.45) |
| | | AQW051 15MG | n | 22 | 22 | 22 |
| | | | Mean (SD) | 44.0 (7.11) | 47.5 (7.68) | 3.5 (6.45) |
| BVMT-Revised | 7 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 31.6 (13.88) | 35.3 (14.63) | 3.7 (9.23) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 30.7 (15.56) | 34.0 (13.26) | 3.3 (9.81) |
| | | AQW051 15MG | n | 22 | 22 | 22 |
| | | | Mean (SD) | 31.4 (15.44) | 34.3 (13.80) | 3.0 (9.29) |
| | 10 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 31.6 (13.88) | 34.1 (17.87) | 2.5 (10.04) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 30.7 (15.56) | 30.5 (18.10) | -0.2 (13.91) |
| | | AQW051 15MG | n | 22 | 22 | 22 |
| | | | Mean (SD) | 31.4 (15.44) | 31.8 (15.39) | 0.4 (9.80) |
| Category Fluency - Animals | 7 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 43.6 (7.84) | 44.1 (8.28) | 0.5 (6.16) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 44.0 (9.28) | 47.4 (10.35) | 3.4 (7.07) |
| | | AQW051 15MG | n | 22 | 22 | 22 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | Mean (SD) | 42.5 (8.37) | 46.8 (9.49) | 4.3 (10.09) |
| | 10 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 43.6 (7.84) | 46.0 (9.26) | 2.4 (6.60) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 44.0 (9.28) | 46.4 (8.91) | 2.4 (8.94) |
| | | AQW051 15MG | n | 22 | 22 | 22 |
| | | | Mean (SD) | 42.5 (8.37) | 46.3 (9.99) | 3.7 (9.45) |
| CPT-IP | 7 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 36.3 (11.70) | 36.5 (11.53) | 0.2 (6.61) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 35.8 (13.49) | 39.0 (12.17) | 3.2 (7.92) |
| | | AQW051 15MG | n | 22 | 22 | 22 |
| | | | Mean (SD) | 36.4 (14.04) | 36.4 (13.62) | 0.0 (7.54) |
| | 10 | PLACEBO | n | 20 | 20 | 20 |
| | | | Mean (SD) | 36.3 (11.70) | 36.7 (15.23) | 0.4 (9.37) |
| | | AQW051 2MG | n | 21 | 21 | 21 |
| | | | Mean (SD) | 35.8 (13.49) | 38.9 (12.90) | 3.1 (10.61) |
| | | AQW051 15MG | n | 22 | 22 | 22 |
| | | | Mean (SD) | 36.4 (14.04) | 36.7 (13.99) | 0.3 (5.83) |

## Correlation of the cognitive domains measured by MCCB versus CogState in patients with chronic stable schizophrenia

### Correlation between CogState and MCCB scales at baseline period 1 - Part A + B (PD analysis set)

| Domain | Tests | Correlation Coefficient | p-value |
|---|---|---|---|
| Verbal learning | HVLT-Revised vs. ISLT | 0.528 | <.0001 |
| Visual learning | BVMT-Revised vs. One Card Learning Task | 0.634 | 0.0004 |

| | | | |
|---|---|---|---|
| Working memory | U. Maryland - Letter-Number Span vs. One-back Memory | 0.469 | 0.0002 |
| Social cognition | MSCEIT - Total Score vs. SECT | 0.092 | 0.4950 |
| Visual learning and Memory | BVMT-Revised vs. CPAL | -0.512 | <.0001 |
| Speed of Processing | Category Fluency - Animals vs. Detection Task | -0.256 | 0.0541 |
| | BACS Symbol Coding vs. Detection Task | -0.371 | 0.0045 |
| | Trail Making Test vs. Detection Task | -0.366 | 0.0052 |
| Reasoning and Problem Solving | NAB Mazes vs. GMLT | 0.160 | 0.2333 |
| Attention/vigilance | CPT-IP vs. Identification | -0.395 | 0.0024 |

