NovartisClinicalTrialResultsTemplate

Sponsor:

Novartis

Generic Drug Name:

Not applicable

Trial Indication:

Cognitive Impairment Associated with Schizophrenia

Protocol Number:

CAQW051A2207

Protocol Title

A 12 week, randomized, double-blind, placebo-controlled, parallel group study to evaluate the effects of once daily doses of AQW051 on cognition, in stable schizophrenia patients

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

25-Sep-2012 (first patient first visit) to 12-Dec-2013 (last patient last visit)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a non-confirmatory study. The study was a 12-week, parallel-group, randomized, double-blind, placebo-controlled, study, of once daily doses of AQW051, for the treatment of cognitive impairment associated with schizophrenia (CIAS). The study consisted of a 28-day screening period, a baseline period, and 12 weeks treatment period followed by a Study Completion evaluation approximately two weeks after the last drug administration.

A total of 147 patients were randomized to AQW051/placebo 10 mg/day (once daily oral doses) in a 1:1 ratio. All groups received daily oral doses of either placebo or active medication during the treatment period. Patients who met the eligibility criteria at screening attended the baseline evaluations (Day -1) and those who met the eligibility criteria at baseline were randomized. On the morning of Day 1 study drug was administered at the study site to the randomized patients. After the dose was administered, scheduled assessments were performed for up to 12 hours, and thereafter the patients were free to leave the site after all assessments were completed to continue the study as an outpatient. Patients were given study drug to take at home and continued to take the study drug as instructed by the investigator before returning to the study site at least 1 hour prior to dosing on the mornings of Day 14, 28, 56 and 84 (+/- 2 days). Patients were contacted by the site at regular intervals to enquire their wellbeing and to assess the need to visit in between study visits.

Centers

Fifteen centers in one country: United States of America

Publication

None

Objectives:

Primary objective:

- To evaluate the effects of once daily doses of 10 mg AQW051 *versus* placebo on visual learning and memory after 4 weeks of treatment as measured by the selected CogState test Continuous Paired Associate Learning Task (CPAL).

Secondary objectives:

- To determine the effects of once daily doses of 10 mg AQW051 *versus* placebo on cognitive function after 12 weeks of treatment, as measured by CogState Schizophrenia Cognitive Test Battery (composite and individual cognitive domains)
- To determine the effects of once daily doses of 10 mg AQW051 *versus* placebo on cognitive function after 12 weeks of treatment, as measured by MATRICS Consensus Cognitive Battery (MCCB) (composite and individual cognitive domains)
- To determine tolerability and safety after 12 weeks of treatment of once daily doses of 10 mg AQW051 in patients with chronic stable schizophrenia.

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

Once daily oral doses of 10 mg AQW051 or placebo for 12 weeks

Statistical Methods

Analysis of the primary variable: The primary pharmacodynamic (PD) variable was Continuous Paired Associate Learning Task (CPAL) test after 4 weeks of once daily doses of 10 mg AQW051 versus placebo.

Statistical hypothesis, model, and method of analysis

The analysis was performed on the primary pharmacodynamics analysis set, which included all patients and visits without major protocol deviations. The absolute change from baseline in CPAL (number of errors) was analyzed using a mixed model for repeated measures, including baseline value as covariate, treatment (AQW051 or Placebo) and time-point(visit/time), the treatment*time-point interaction term as fixed effects, and patient as random effect. The contrast in treatment effect at Week 4 was estimated and the null hypothesis of no difference was tested at the one-sided 10% level of significance. The magnitude of the treatment effect at Week 4 was also assessed by calculating the 'effect size', defined as the difference between the adjusted means (estimated using the model above) at Week 4 (placebo minus AQW051 – so that the effect size is positive when AQW051 is better than placebo) divided by the pooled standard deviation. The confidence interval of the effect size was estimated by dividing the upper and lower confidence interval of the adjusted means by the pooled standard deviation. Additionally, in order to assess the clinical relevance of the results, the Bayesian probability that AQW051 is superior to placebo and the Bayesian probability that the effect size at Week 4 is at least 0.30 (minimal clinical relevant effect size) would be calculated, assuming non informative priors. If:

- the Bayesian posterior probability that AQW051 is superior to placebo is at least 90% and
- the Bayesian posterior probability that the effect size is at least 0.30 is at least 50% then this would contribute to the evidence of a positive signal of efficacy.

