

# **Long term safety and efficacy of Clioquinol (PBT-01) in the management of Alzheimer's disease**

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## **Background**

Alzheimer's disease (AD) is an invariably progressive and incurable disease. Current drug treatment provides symptomatic management that equates to a delay of symptom progression of approximately 6 months. These drugs have no observable clinical effect on the underlying pathology of AD.

A 36 week double blind study in AD patients on a background of Aricept treatment demonstrated significant benefit of treatment with clioquinol (CQ) over placebo in those trial subjects with more severe disease (the CQAD study)(1). This study also demonstrated a very low drop-out rate (11% after 36 weeks) which favourably compares with drop-out rates observed in shorter studies with low doses of acetyl-cholinesterase inhibitors (2). To generate further safety data and to assess cognition over a longer time period, patients who successfully completed the double blind study, were invited to participate in an open-label, single arm 48-week extension study (CQADDEX). The results from this trial are reported here.

## **Methods**

Patients who completed the double-blind study (1) were invited to participate in a 48 week extension. The extension study received ethical approval from the appropriate authorities. All patients received CQ titrated to 375mg *bid* over 4 weeks. Safety was assessed using standard adverse event reporting, biochemical and haematological testing and neurological and ophthalmologic examination, including nerve conduction studies and visual evoked potentials. Efficacy was measured using the ADAS-Cog, MMSE and CIBIC+. Patients were assessed every 12 weeks for both safety and efficacy.

Due to the absence of a parallel control group, no between group analyses were appropriate. Within group analysis of efficacy variables was planned for the population randomized to CQ in the CQAD study using the paired t-test to allow an analysis of the changes from the original baseline over the full 84 week period. Both observed case (OC) and an intention to treat (ITT) analysis (using the last observation carried forward (LOCF) method) were conducted. As AD is an inevitably deteriorating illness, a slowing of decline compared with natural history data or an absence of deterioration from baseline would be considered clinically relevant. Each individual on CQ from CQAD had their predicted decline calculated from their CQAD baseline score. Comparative “natural history” data was generated from Stern et al (3). The mean value for decline of all the subjects was then plotted. Natural history data for untreated patients with AD from Stern et al (3) was selected as the comparator for 2 reasons (i) no appropriate long term data for patients on donepezil who had failed treatment on donepezil is available and (ii) the placebo arm in CQAD deteriorated at a rate which would have been predicted by Stern’s untreated cohort despite our population still receiving donepezil (Figure 1A). It would seem therefore that the population receiving donepezil alone in this study was deteriorating cognitively at a rate consistent with no treatment.

## **Results**

Eighteen (66.7%) of the 27 patients who started CQAD completed the study – 9 patients remained on CQ for 84 weeks. In the whole group, 3 withdrew consent due to the inconvenience of the clinical trial visits, 3 developed cognitive deficits (namely agnosia or dysphasia) that prevented them from reliably completing safety and efficacy assessments, 1 (originally on placebo) deteriorated to a point clinically where trial involvement was no longer possible, and 2 had unrelated serious adverse events (fatal myocardial infarction and in the other seizures requiring hospitalization).

## **Safety**

Safety analysis was conducted on all data obtained. In CQAD, there were no significant between group differences in terms of adverse events (AE’s) or neurophysiological tests, although subjects on CQ were significantly more likely to exhibit elevation of transaminases and a

reduction in haemoglobin (Hb) (1). In CQADEX, comparison of baseline mean values (at the start of the open label study) with week 84 mean values demonstrated stabilisation of (i) Hb (134  $\text{g l}^{-1}$  (SD=10) vs 133  $\text{g l}^{-1}$  (SD=9.9)) (ii)  $\gamma$ -GT (35 U/L (SD=49.8) vs 25 U/L (SD=10.6)), (iii) AST (22 U/L (SD=14.9) vs 20 U/L (SD=2.8)) and (iv) serum urea (2.6 mMol/L (SD=1.0) vs 2.49 mMol/L (SD=1.0)). The elevated ALT levels seen in CQAD fell from 41 U/L (SD=53.7) at the start of CQADEX to 20 U/L (SD=7.3) by week 84. In CQADEX, those patients who had previously taken placebo exhibited no significant changes using OC analysis in any haemodynamic, haematological, biochemical or ECG parameters. In particular, they did not demonstrate alterations in transaminases or Hb.

All patients experienced at least one AE in both the double-blind trial and the current study. AE's for both trials are summarized in Table 1. One patient in the CQADEX study died from a myocardial infarct which was considered unrelated to the study medication. This subject was obese, hypertensive, an ex-smoker, with pre-existing cardiac failure and had been taking placebo in the original CQAD study.