* Pearson correlation coefficient

## Pharmacokinetics of AQW051 in patients with schizophrenia

## Part A

### Mean (plus/minus SD) pharmacokinetic parameters of AQW051 in patients with schizophrenia (N = 32 for Day 1 and 7 or 8 for Day 9)

| **Dose** | | **2 mg** | | **15 mg** | **100 mg** | **50 mg** |
|---|---|---|---|---|---|---|
| **Day** | **Day 1** | **Day 9** | **Day 1** | **Day 9** | **Day 1** | **Day 9** |
| Tmax[1] [h] | 8.5 (2.5 – 12.1) | 4.5 (4.5 – 12.0) | 4.6 (2.5 – 28) | 4.5 (4.5 – 8.5) | 4.5 (2.5 – 12.0) | 4.5 (2.5 – 8.5) |
| Cmax [ng/mL] | 0.591 (0.236) | 0.958 (0.211) | 5.35 (1.47) | 10.6 (3.15) | 38.2 (10.7) | 32.8 (5.6) |
| AUC0-24h [ng*h/mL] | 9.35 (3.42) | 17.0 (4.82) | 83.0 (23.0) | 190 (55.8) | 552 (140) | 540 (114) |

| | | | | | | |
|---|---|---|---|---|---|---|
| AUClast [ng*h/mL] | 11.8 (4.28) | 20.9 (6.09) | 102 (27.3) | 235 (72.5) | 666 (175) | 648 (142) |

[1] Tmax reported in median (min – max)

**Part B**

**Comparison of mean (plus/minus SD) C8.5h [ng/mL] between Parts A and B**

| **Dose** | **2 mg** | | **15 mg** | |
|---|---|---|---|---|
| Day | Day 1 | Day 7/9 | Day 1 | Day 7/9 |
| Part A | 0.505 (0.181) | 0.883 (0.176) | 4.58 (1.36) | 9.61 (3.08) |
| Part B | 0.694 (0.317) | 1.29 (0.612) | 5.57 (2.00) | 9.79 (4.71) |

## Summaryof Safety

## Safety Results

### Adverse Events by System Organ Class

**Subjects with adverse events by body system - Periods 1 to 3 - Part A (Safety analysis set)**

| **Body system** | **Placebo N=25 n (%)** | **AQW051 2MG N=25 n (%)** | **AQW051 15 mg N=23 n (%)** | **AQW051 100 mg N=24 n (%)** | **Total N=33 n (%)** |
|---|---|---|---|---|---|
| Any Body System | 5 (20.0) | 3 (12.0) | 3 (13.0) | 2 (8.3) | 10 (30.3) |
| Cardiac disorders | 0 | 1 (4.0%) | 0 | 0 | 1 (3.0%) |
| Gastrointestinal disorders | 0 | 1 (4.0%) | 0 | 0 | 1 (3.0%) |
| General disorders and administration site conditions | 1 (4.0%) | 0 | 0 | 1 (4.2%) | 2 (6.1%) |

| Body system | Placebo N=25 n (%) | AQW051 2MG N=25 n (%) | AQW051 15 mg N=23 n (%) | AQW051 100 mg N=24 n (%) | Total N=33 n (%) |
|---|---|---|---|---|---|
| Metabolism and nutrition disorders | 1 (4.0%) | 0 | 0 | 0 | 1 (3.0%) |
| Musculoskeletal and connective tissue disorders | 2 (8.0%) | 0 | 0 | 0 | 2 (6.1%) |
| Nervous system disorders | 2 (8.0%) | 1 (4.0%) | 1 (4.3%) | 1 (4.2%) | 5 (15.2%) |
| Psychiatric disorders | 1 (4.0%) | 1 (4.0%) | 2 (8.7%) | 0 | 2 (6.1%) |
| Skin and subcutaneous tissue disorders | 1 (4.0%) | 0 | 0 | 0 | 1 (3.0%) |

Under one treatment,

A subject with multiple occurrences of an adverse event is counted only once in the AE category.

A subject with multiple adverse events within a body system is counted only once in the total row.