Supportive analysis: In order to assess the robustness of the results, the primary analysis of CPAL was repeated on the secondary PD analysis set, which included all patients and visits.

Analysis of secondary variables:

Secondary pharmacodynamic variables: Included assessment of effects of once daily doses of 10 mg AQW051 versus placebo on cognitive function after 12 weeks of treatment, as measured by:

- CogState Schizophrenia Cognitive Test Battery, 3 composites (Memory, Psychomotor/Attention and Overall), and individual cognitive domains with following cognitive tasks:

- Groton Maze Learning Task (GMLT), Identification (IDN), Detection Task (DET), One Card Learning Task (OCL), One-back Memory (OBN), Social Emotional Cognition Task (SECT) and International Shopping List Task (ISLT)

- MCCB, overall composite and individual cognitive domains:
  - Speed of processing, Attention/Vigilance, Working memory (nonverbal), Working memory (verbal), Verbal learning, Visual learning, Reasoning and problem solving and Social cognition

For Cogstate and MCCB, the change from baseline was analyzed using a mixed model for repeated measures, including baseline value as covariate, time (time-point), treatment as fixed effects and treatment*time interaction term and patient as random effect. Appropriate contrasts were used to compare treatments at each time-point.

Safety: Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of hematology, blood chemistry and urine performed at (study center/central laboratory/local laboratory only for hemoglobin analysis) and regular assessments of vital signs, physical condition and body weight. Additional to the standard safety evaluations included insulin, hemoglobin A1c (HbA1c), C-reactive protein (CRP) laboratory assessments, prospective suicidality assessment (C-SSRS) and Simpson-Angus Extrapyramidal Symptom rating scale Simpson-Angus Extrapyramidal Symptom rating scale (SAS).

Safety data were considered as secondary endpoint of this trial. Descriptive summaries of safety data by treatment were produced, which included boxplots to visualize trends in longitudinal safety data (vital signs, ECG, lab parameters). All vital signs, ECG and clinical laboratory evaluations data were listed by treatment, patient, and visit/time and if ranges were available, abnormalities (and relevant orthostatic changes) were flagged. Summary statistics were provided by treatment and visit/time. All information obtained on adverse events was displayed by treatment and patient. The number and percentage of patients with adverse events were tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple adverse events within a body system was only counted once towards the total of this body system.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male and female patients 18 to 55 years of age (inclusive), weighing at least 50 kg
- Diagnosed with schizophrenia, symptomatically stable and not suffering from an acute exacerbation of their psychosis.
- Patients were being treated with a stable regimen 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 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.
- The following cognitive performance criteria:
  - Maximum performance level: At least 25 errors on CPAL on each of the three CogState practice sessions at screening, and at baseline. If one or more of the three sessions was performed with fewer than 25 errors, the subject was not eligible.
  - Minimum performance level: patient was able to perform and complete the CogState practice sessions
  - Wechsler Test of Adult Reading (WTAR): at least 5th grade reading level assessment

Exclusion criteria

- At the time of eligibility assessment, patients receiving anticholinergic or other agent known to significantly adversely interfere with the cholinergic system
- At the time of eligibility assessment, patients receiving conventional antipsychotics (e.g. fluphenazine, haloperidol) or clozapine
- Patients with an history of neuroleptic malignant syndrome
- Patients with diagnosis of substance abuse, alcohol or substance dependence (other than nicotine) assessed by Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV).
- Medical or neurological disorder or treatment for such disorder that could interfere with the study medication or assessment of the patient.
- Score 4 or 5 on the Suicidal Ideation item or any “yes” on the Suicidal Behavior item of the Columbia-Suicide Severity Rating Scale (CSSR-S) that was related to suicidal behavior occurred during the last 2 years.
- A history of significant head injury/trauma:
- Use of concomitant medication that are strong inhibitors of CYP3A4 and CYP1A2
- Pregnant or nursing (lactating) women or women of child-bearing potential

