Sponsor

Novartis

Generic drug name

AQW051

Trial indication(s)

Mild Alzheimer’s disease (AD) or Mild Cognitive Impairment (amnestic MCI)

Protocol number

CAQW051A2104

Protocol title

A 4-week, parallel-group, randomized, double-blind, placebo-controlled, adaptive proof of concept study of AQW051 at up to three dose levels for the treatment of patients with findings consistent with mild Alzheimer's disease (AD) or Mild Cognitive Impairment (amnestic MCI)

Phase of Drug Development

Phase IIa

Study Start/End Dates

19 Dec 2007 to 25 Feb 2009

Reason for Termination (If applicable)

The study was terminated because as the study results after completion of stage 1 did not meet all efficacy objectives

Study Design/Methodology

The study was a 4-week, parallel-group, randomized, double-blind, placebo-controlled, adaptive proof of concept study of AQW051 at up to three dose levels for the treatment of patients with findings consistent with mild AD or amnestic MCI. The study was to be conducted in two stages.

Centers

The study was conducted at 15 centres in 3 countries: UK (6); Canada (6); and South Africa (3)

Objectives:

Primary objective(s)

To assess AQW051 as a cognitive enhancer, as measured by selected tests [Paired Associates Learning (PAL), Spatial Working Memory (SWM), Rapid Visual Information Processing (RVP)] from the Cambridge Neuropsychological Test Automated Battery (CANTAB) computerized cognitive test battery, in patients with findings consistent with mild AD or amnestic MCI

Key secondary objective(s)

- To explore effects of AQW051 on other cognitive functions not assessed by the primary measures (CANTAB tests Pattern Recognition Memory (PRM), Choice Reaction Time (CRT), Graded Naming Test-Revised (GNT)
- To explore the safety and tolerability of AQW051 in patients with findings consistent with mild AD or amnestic MCI

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

The investigational drug AQW51 was provided as either 0.5 mg, 5 mg, or 25 mg capsules. In stage I only 5 mg capsules were used. All groups received 15 mg of AQW051 daily for 4 weeks.
On Day 1, 8, 15, 22 and 28 study drug was administered by the study personnel and was taken orally with 240 ml of water after light breakfast. On all other study treatment days, patients self-administered the study medication in the morning after light breakfast.

Statistical Methods

The different CANTAB readouts were analyzed separately by rank analyses of covariance, including “treatment” and “stratum” (MCI, AD) as fixed effects and the corresponding baseline value as covariate. The comparison of interest was the contrast between active treatment and placebo; tests were performed to the one-sided 10% level without multiplicity-adjustment. Point and interval estimates were produced by the baseline-adjusted stratified Hodges-Lehmann method. In addition, sensitivity analyses were performed using standard analyses of covariance, to complement the aforementioned nonparametric methods. The items “errors at the 6 pattern stage” and “total trials adjusted” of the PAL task at day 28 played a key role at the interim analysis. At the end of stage 1, the conditional power of the study to reach an overall significant result in both these key endpoints at the final analysis was estimated by bootstrap methods. The different scores from the ADAS-Cog, QoL-AD, the DAD and the MMSE were analyzed using standard analyses of covariance. Safety and tolerability variables measures were analyzed by means of descriptive statistics.

Study Population:

Inclusion Criteria:

- Willing and able to give written informed consent
- Meet the diagnostic criteria for either amnestic MCI or mild AD.
- Structural brain scan within the last 6 months prior to randomization that indicates no other underlying disease, in particular no evidence for vascular pathology except for normal age-related white matter/incidental white matter changes which is normal for this age group.
- Daily contact with a primary caregiver/partner

Exclusion Criteria:

- Immune therapy targeting Alzheimer beta amyloid within the last 12 months
- Institutionalized
- Disability that may prevent completion of all study requirements (e.g., blindness, deafness, or communication difficulty)
- Reported use of tobacco products in the previous 3 months or have a urine cotinine level greater than 500 ng/ml
- Past medical history of clinically significant electrocardiogram (ECG) abnormalities or a family history (grandparents, parents, and siblings) of prolonged QT-interval syndrome
- History or current diagnosis of conditions specified in the protocol.