N = number of subjects studied n = number of subjects with at least one AE on the category

Only adverse events occurring at or after first drug intake are included

**Subjects with adverse events by body system - Part B (Safety analysis set)**

| Body system | Placebo N=23 n (%) | AQW051 2MG N=23 n (%) | AQW051 15 mg N=23 n (%) | Total N=24 n (%) |
|---|---|---|---|---|
| Any Body System | 6 (26.1%) | 11 (47.8%) | 9 (39.1%) | 14 (58.3%) |
| Eye disorders | 0 | 0 | 1 (4.3%) | 1 (4.2%) |
| Gastrointestinal disorders | 2 (8.7%) | 4 (17.4%) | 3 (13.0%) | 6 (25.0%) |

| | | | | |
|---|---|---|---|---|
| General disorders and administration site conditions | 0 | 0 | 1 (4.3%) | 1 (4.2%) |
| Infections and infestations | 1 (4.3%) | 0 | 0 | 1 (4.2%) |
| Injury, poisoning and procedural complications | 0 | 1 (4.3%) | 0 | 1 (4.2%) |
| Investigations | 0 | 1 (4.3%) | 0 | 1 (4.2%) |
| Musculoskeletal and connective tissue disorders | 1 (4.3%) | 1 (4.3%) | 3 (13.0%) | 4 (16.7%) |
| Nervous system disorders | 4 (17.4%) | 5 (21.7%) | 4 (17.4%) | 8 (33.3%) |
| Psychiatric disorders | 1 (4.3%) | 2 (8.7%) | 1 (4.3%) | 3 (12.5%) |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 (4.3%) | 0 | 1 (4.2%) |

Under one treatment,
A subject with multiple occurrences of an adverse event is counted only once in the AE category.
A subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied n = number of subjects with at least one AE on the category
Only adverse events occurring at or after first drug intake are included

**Subjects with adverse events by body system - Period 4 - Part A (Safety analysis set)**

| Body system | Placebo N=7 n (%) | AQW051 2MG N=7 n (%) | AQW051 15 mg N=9 n (%) | AQW051 100 mg N=8 n (%) | Total N=31 n (%) |
|---|---|---|---|---|---|
| Any Body System | 5 (71.4%) | 4 (57.1%) | 5 (55.6%) | 3 (37.5%) | 17 (54.8%) |
| Gastrointestinal disorders | 3 (42.9%) | 1 (14.3%) | 1 (11.1%) | 1 (12.5%) | 6 (19.4%) |
| General disorders and administration site conditions | 1 (14.3%) | 0 | 0 | 0 | 1 (3.2%) |
| Musculoskeletal and connective tissue disorders | 1 (14.3%) | 2 (28.6%) | 2 (22.2%) | 0 | 5 (16.1%) |
| Nervous system disorders | 1 (14.3%) | 2 (28.6%) | 5 (55.6%) | 1 (12.5%) | 9 (29.0%) |
| Psychiatric disorders | 3 (42.9%) | 2 (28.6%) | 1 (11.1%) | 1 (12.5%) | 7 (22.6%) |

| Body system | Placebo N=7 n (%) | AQW051 2MG N=7 n (%) | AQW051 15 mg N=9 n (%) | AQW051 100 mg N=8 n (%) | Total N=31 n (%) |
|---|---|---|---|---|---|
| Reproductive system and breast disorders | 0 | 0 | 0 | 1 (12.5%) | 1 (3.2%) |
| Respiratory, thoracic and mediastinal disorders | 0 | 0 | 1 (11.1%) | 0 | 1 (3.2%) |
| Skin and subcutaneous tissue disorders | 0 | 0 | 1 (11.1%) | 0 | 1 (3.2%) |
| Vascular disorders | 1 (14.3%) | 0 | 0 | 1 (12.5%) | 2 (6.5%) |