Participant Flow Table

Patient disposition (full analysis set)

	AQW051A 10mg N=74	Placebo N=73	Total N=147

	AQW051A 10mg N=74	Placebo N=73	Total N=147
Completed	54 (73.0%)	58 (79.5%)	112 (76.2%)
Discontinued	20 (27.0%)	15 (20.5%)	35 (23.8%)
Adverse Event(s)	3 (4.1%)	3 (4.1%)	6 (4.1%)
Lost to follow-up	9 (12.2%)	2 (2.7%)	11 (7.5%)
Protocol deviation	2 (2.7%)	4 (5.5%)	6 (4.1%)
Patient withdrew consent	6 (8.1%)	4 (5.5%)	10 (6.8%)
Administrative problems	0	1 (1.4%)	1 (0.7%)
Death	0	1 (1.4%)	1 (0.7%)

Baseline Characteristics

Demographic summary and baseline characteristics - Safety analysis set

		AQW051A 10mg N=74	Placebo N=73	Total N=147
Age (years)	Mean (SD)	46.6 (7.4)	44.4 (7.6)	45.5 (7.5)
	Median	48.0	46.0	48.0
	Range	22 - 55	25 - 55	22 - 55
Gender – n (%)	Male	49 (66%)	45 (62%)	94 (64%)
	Female	25 (34%)	28 (38%)	53 (36%)
Predominant race – n (%)	Caucasian	10 (14%)	9 (12%)	19 (13%)
	Black	59 (80%)	59 (81%)	118 (80%)
	Asian	2 (3%)	2 (3%)	4 (3%)
	Native American	1 (1%)		1 (1%)
	Other	2 (3%)	3 (4%)	5 (3%)
Ethnicity – n (%)	Other	62 (84%)	61 (84%)	123 (84%)
		2 (3%)		2 (1%)
	Hispanic/Latino	3 (4%)	6 (8%)	9 (6%)

		AQW051A 10mg N=74	Placebo N=73	Total N=147
	Chinese	1 (1%)		1 (1%)
	Mixed Ethnicity	6 (8%)	6 (8%)	12 (8%)
Weight (kg)	Mean (SD)	96.8 (18.1)	90.6 (18.7)	93.7 (18.6)
	Median	98.1	92.5	94.6
	Range	58 - 136	56 - 138	56 - 138
Height (cm)	Mean (SD)	173.2 (9.3)	173.7 (8.1)	173.5 (8.7)
	Median	172.3	173.0	173.0
	Range	155 - 198	155 - 190	155 - 198
BMI (kg/m^2)	Mean (SD)	32.4 (6.5)	30.1 (6.3)	31.3 (6.5)
	Median	32.9	29.8	31.5
	Range	20 - 49	18 - 46	18 - 49
Formal education (years)	Mean (SD)	11.9 (1.9)	11.9 (2.3)	11.9 (2.1)
	Median	12.0	12.0	12.0
	Range	7 - 18	6 - 18	6 - 18
Smoking history	Never smoked	14 (19%)	6 (8%)	20 (14%)
	Ex-smoker	5 (7%)	9 (12%)	14 (10%)
	Current smoker	55 (74%)	58 (79%)	113 (77%)

BMI = body mass index

Summaryof Efficacy

Primary Outcome Results

Effect of once daily doses 10 mg AQW051 versus placebo on visual learning and memory after 4 weeks of treatment:

Inference for change from baseline in CPAL at Week 4 (PD analysis set)

			Comparison versus Placebo				
			Mean difference			_Effect size_	
Treatment	**Mean**	**Standard Error**	**Estimate**	**(80% CI)**	**P-value**	**Estimate**	**(80% CI)**
AQW051	−16.244	6.309	0.070	(−10.94, 11.08)	0.503	−0.002	(−0.25, 0.24)
Placebo	−16.314	5.810					

A positive effect size denotes an improvement on active *versus* placebo.