Given the association of CQ with subacute myelopathic optic neuropathy (SMON), neurological adverse events were of particular interest during both studies. There were 61 neurological adverse events, only one serious (seizures), all but 4 (6%) of which (2 headache, 1 myoclonic jerks and 1 altered visual evoked potentials) were well recognized symptoms or consequences of AD. Although decreased visual evoked potentials were noted in one patient at their week 16 assessment, the clinical findings for this patient remained unchanged, and the VEP's normalized by week 32. It was noted at the time that findings from week 16 may have been technically flawed.

> [View Table 1](#)

### Efficacy

Data from Stern et al (3) predicts that after 84 weeks with no treatment, ADAS-cog scores in patients with AD of a similar stage to those within the CQAD and CQADEX studies, would decline on average by over 18 points (Figure 1A). OC analysis, and the more conservative ITT (using LOCF) analysis showed significant declines from baseline of 8.2 points (95%CI = 0.9 to

15.5;  $df=8$ ;  $p=0.03$ ) and 7.6 points (95%CI = 3.1 – 12.1;  $df=16$ ;  $p=0.004$ ) (figure 1A) respectively: a difference of over 10 points from that predicted without treatment.

A recent study by Lopez has demonstrated a 4-point decline in MMSE scores over 52 weeks in a population starting with an average MMSE of 18.4 (4). This would equate to an 84-week decline (assuming a constant rate) of ~6.5 points (Fig. 1B). Within group changes in the subjects who completed 84 weeks of CQ treatment on the MMSE showed no significant decline from baseline in OC analysis (mean change = -2.9; 95%CI = 0.3 to -6.1;  $df=8$ ;  $p=0.07$ ). CGI (Table 1a) demonstrated that in OC analysis, both groups exhibited no change from visit to visit (represented by the scores consistently of ~4 on the CGI). The ADAS-Non-Cog in OC analysis (Table 1b) showed very low levels of symptomatology in our sample which changed little during the course of the extension study.

> [View Table 2a and Table 2b](#)

> [View Figure 1a and Figure 1b](#)

## **Discussion**

The safety profile of CQ appears favourable, abnormal parameters from the double-blind study normalized and newly treated patients in CQADEX did not show any biochemical or haematological abnormalities. Vigilance for SMON demonstrated frequent neurological and eye symptoms, though there were no cases that suggested incipient SMON. Although the efficacy data must be interpreted conservatively, it is encouraging that on all measures, cognitive decline was attenuated by CQ when compared to the well documented natural history of the disease. The MMSE showed no significant decline over 84 weeks and with regard to the ADAS-Cog, untreated patients would be predicted by Stern et al to decline twice as fast as those treated with CQ. Taken in conjunction with our observations in the double-blind study, it is certainly suggestive that CQ is having a longer-term effect on, at least, symptom progression. On the basis of these results, a larger study with CQ is an optimistic prospect.

	<b>Double-blind study</b>		<b>Open-label study</b>	
	Placebo arm (n=18)	Clioquinol arm (n=18)	Placebo arm in CqAD (n=14)	Clioquinol arm in CqAD (n=13)
Cardiovascular	14(78%)	14 (78%)	12(86%)	10 (77%)
Neurological	13(72%)	13 (72%)	9 (64%)	6 (46%)
Metabolic/Lab	11(61%)	8 (44%)	13(93%)	9 (69%)
Renal/GUT	5 (28%)	8 (44%)	2 (14%)	2 (14%)
Gastrointestinal	7 (39%)	7 (39%)	3 (21%)	1 (8%)
Constitutional	4 (22%)	7 (39%)	7 (50%)	3 (23%)
Hemorrhage	1 (6%)	2 (11%)	0 (0%)	0 (0%)
Infection	0 (0%)	2 (11%)	0 (0%)	0 (0%)
Musculoskeletal	3 (17%)	2 (11%)	0 (0%)	1 (8%)
Ocular/visual	3 (17%)	2 (11%)	1 (7%)	2 (14%)
Pulmonary	1 (6%)	2 (11%)	0 (0%)	0 (0%)
Arrhythmia	2(11%)	1 (6%)	2 (14%)	3 (23%)
Dermatological	3 (17%)	1 (6%)	0 (0%)	1 (8%)
Endocrine	0 (0%)	0 (0%)	3 (21%)	0 (0%)
Other	5 (28%)	1 (6%)	1 (7%)	1 (7%)

Table 1: Summary of adverse events by body system for double-blind and open-label phase trials, broken down by patient assignment in the double-blind trial. Percentages ( ) denote the proportion of patients reporting at least one event for the specified body system. Only events occurring in greater than 10% of patients reported