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Patient disposition - n (%) of patients

Disposition Reason	All Treatments N=54	AQW051 15 mg N=27	Placebo N=27
Completed	54 (100%)	27 (100%)	27 (100%)

Baseline Characteristics

		AQW051 15 mg N=27	Placebo N=27	All Treatments N=54
Age (years)	Mean (SD)	69.4 (6.05)	71.9 (7.14)	70.6 (6.68)
	Median	67.0	74.0	70.0
	Range	60 – 83	56 – 84	56 – 84
Gender - n(%)	Male	14 (52 %)	10 (37 %)	24 (44 %)
	Female	13 (48 %)	17 (63 %)	30 (56 %)
Race - n(%)	Caucasian	27 (100 %)	27 (100 %)	54 (100 %)
Ethnicity - n(%)	Other	27 (100 %)	27 (100 %)	54 (100 %)
Disease group - n(%)	Alzheimer's disease	7 (26 %)	9 (33 %)	16 (30 %)
	Mild Cognitive Impairment	20 (74 %)	18 (67 %)	38 (70 %)
Body Mass Index (kg/m2)	Mean (SD)	26.42 (4.023)	25.25 (4.531)	25.83 (4.285)
	Median	26.17	23.53	25.10
	Range	18.2 - 36.2	19.5 - 36.4	18.2 - 36.4
Weight (kg)	Mean (SD)	73.76 (12.09)	68.53 (13.073)	71.15 (12.748)
	Median	74.00	69.00	72.00
	Range	49.5 - 98.0	49.0 - 98.0	49.0 - 98.0
Height (cm)	Mean (SD)	167.0 (6.95)	164.8 (10.42)	165.9 (8.84)
	Median	166.0	164.0	165.0
	Range	151 - 179	151 - 193	151 – 193

Summary of Efficacy

Primary Outcome Result(s)

Summary of Statistical analyses of CANTAB statistically significant endpoints for all patients and MCI patients only

Population Target variable	Study day	N	Difference AQW015 mg vs Placebo	LCLof Difference	UCL of Difference	p-value of test vs placebo
All patients						
PAL						
PAL total errors (2 shapes adj)	1	54	0	-1	0	0.0142
PAL total trials (adj)	1	54	-1	-3	1	0.0846
PAL total errors (6 shapes adj)	1	54	-2	-5	2	0.0840
SWM						
Between errors (4 boxes)	28	54	-0.5	-2	1	0.0866
Between errors (6 boxes)	28	54	-2	-4	1	0.0430
Between errors	28	54	-3.5	-10	2	0.0701
RVP						
Mean latency	1	54	-21.5	-42	1	0.0292
CRT						
Percent correct trials	28	54	0.5	-1	1	0.0632
MCI patient only						
PAL						
PAL of total errors (2 shapes adj)	1	38	0	-1	0	0.0239
Total trials (adj)	1	38	-1.5	-4	1	0.0877

Population Target variable	Study day	N	Difference AQW015 mg vs Placebo	LCLof Difference	UCL of Difference	p-value of test vs placebo
SWM						
Between errors (6 boxes)	28	38	-2.5	-5	1	0.0290
Between errors	28	38	-5	-12	3	0.0845
RVP						
Mean latency	1	38	-22	-48	4	0.0419
CRT						
Percent correct trials	28	38	0.5	-1	1	0.0918
Median latency	28	38	-23	-59	19	0.0966

*One sided p-value, α <0.1

LCL: lower 95% confidence limit; UCL: upper 95% confidence limit

Key Secondary Outcome Result(s)

Statistical analysis of CANTAB - GNT

Statistical analysis of CANTAB - GNT
PD analysis set

Target variable	Study day	N	Difference, AQW051 15 mg vs placebo	LCL of Difference	UCL of Difference	p-value of test vs placebo
Total Correct	28	54	-1.5	-5	3	0.8191