Bayesian inference for effect size on CPAL change at Week 4 (PD analysis set)

	Comparison *versus* Placebo
Treatment	Probability effect size is at least 0.3
AQW051A	0.0598

A positive effect size denotes an improvement on active *versus* placebo.

Secondary Outcome Results

CogState Schizophrenia Cognitive Test Battery (composites and individual cognitive domains):

- **Cogstate overall composite after 12 weeks**

Inference for overall composite change from baseline in CogState at Week 12 (PD analysis set)

				Comparison *versus* Placebo _Mean difference_			_Effect size_	
CogState domain	**Treatment**	**Mean**	**Standard Error**	**Estimate**	**(80% CI)**	**P-value**	**Estimate**	**(80% CI)**
Overall composite	AQW051	0.264	0.093	−0.072	(−0.23, 0.09)	0.720	−0.119	(−0.38, 0.14)
	Placebo	0.336	0.082					

A positive effect size denotes an improvement on active *versus* placebo.

- **Cogstate individual cognitive domains and composites after 12 weeks**

Inference for overall composite change from baseline in CogState at Week 12 (PD analysis set)

				Comparison *versus* Placebo _Mean difference_			_Effect size_	
CogState domain	**Treatment**	**Mean**	**Standard Error**	**Estimate**	**(80% CI)**	**P-value**	**Estimate**	**(80% CI)**
Visual learning	AQW051	0.067	0.017	0.013	(−0.02, 0.04)	0.289	0.114	(−0.15, 0.38)
	Placebo	0.054	0.015					
Working memory	AQW051	0.038	0.029	−0.033	(−0.08, 0.02)	0.804	−0.175	(−0.44, 0.09)
	Placebo	0.071	0.025					
Verbal learning	AQW051	0.661	0.591	−0.148	(−1.16, 0.86)	0.575	−0.039	(−0.30, 0.22)
	Placebo	0.809	0.514					
Memory composite	AQW051	0.339	0.113	−0.044	(−0.24, 0.15)	0.617	−0.061	(−0.32, 0.20)
	Placebo	0.383	0.098					
Speed of processing	AQW051	−0.017	0.015	0.015	(−0.01, 0.04)	0.782	−0.160	(−0.42, 0.10)
	Placebo	−0.032	0.013					
Attention/vigilance	AQW051	−0.010	0.011	−0.019	(−0.04, −0.00)	0.096	0.268	(0.01, 0.53)

				Comparison *versus* Placebo				
				Mean difference			_Effect size_	
CogState domain	**Treatment**	**Mean**	**Standard Error**	**Estimate**	**(80% CI)**	**P-value**	**Estimate**	**(80% CI)**
	Placebo	0.009	0.010					
Psych/Att. Composite	AQW051	0.115	0.100	0.021	(−0.15, 0.19)	0.438	0.032	(−0.23, 0.29)
	Placebo	0.094	0.087					
Reasoning and problem solving	AQW051	−0.309	5.243	8.625	(−0.29, 17.54)	0.892	−0.263	(−0.53, 0.01)
	Placebo	−8.934	4.519					
Social cognition	AQW051	0.070	0.021	0.043	(0.01, 0.08)	0.060	0.317	(0.06, 0.58)
	Placebo	0.027	0.018					

A positive effect size denotes an improvement on active *versus* placebo.

MCCB (Overall composite and individual cognitive domains)

- **MCCB overall composite (T-Score) after 12 weeks**

Inference for overall composite change from baseline in MCCB at Week 12 (PD analysis set)

				Comparison *versus* Placebo				
				Mean difference			_Effect size_	
MCCB domain	**Treatment**	**Mean**	**Standard Error**	**Estimate**	**(80% CI)**	**P-value**	**Estimate**	**(80% CI)**
Overall composite	AQW051	5.549	0.811	−0.742	(−2.12, 0.63)	0.755	−0.148	(−0.42, 0.13)
	Placebo	6.291	0.699					

A positive effect size denotes an improvement on active *versus* placebo.