In the multiple dose period, patients randomized to the 100mg AQW051 dose switched to the 50mg AQW051 dose.
Under one treatment,
A subject with multiple occurrences of an adverse event is counted only once in the AE category.
A subject with multiple adverse events within a body system is counted only once in the total row.
N = number of subjects studied n = number of subjects with at least one AE on the category
Only adverse events occurring at or after first drug intake are included

**Adverse events overall and most frequent events - n (%) of patients - Periods 1 to 3 - Part A (Safety analysis set)**

| | Placebo N=25 n (%) | AQW051 2MG N=25 n (%) | AQW051 15 mg N=23 n (%) | AQW051 100 mg N=24 n (%) | Total N=33 n (%) |
|---|---|---|---|---|---|
| Patients with AE(s) | 5 (20.0) | 3 (12.0) | 3 (13.0) | 2 (8.3) | 10 (30.3) |
| Headache | 0 | 1 (4.0) | 1 (4.3) | 0 | 2 (6.1) |
| Insomnia | 0 | 0 | 2 (8.7) | 0 | 2 (6.1) |
| Somnolence | 1 (4.0) | 0 | 0 | 1 (4.2) | 2 (6.1) |
| Abnormal dreams | 1 (4.0) | 0 | 0 | 0 | 1 (3.0) |
| Arthralgia | 1 (4.0) | 0 | 0 | 0 | 1 (3.0) |
| Back pain | 1 (4.0) | 0 | 0 | 0 | 1 (3.0) |
| Burning sensation | 1 (4.0) | 0 | 0 | 0 | 1 (3.0) |
| Constipation | 0 | 1 (4.0) | 0 | 0 | 1 (3.0) |

| | Placebo N=25 n (%) | AQW051 2MG N=25 n (%) | AQW051 15 mg N=23 n (%) | AQW051 100 mg N=24 n (%) | Total N=33 n (%) |
|---|---|---|---|---|---|
| Energy increased | 1 (4.0) | 0 | 0 | 0 | 1 (3.0) |
| Fatigue | 0 | 0 | 0 | 1 (4.2) | 1 (3.0) |
| Increased appetite | 1 (4.0) | 0 | 0 | 0 | 1 (3.0) |
| Palpitations | 0 | 1 (4.0) | 0 | 0 | 1 (3.0) |
| Psychotic disorder | 0 | 1 (4.0) | 0 | 0 | 1 (3.0) |
| Rash | 1 (4.0) | 0 | 0 | 0 | 1 (3.0) |

Arranged by frequency in the total column

**Adverse events overall and most frequent events - n (%) of patients – Period 4 - Part A (Safety analysis set)**

| | Placebo N=7 n (%) | AQW051 2 mg N=7 n (%) | AQW051 15 mg N=9 n (%) | AQW051 100 mg N=8 n (%) | Total N=31 n (%) |
|---|---|---|---|---|---|
| Patients with AE(s) | 5 (71.4) | 4 (57.1) | 5 (55.6) | 3 (37.5) | 17 (54.8) |
| Headache | 1 (14.3) | 1 (14.3) | 4 (44.4) | 1 (12.5) | 7 (22.6) |
| Abnormal dreams | 0 | 1 (14.3) | 1 (11.1) | 1 (12.5) | 3 (9.7) |
| Constipation | 1 (14.3) | 1 (14.3) | 0 | 1 (12.5) | 3 (9.7) |
| Anxiety | 1 (14.3) | 1 (14.3) | 0 | 0 | 2 (6.5) |
| Back pain | 0 | 1 (14.3) | 1 (11.1) | 0 | 2 (6.5) |
| Toothache | 2 (28.6) | 0 | 0 | 0 | 2 (6.5) |
| Abdominal pain upper | 0 | 0 | 1 (11.1) | 0 | 1 (3.2) |
| Arthralgia | 0 | 0 | 1 (11.1) | 0 | 1 (3.2) |
| Confusional state | 1 (14.3) | 0 | | 0 | 1 (3.2) |
| Dermatitis | 0 | 0 | 1 (11.1) | 0 | 1 (3.2) |
| Dry mouth | 1 (14.3) | 0 | 0 | 0 | 1 (3.2) |
| Dysmenorrhoea | 0 | 0 | 0 | 1 (12.5) | 1 (3.2) |