Difference to Placebo: stratified Hodges-Lehmann estimate and confidence limits
Test vs Placebo: stratified rank analysis of covariance, one-sided p-value
Estimates and confidence limits are restricted to integer values. If two neighbouring integers are equally valid as point estimates, they are averaged.
LCL: lower 95% confidence limit; UCL: upper 95% confidence limit

Statistical analysis of CANTAB - PRM

Statistical analysis of CANTAB - PRM
PD analysis set

Target variable	Study day	N	Difference, AQW051 15 mg vs placebo	LCL of Difference	UCL of Difference	p-value of test vs placebo
Percent correct immediate	28	54	-4	-10	8	0.8090
Percent correct delayed	28	54	0	-9	9	0.4244
Mean correct latency immediate	28	54	198	-212	693	0.8328
Mean correct latency delayed	28	54	150	-168	515	0.7864

Difference to Placebo: stratified Hodges-Lehmann estimate and confidence limits
Test vs Placebo: stratified rank analysis of covariance, one-sided p-value
Estimates and confidence limits are restricted to integer values. If two neighbouring integers are equally valid as point estimates, they are averaged.
LCL: lower 95% confidence limit; UCL: upper 95% confidence limit

Statistical analysis of CANTAB - CRT

Statistical analysis of CANTAB - CRT
PD analysis set

Target variable	Study day	N	Difference, AQW051 15 mg vs placebo	LCL of Difference	UCL of Difference	p-value of test vs placebo
Percent correct trials	28	54	0.5	-1	1	0.0632
Median latency	28	54	-9.5	-40	46	0.3273

Difference to Placebo: stratified Hodges-Lehmann estimate and confidence limits
Test vs Placebo: stratified rank analysis of covariance, one-sided p-value
Estimates and confidence limits are restricted to integer values. If two neighbouring integers are equally valid as point estimates, they are averaged.
LCL: lower 95% confidence limit; UCL: upper 95% confidence limit

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Adverse events overall and frequently affected system organ classes -n (%) of subjects (all patients in any group) Safety analysis set

	AQW051 15mg		Placebo		Total	
	N=27		N=27		N=54	
Body system	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with AE(s)	11	(40.7)	10	(37.0)	21	(38.9)
Nervous system disorders	2	(7.4)	4	(14.8)	6	(11.1)
Infections and infestations	3	(11.1)	2	(7.4)	5	(9.3)
Gastrointestinal disorders	2	(7.4)	2	(7.4)	4	(7.4)
Musculoskeletal and connective tissue disorders	2	(7.4)	2	(7.4)	4	(7.4)
Injury, poisoning and procedural complications			3	(11.1)	3	(5.6)
Eye disorders	1	(3.7)	1	(3.7)	2	(3.7)
Respiratory, thoracic and mediastinal disorders	1	(3.7)	1	(3.7)	2	(3.7)
Skin and subcutaneous tissue disorders	2	(7.4)			2	(3.7)
Ear and labyrinth disorders	1	(3.7)			1	(1.9)
Hepatobiliary disorders	1	(3.7)			1	(1.9)
Psychiatric disorders			1	(3.7)	1	(1.9)

Under one treatment,
A subject with multiple occurrences of an adverse event is counted only once in the AE category.
N = number of subject studied; n = number of subjects with at least 1 AE in the category
Only adverse events occurring at or after first drug intake are included

Adverse events overall and most frequent events - n (%) of subjects (all patients in any group) Safety analysis set