- **MCCB individual cognitive domains (T-Scores) after 12 weeks**

Inference for change from baseline in Matrics Consensus Cognitive Battery (MCCB) at Week 12 (PD analysis set)

				Comparison *versus* Placebo				
				Mean difference			_Effect size_	
MCCB domain	**Treatment**	**Mean**	**Standard Error**	**Estimate**	**(80% CI)**	**P-value**	**Estimate**	**(80% CI)**
Visual learning	AQW051	4.587	1.309	0.928	(−1.30, 3.16)	0.297	0.110	(−0.15, 0.37)
	Placebo	3.659	1.142					
Working memory	AQW051	3.231	0.914	0.162	(−1.39, 1.72)	0.447	0.027	(−0.24, 0.29)
	Placebo	3.069	0.793					
Verbal learning	AQW051	2.339	0.816	0.343	(−1.03, 1.72)	0.375	0.066	(−0.20, 0.33)
	Placebo	1.996	0.693					
Speed of processing	AQW051	5.539	0.918	−2.499	(−4.06, −0.93)	0.979	−0.421	(−0.69, −0.16)
	Placebo	8.039	0.797					
Attention/vigilance	AQW051	3.033	1.317	−0.903	(−3.14, 1.34)	0.697	−0.110	(−0.38, 0.16)
	Placebo	3.935	1.140					
Reasoning and problem solving	AQW051	3.983	1.000	−1.349	(−3.04, 0.34)	0.847	−0.213	(−0.48, 0.05)
	Placebo	5.333	0.856					
Social cognition	AQW051	1.294	1.249	−0.339	(−2.46, 1.78)	0.581	−0.042	(−0.31, 0.22)
	Placebo	1.633	1.083					

A positive effect size denotes an improvement on active *versus* placebo

Summaryof Safety

Safety Results

Adverse Events by System Organ Class

Incidence of AEs by primary system organ class (Safety set)

	AQW051 10mg N=74 n (%)	**Placebo N=73 n (%)**	**Total N=147 n (%)**

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)
Patients with AE(s)	33 (44.6%)	33 (45.2%)	66 (44.9%)
Nervous system disorders	10 (13.5%)	10 (13.7%)	20 (13.6%)
Infections and infestations	10 (13.5%)	7 (9.6%)	17 (11.6%)
Gastrointestinal disorders	9 (12.2%)	7 (9.6%)	16 (10.9%)
Psychiatric disorders	5 (6.8%)	6 (8.2%)	11 (7.5%)
Musculoskeletal and connective tissue disorders	5 (6.8%)	5 (6.8%)	10 (6.8%)
Investigations	3 (4.1%)	4 (5.5%)	7 (4.8%)
Skin and subcutaneous tissue disorders	4 (5.4%)	2 (2.7%)	6 (4.1%)
Injury, poisoning and procedural complications	2 (2.7%)	4 (5.5%)	6 (4.1%)
Reproductive system and breast disorders	2 (2.7%)	2 (2.7%)	4 (2.7%)
Metabolism and nutrition disorders	1 (1.4%)	3 (4.1%)	4 (2.7%)
Vascular disorders	1 (1.4%)	2 (2.7%)	3 (2.0%)
General disorders and administration site conditions	1 (1.4%)	2 (2.7%)	3 (2.0%)
Renal and urinary disorders	1 (1.4%)	1 (1.4%)	2 (1.4%)
Ear and labyrinth disorders	2 (2.7%)	0	2 (1.4%)
Blood and lymphatic system disorders	2 (2.7%)	0	2 (1.4%)
Surgical and medical procedures	0	1 (1.4%)	1 (0.7%)
Immune system disorders	1 (1.4%)	0	1 (0.7%)

AEs by SOC are presented in descending order of frequency in the total group.

