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ZT-1 for the Symptomatic Treatment of Mild to Moderate Alzheimer's Disease: Preliminary Results of a Multicentre, Randomised, Double-blind Placebo and Active Controlled Phase II Study

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Introduction

Acetylcholinesterase inhibitors (AChE-I) improve the cognitive, functional and general symptoms of Alzheimer's Disease (AD). ZT-1, a huperzine A derivative, is a new reversible selective AChE-I currently undergoing clinical trials. *In vitro* studies have shown ZT-1, through its biotransformation into huperzine A, to be a highly potent and selective AChE inhibitor. *In vivo*, ZT-1 resulted in a marked dose-dependent inhibition of AChE and increased acetylcholine brain cortical levels in rats and reversal of scopolamine-induced memory deficits in both rats and monkeys. In the first studies in young and elderly volunteers, ZT-1 was generally safe and well tolerated. Most side effects corresponded to those known of currently marketed AChE-Is. ZT-1 exhibited marked improvement of some common gastrointestinal side effects. Based on the cholinergic neurotransmitter deficit hypothesis, ZT-1 might prove useful for the symptomatic therapy of AD.

Objectives

The objectives of the present phase II study were the following:

- To assess the efficacy, safety and tolerance of two ZT-1 dose levels (1.5 mg and 2 mg 1x/day) versus placebo and donepezil in patients with mild to moderate AD;
- To measure plasma concentrations of ZT-1 and huperzine A, its active metabolite, for a subsequent population pharmacokinetic (PK) analysis of pooled data to establish standard PK parameters.

Materials & Methods

Patients with mild to moderate AD, diagnosed according to the DSM-IV and NINCDS-ARDRA criteria, and with a MMSE score at study entry ≥ 12 and ≤ 26, were included into this 12-week double-blind, placebo and active controlled study comprising 4 weeks dose titration followed by 8 weeks maintenance therapy. Patients were randomised into 4 parallel treatment groups of multiple oral doses of either placebo, ZT-1 or donepezil administered according to the schedule in Table 1. Following the 12-week double-blind treatment phase, patients were offered a 6-months ZT-1 open-label extension phase after a 2 weeks washout period. Dose reductions during the titration and/or maintenance periods were authorised during both treatment phases.

Table 1 Daily treatment schedule per treatment group and phase

	DOUBLE-BLIND PHASE		OPEN LABEL PHASE	
	TITRATION	MAINTENANCE	TITRATION	MAINTENANCE
TREATMENT GROUP	WEEKS 1-4	WEEKS 5-12	WEEKS 15-18	WEEKS 19-38
Placebo	Placebo	Placebo	ZT-1 1 mg (0.5 mg)	ZT-1 2 mg (1.5 mg)
ZT-1 1.5 mg	ZT-1 1 mg (0.5 mg)	ZT-1 1.5 mg (1 mg)		
ZT-1 2 mg	ZT-1 1 mg (0.5 mg)	ZT-1 2 mg (1.5 mg)		
Donepezil	Donepezil 5 mg (5 mg)	Donepezil 10 mg (5 mg)		

In red: authorised dose reductions

Efficacy was assessed on the Alzheimer's disease assessment cognitive sub-scale (ADAS-cog), the mini mental state examination (MMSE), the clinical dementia rating (CDR), the neuropsychiatric inventory questionnaire (NPI-Q), the activities of daily living scale (IADL), and on time spent on care giving. Safety was assessed on incidence of adverse events (AEs), changes in vital signs, ECG, and laboratory parameters.