	AQW051 15mg		Placebo		Total	
	N=27		N=27		N=54	
Adverse event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with AE(s)	11	(40.7)	10	(37.0)	21	(38.9)
Headache	2	(7.4)	4	(14.8)	6	(11.1)
Pain in extremity	2	(7.4)	1	(3.7)	3	(5.6)
Contusion			2	(7.4)	2	(3.7)
Abscess oral			1	(3.7)	1	(1.9)
Bronchitis	1	(3.7)			1	(1.9)
Cellulitis			1	(3.7)	1	(1.9)
Chalazion	1	(3.7)			1	(1.9)
Clumsiness			1	(3.7)	1	(1.9)
Cognitive disorder			1	(3.7)	1	(1.9)
Confusional state			1	(3.7)	1	(1.9)
Constipation	1	(3.7)			1	(1.9)
Diarrhoea			1	(3.7)	1	(1.9)
Dysgraphia	1	(3.7)			1	(1.9)
Epistaxis	1	(3.7)			1	(1.9)
Fall			1	(3.7)	1	(1.9)
Flatulence	1	(3.7)			1	(1.9)
Hepatic function abnormal	1	(3.7)			1	(1.9)
Increased tendency to bruise	1	(3.7)			1	(1.9)
Laryngitis	1	(3.7)			1	(1.9)
Mental impairment			1	(3.7)	1	(1.9)
Mouth ulceration			1	(3.7)	1	(1.9)
Muscle fatigue			1	(3.7)	1	(1.9)
Muscle spasms	1	(3.7)			1	(1.9)
Nasal congestion			1	(3.7)	1	(1.9)
Nasopharyngitis	1	(3.7)			1	(1.9)
Pruritus	1	(3.7)			1	(1.9)
Skin laceration			1	(3.7)	1	(1.9)
Skin lesion	1	(3.7)			1	(1.9)
Tympanic membrane perforation	1	(3.7)			1	(1.9)
Vision blurred			1	(3.7)	1	(1.9)

Under one treatment,
A subject with multiple occurrences of an adverse event is counted only once in the AE category.
N = number of subject studied; n = number of subjects with at least 1 AE in the category
Only adverse events occurring at or after first drug intake are included

Adverse events related to study drug and most frequent events - n (%) of subjects (all patients in any group) Safety analysis set

	AQW051 15mg			Placebo			Total		
Adverse event	AD N=7 n (%)	MCI N=20 n (%)	Total N=27 n (%)	AD N=9 n (%)	MCI N=18 n (%)	Total N=27 n (%)	AD N=16 n (%)	MCI N=38 n (%)	Total N=54 n (%)
Patients with AE(s)	1 (14.3)	3 (15.0)	4 (14.8)	2 (22.2)		2 (7.4)	3 (18.8)	3 (7.9)	6 (11.1)
Headache		2 (10.0)	2 (7.4)	2 (22.2)		2 (7.4)	2 (12.5)	2 (5.3)	4 (7.4)
Clumsiness				1 (11.1)		1 (3.7)	1 (6.3)		1 (1.9)
Cognitive disorder				1 (11.1)		1 (3.7)	1 (6.3)		1 (1.9)
Confusional state				1 (11.1)		1 (3.7)	1 (6.3)		1 (1.9)
Constipation		1 (5.0)	1 (3.7)					1 (2.6)	1 (1.9)
Diarrhea				1 (11.1)		1 (3.7)	1 (6.3)		1 (1.9)
Dysgraphia		1 (5.0)	1 (3.7)					1 (2.6)	1 (1.9)
Flatulence	1 (14.3)		1 3.7)				1 (6.3)		1 (1.9)
Increased tendency to bruise		1 (5.0)	1 (3.7)					1 (2.6)	1 (1.9)
Mental impairment				1 (11.1)		1 (3.7)	1 (6.3)		1 (1.9)
Muscle spasms		1 (5.0)	1 (3.7)					1 (2.6)	1 (1.9)
Pain in extremity		1 (5.0)	1 (3.7)					1 (2.6)	1 (1.9)
Pruritus		1 (5.0)	1 (3.7)					1 (2.6)	1 (1.9)
Vision blurred				1 (11.1)		1 (3.7)	1 (6.3)		1 (1.9)

Under one treatment,
A subject with multiple occurrences of an adverse event is counted only once in the AE category.
N = number of subject studied; n = number of subjects with at least 1 AE in the category
Only adverse events occurring at or after first drug intake are included

Serious Adverse Events and Deaths

No patients died during the study. No patients experienced SAEs or were discontinued from the study due to AE.

Other Relevant Findings

None

Date of Clinical Trial Report

29-Oct-2009