Incidence of AEs by preferred term - n (%) of patients (Safety analysis set)

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)
Patients with AE(s)	33 (44.6%)	33 (45.2%)	66 (44.9%)

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)
Nasopharyngitis	4 (5.4%)	2 (2.7%)	6 (4.1%)
Somnolence	3 (4.1%)	3 (4.1%)	6 (4.1%)
Upper respiratory tract infection	3 (4.1%)	1 (1.4%)	4 (2.7%)
Diarrhoea	2 (2.7%)	1 (1.4%)	3 (2.0%)
Dry mouth	2 (2.7%)	0	2 (1.4%)
Headache	2 (2.7%)	4 (5.5%)	6 (4.1%)
Leukocytosis	2 (2.7%)	0	2 (1.4%)
Pruritus	2 (2.7%)	0	2 (1.4%)
Tremor	2 (2.7%)	1 (1.4%)	3 (2.0%)
Abdominal hernia	1 (1.4%)	0	1 (0.7%)
Abdominal pain upper	1 (1.4%)	0	1 (0.7%)
Angioedema	1 (1.4%)	0	1 (0.7%)
Anxiety	1 (1.4%)	0	1 (0.7%)
Arthralgia	1 (1.4%)	1 (1.4%)	2 (1.4%)
Arthropod bite	1 (1.4%)	0	1 (0.7%)
Aspartate aminotransferase increased	1 (1.4%)	0	1 (0.7%)
Blood creatine phosphokinase increased	1 (1.4%)	0	1 (0.7%)
Constipation	1 (1.4%)	2 (2.7%)	3 (2.0%)
Dental caries	1 (1.4%)	0	1 (0.7%)
Drug hypersensitivity	1 (1.4%)	0	1 (0.7%)
Dysmenorrhoea	1 (1.4%)	0	1 (0.7%)
Dystonia	1 (1.4%)	0	1 (0.7%)
Ear haemorrhage	1 (1.4%)	0	1 (0.7%)
Electrocardiogram QT prolonged	1 (1.4%)	0	1 (0.7%)
External ear inflammation	1 (1.4%)	0	1 (0.7%)
Extrapyramidal disorder	1 (1.4%)	0	1 (0.7%)

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)
Fatigue	1 (1.4%)	1 (1.4%)	2 (1.4%)
Glycosuria	1 (1.4%)	1 (1.4%)	2 (1.4%)
Head injury	1 (1.4%)	0	1 (0.7%)
Hyperglycaemia	1 (1.4%)	0	1 (0.7%)
Hypersomnia	1 (1.4%)	0	1 (0.7%)
Hypertension	1 (1.4%)	2 (2.7%)	3 (2.0%)
Insomnia	1 (1.4%)	1 (1.4%)	2 (1.4%)
Menstruation irregular	1 (1.4%)	0	1 (0.7%)
Muscle rigidity	1 (1.4%)	1 (1.4%)	2 (1.4%)
Muscle twitching	1 (1.4%)	0	1 (0.7%)
Musculoskeletal pain	1 (1.4%)	0	1 (0.7%)
Nausea	1 (1.4%)	2 (2.7%)	3 (2.0%)
Neutrophilia	1 (1.4%)	0	1 (0.7%)
Pain in extremity	1 (1.4%)	0	1 (0.7%)
Pharyngitis	1 (1.4%)	0	1 (0.7%)
Psychotic disorder	1 (1.4%)	2 (2.7%)	3 (2.0%)
Rash	1 (1.4%)	1 (1.4%)	2 (1.4%)
Restlessness	1 (1.4%)	0	1 (0.7%)
Schizophrenia	1 (1.4%)	1 (1.4%)	2 (1.4%)
Tooth infection	1 (1.4%)	1 (1.4%)	2 (1.4%)
Vaginitis bacterial	1 (1.4%)	0	1 (0.7%)
Weight increased	1 (1.4%)	0	1 (0.7%)
Abdominal discomfort	0	1 (1.4%)	1 (0.7%)
Akathisia	0	1 (1.4%)	1 (0.7%)
Alanine aminotransferase increased	0	1 (1.4%)	1 (0.7%)
Back pain	0	1 (1.4%)	1 (0.7%)
Blood bilirubin increased	0	2 (2.7%)	2 (1.4%)