| | Placebo N=7 n (%) | AQW051 2 mg N=7 n (%) | AQW051 15 mg N=9 n (%) | AQW051 100 mg N=8 n (%) | Total N=31 n (%) |
|---|---|---|---|---|---|
| Haemorrhoids | 0 | 1 (14.3) | 0 | 0 | 1 (3.2) |
| Hypertension | 1 (14.3) | 0 | 0 | 0 | 1 (3.2) |
| Hypotension | 0 | 0 | 0 | 1 (12.5) | 1 (3.2) |
| Insomnia | 1 (14.3) | 0 | 0 | 0 | 1 (3.2) |
| Irritability | 1 (14.3) | 0 | 0 | 0 | 1 (3.2) |
| Muscular weakness | 1 (14.3) | 0 | 0 | 0 | 1 (3.2) |
| Musculoskeletal pain | 0 | 1 (14.3) | 0 | 0 | 1 (3.2) |
| Nasal congestion | 0 | 0 | 1 (11.1) | 0 | 1 (3.2) |
| Oropharyngeal pain | 0 | 0 | 1 (11.1) | 0 | 1 (3.2) |
| Sedation | 0 | 1 (14.3) | 0 | 0 | 1 (3.2) |
| Somnolence | 0 | 0 | 1 (11.1) | 0 | 1 (3.2) |

In the multiple dose period, patients randomized to the 100 mg AQW051 dose switched to the 50 mg AQW051 dose

Arranged by frequency in the total column

**Adverse events overall and most frequent events - n (%) of patients - Part B (Safety analysis set)**

| | Placebo N=23 n (%) | AQW051 2 mg N=23 n (%) | AQW051 15 mg N=23 n (%) | Total N=24 n (%) |
|---|---|---|---|---|
| Patients with AE(s) | 6 (26.1) | 11 (47.8) | 9 (39.1) | 14 (58.3) |
| Headache | 3 (13.0) | 2 (8.7) | 3 (13.0) | 5 (20.8) |
| Somnolence | 1 (4.3) | 4 (17.4) | 2 (8.7) | 5 (20.8) |
| Insomnia | 0 | 2 (8.7) | 1 (4.3) | 3 (12.5) |
| Toothache | 0 | 2 (8.7) | 1 (4.3) | 3 (12.5) |
| Constipation | 1 (4.3) | 2 (8.7) | 1 (4.3) | 2 (8.3) |
| Abdominal pain | 0 | 0 | 1 (4.3) | 1 (4.2) |
| Abnormal sensation in eye | 0 | 0 | 1 (4.3) | 1 (4.2) |

| | Placebo N=23 n (%) | AQW051 2 mg N=23 n (%) | AQW051 15 mg N=23 n (%) | Total N=24 n (%) |
|---|---|---|---|---|
| Alanine aminotransferase increased | 0 | 1 (4.3) | 0 | 1 (4.2) |
| Back pain | 1 (4.3) | 0 | 1 (4.3) | 1 (4.2) |
| Bone pain | 0 | 0 | 1 (4.3) | 1 (4.2) |
| Dizziness | 0 | 0 | 1 (4.3) | 1 (4.2) |
| Dyspepsia | 0 | 0 | 1 (4.3) | 1 (4.2) |
| Gastrooesophageal reflux disease | 1 (4.3) | 0 | 0 | 1 (4.2) |
| Infected sebaceous cyst | 1 (4.3) | 0 | 0 | 1 (4.2) |
| Muscle tightness | 0 | 0 | 1 (4.3) | 1 (4.2) |
| Musculoskeletal chest pain | 0 | 0 | 1 (4.3) | 1 (4.2) |
| Myalgia | 0 | 0 | 1 (4.3) | 1 (4.2) |
| Neck pain | 0 | 1 (4.3) | 0 | 1 (4.2) |
| Oropharyngeal pain | 0 | 1 (4.3) | 0 | 1 (4.2) |
| Pain | 0 | | 1 (4.3) | 1 (4.2) |
| Pain in extremity | 0 | 1 (4.3) | 0 | 1 (4.2) |
| Psychotic disorder | 1 (4.3) | 0 | 0 | 1 (4.2) |
| Tooth fracture | 0 | 1 (4.3) | 0 | 1 (4.2) |