	<b>Drug at Baseline CQAD</b>					
<b>CIBIC+</b>		<b>Compared with preceding visit</b>				
		<b>Baseline CQAD</b>	<b>Week 12</b>	<b>Week 24</b>	<b>Week 36</b>	<b>Week 48</b>
	<b>Clioquinol mean change (SD)</b>	NA	4.42 (0.9) n=12	3.91 (0.9) n=12	4.4 (0.7) n=10	4.56 (0.7) n=9
	<b>Placebo mean change (SD)</b>	NA	4.36 (1.1) n=11	4.1 (0.9) n=10	4.4 (0.8) n=10	4.89 (0.3) n=9
<b>ADAS-noncog</b>		<b>Baseline CQAD</b>	<b>Week 12</b>	<b>Week 24</b>	<b>Week 36</b>	<b>Week 48</b>
	<b>Clioquinol mean score (SD)</b>	2.1 (2) n=18	2.2 (1.6) n=12	2.9 (2.6) n=12	2.3 (3.1) n=10	3.3 (3.2) n=9
	<b>Placebo mean score (SD)</b>	2.7 (2.4) n=18	2.5 (2.6) n=11	3.8 (2.8) n=10	4.6 (3.5) n=9	4.6 (2.9) n=9

Table 2a: Observed mean change in CIBIC+ (SD) by randomization drug from CQAD study.  
Table 2b: Observed mean scores in ADAS-noncog by randomization drug. Higher scores represent more severe symptoms. (Maximum score = 50)

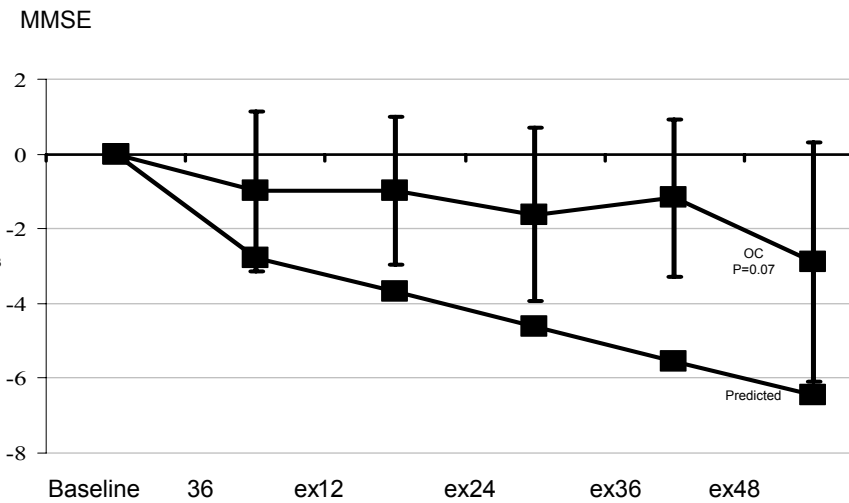
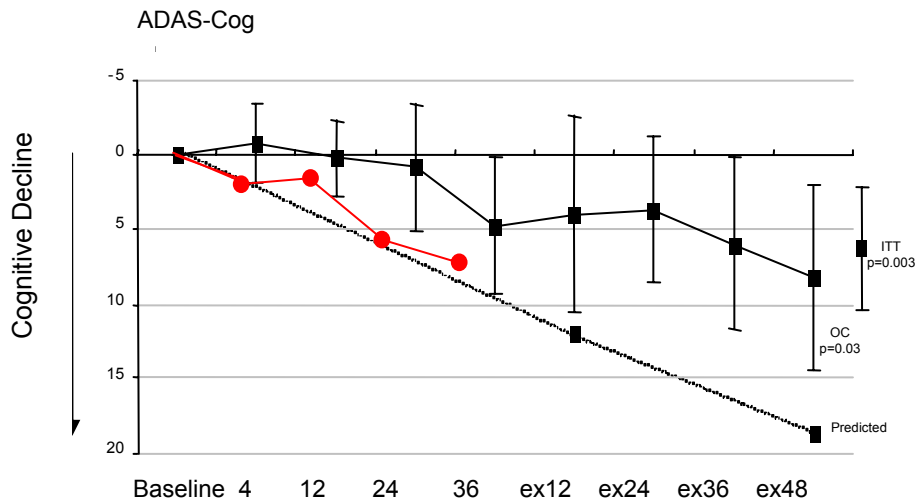


Figure 1A -ADAS-Cog change (95%CI) from baseline compared with predicted decline after Stern et al. ITT=Intention to Treat Analysis (n=17), OC=Observed Cases (n=9); p-values represent within group paired t-test of change from baseline. Red line refers to the placebo decline in the original double blind study.

Figure 1B -Observed decline (95% CI) in CQ treated group (n=9) compared with predicted decline after Lopez et al. OC=Observed Cases; p-value represents within group paired t-test of change from baseline.

## References

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