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)
Blood bilirubin unconjugated increased	0	1 (1.4%)	1 (0.7%)
Blood glucose increased	0	1 (1.4%)	1 (0.7%)
Bronchitis	0	1 (1.4%)	1 (0.7%)
Concussion	0	1 (1.4%)	1 (0.7%)
Contusion	0	1 (1.4%)	1 (0.7%)
Cyst	0	1 (1.4%)	1 (0.7%)
Decreased appetite	0	1 (1.4%)	1 (0.7%)
Disturbance in attention	0	1 (1.4%)	1 (0.7%)
Erectile dysfunction	0	1 (1.4%)	1 (0.7%)
Food poisoning	0	1 (1.4%)	1 (0.7%)
Gastrooesophageal reflux disease	0	1 (1.4%)	1 (0.7%)
Hallucination, visual	0	1 (1.4%)	1 (0.7%)
Hyperlipidaemia	0	1 (1.4%)	1 (0.7%)
Increased appetite	0	1 (1.4%)	1 (0.7%)
Laceration	0	1 (1.4%)	1 (0.7%)
Ligament sprain	0	1 (1.4%)	1 (0.7%)
Musculoskeletal stiffness	0	1 (1.4%)	1 (0.7%)
Myalgia	0	1 (1.4%)	1 (0.7%)
Nightmare	0	1 (1.4%)	1 (0.7%)
Photosensitivity reaction	0	1 (1.4%)	1 (0.7%)
Retrograde ejaculation	0	1 (1.4%)	1 (0.7%)
Sinusitis	0	1 (1.4%)	1 (0.7%)
Stab wound	0	1 (1.4%)	1 (0.7%)
Tooth extraction	0	1 (1.4%)	1 (0.7%)
Tooth fracture	0	1 (1.4%)	1 (0.7%)
Toothache	0	2 (2.7%)	2 (1.4%)
Urinary tract infection	0	1 (1.4%)	1 (0.7%)

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)
Vomiting	0	2 (2.7%)	2 (1.4%)

AEs by preferred terms are presented in descending order of frequency in total group.

Serious Adverse Events and Deaths

One death was reported during the study. One patient who was receiving placebo had multiple stab wound injuries at Day 55. The investigator considered the event to be serious in nature and did not suspect a causal relationship between the study drug (placebo) and the SAE.

Summary of adverse events n (%) of patients - (Safety analysis set)

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)
Total number of AE(s)	62	66	128
No. (%) of patients with AE(s)	33 (44.6)	33 (45.2)	66 (44.9)
AEs of grade 1	18 (24.3)	19 (26.0)	37 (25.2)
AEs of grade 2	11 (14.9)	11 (15.1)	22 (15.0)
AEs of grade 3	3 (4.1)	2 (2.7)	5 (3.4)
AEs of grade 4	1 (1.4)	0	1 (0.7)
AEs with missing grade	0	1 (1.4)	1 (0.7)
Number (%) of patients with serious adverse events	2 (2.7)	2 (2.7)	4 (2.7)
Death	0	1 (1.4)	1 (0.7)
SAE(s)	2 (2.7)	2 (2.7)	4 (2.7)
Discontinued due to SAE(s)	2 (2.7)	1 (1.4)	3 (2.3)

	AQW051 10mg N=74 n (%)	Placebo N=73 n (%)	Total N=147 n (%)

A serious adverse event (Stab wound) has a missing CTCAE Grade because Grade 5 couldn't be recorded in the database.

Under one treatment,

A patient experiencing multiple AEs of different severity is counted with the worst severity only.

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

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

OtherRelevantFindings

None

Conclusion

Visual learning and Memory as measured by the selected CogState test CPAL did not show clinically meaningful improvement from baseline compared to the placebo after 4 weeks of once daily oral administration of 10 mg AQW051

There was no clinically meaningful improvement in the overall cognitive composites or individual cognitive domains as measured by CogState Test Battery and MCCB

Overall, AQW051 10 mg oral dose administered once daily was well tolerated and its safety profile was in line with previous trials

Date of Clinical Trial Report

09-Jul-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

29 Oct 2014

Date of Latest Update

Not applicable

ReasonforUpdate

Not applicable