Arranged by frequency in the total column

## Serious Adverse Events and Deaths

There were no deaths reported in this study. One serious adverse event (psychotic disorder) was reported in Part B of the study.

**Serious Adverse Events and Deaths - n (%) of patients - Periods 1 to 3 - Part A (Safety analysis set)**

| | Placebo n (%) | AQW051 2 mg n (%) | AQW051 15 mg n (%) | AQW051 100 mg n (%) | Total n (%) |
|---|---|---|---|---|---|
| No. (%) of subjects studied | 7 | 7 | 9 | 8 | 31 |
| No. (%) of subjects with AE(s) | 5 (20.0) | 3 (12.0) | 3 (13.0) | 2 (8.3) | 10 (30.3) |

| | Placebo n (%) | AQW051 2 mg n (%) | AQW051 15 mg n (%) | AQW051 100 mg n (%) | Total n (%) |
|---|---|---|---|---|---|
| Number (%) of subjects with serious or other significant events | | | | | |
| Death | 0 | 0 | 0 | 0 | 0 |
| SAE(s) | 0 | 0 | 0 | 0 | 0 |
| Discontinued due to SAE(s) | 0 | 0 | 0 | 0 | 0 |

**Serious Adverse Events and Deaths - n (%) of patients – Period 4 - Part A (Safety analysis set)**

| | Placebo n (%) | AQW051 2 mg n (%) | AQW051 15 mg n (%) | AQW051 100 mg n (%) | Total n (%) |
|---|---|---|---|---|---|
| No. (%) of subjects studied | 7 | 7 | 9 | 8 | 31 |
| No. (%) of subjects with AE(s) | 5 (71.4) | 4 (57.1) | 5 (55.6) | 3 (37.5) | 17 (54.8) |
| Number (%) of subjects with serious or other significant events | | | | | |
| Death | 0 | 0 | 0 | 0 | 0 |
| SAE(s) | 0 | 0 | 0 | 0 | 0 |
| Discontinued due to SAE(s) | 0 | 0 | 0 | 0 | 0 |

**Serious Adverse Events and Deaths - n (%) of patients – Part B (Safety analysis set)**

| | Placebo n (%) | AQW051 2 mg n (%) | AQW051 15 mg n (%) | Total n (%) |
|---|---|---|---|---|
| No. (%) of subjects studied | 23 | 23 | 23 | 24 |
| No. (%) of subjects with AE(s) | 6 (26.1) | 11 (47.8) | 9 (39.1) | 14 (58.3) |
| Number (%) of subjects with serious or other significant events | | | | |
| Death | 0 | 0 | 0 | 0 |
| SAE(s) | 1 (4.3) | 0 | 0 | 1 (4.2) |
| Discontinued due to SAE(s) | 0 | 0 | 0 | 0 |

## OtherRelevantFindings

None

## Conclusion

AQW051 was both safe and well-tolerated in schizophrenia patients, confirming data already obtained with healthy volunteers and Alzheimer disease patients. The analysis in a representative chronic schizophrenic population (Part A) of the CPAL measurement, suggested that AQW051 had a moderate effect on cognition. There was no clear dose-response effect. While GMLT scores showed no difference between AQW051-treated and placebo-treated patients, a trend towards efficacy in a secondary cognitive endpoint, the MCCB-NAB maze test was also observed.

The benefit-risk profile of AQW051 remains favorable and supports further studies of AQW051 in CIAS.

## Date of Clinical Trial Report

04-May-2012

## Date of Initial Inclusion on Novartis Clinical Trial Results website

05 Sep 2014