Results

Populations

The results section presents complete data from the double-blind phase, as well as preliminary results on the ADAS-cog and the MMSE of the subgroup that received ZT-1 in the double-blind and open label phases of the study (defined as the 'ZT-1 subgroup'). The patient populations in the two phases are tabulated below:

Table 2 Patient populations per treatment group and phase

DOUBLE-BLIND PHASE	TOTAL	Placebo	ZT-1 1.5 mg	ZT-1 2 mg	Donepezil
Safety	186	46	50	43	47
ITT	177	46	47	40	44

OPEN LABEL PHASE	TOTAL	ZT-1 2 mg			
Safety	91	24	27	17	23
ITT	81	23*	23*§	15*§	20*

* = Patients from above treatment groups who entered the open label phase (N);
§ = ZT-1 subgroup

Safety

In the double-blind treatment phase, ZT-1 was well tolerated at both dose levels. Adverse events were evenly distributed between treatment groups: 34 (74%) patients reported AEs in the placebo group vs. 33 (66%), 32 (74%) and 35 (75%) in the ZT-1 1.5 mg, ZT-1 2 mg and donepezil groups, respectively. Most AEs were mild to moderate in intensity. The most clinically important AEs were of gastrointestinal origin, and were markedly lower in the ZT-1 1.5 mg group (36%) than in the donepezil group (43%) (Table 3).

Interestingly, ZT-1 shortened the $QTc_{(B)}$ interval in both the 1.5 mg (-5.1 bpm) and 2 mg (-4.2 bpm) arms. This positive effect on $QTc_{(B)}$ seemed to be ZT-1 specific as on donepezil the $QTc_{(B)}$ remained unchanged.

A total of 13 serious AEs evenly distributed amongst treatment arms occurred during this phase, and one death of presumed cardiac origin was reported in a patient receiving active treatment (ZT-1 1.5 mg). This event was considered as unlikely related to the study drug. One patient died in the placebo group of post surgery pulmonary embolism or fatal cardiac arrhythmia.

Table 3 Incidence of main adverse events during the double-blind phase

SYSTEM ORGAN CLASS	ALL SUBJECTS (N=186)	PLACEBO (N=46)	ZT-1 1.5 mg (N=50)	ZT-1 2 mg (N=43)	DONEPEZIL (N=47)
Gastrointestinal disorders*	67 (129) 36%	10 (16) 22%	18 (34) 36%	19 (39) 44%	20 (40) 43%
Nervous system disorders*	41 (58) 22%	8 (8) 17%	11 (15) 22%	11 (15) 26%	11 (20) 23%
Cardiac disorders*	16 (21) 9%	3 (3) 7%	5 (6) 10%	4 (6) 9%	4 (6) 9%

* Total number of subjects (mentions) %

Vital signs and laboratory parameters did not show any clinically significant changes from pre-dosing to end of treatment (week 12).

Six serious AEs occurent during the open label phase: 3 were considered as not related, 2 as unlikely, and 1 as possibly related by the investigators.

Efficacy

ADAS-COG

In the double-blind treatment phase, ZT-1 1.5 mg and donepezil 10 mg both demonstrated a mean decrease from baseline of approximately 2.5 points after 12 weeks of administration on the **ADAS-cog** scale. Although these changes were not statistically different when compared to placebo, changes from baseline to end of treatment were statistically significant both in the ZT-1 1.5 mg (p=0.007) and in the donepezil 10 mg (p=0.011) arms (Figure 1).

The mean **ADAS-cog** scores of the 'ZT-1 subgroup' confirmed the sustained positive effect of ZT-1 over 38 weeks, as shown by the light blue curve in Figure 1.

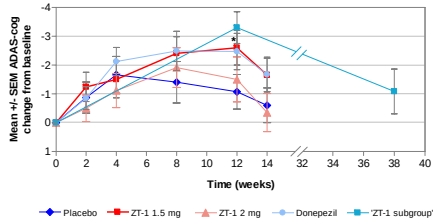

Figure 1 Mean ± SEM ADAS-cog change from baseline per treatment group during the double-blind treatment phase including the washout period (weeks 1 to 14) and in the ZT-1 subgroup (weeks 1 to 38)

In the double blind treatment phase, a 38.3% responder rate (defined as at least 4 points improvement on the ADAS-cog) was reached in the ZT-1 1.5 mg group. This result was statistically significantly higher than that of the placebo group (19.6%; p=0.047) (Figure 2). In the ZT-1 2 mg and donepezil groups responder rates reached 27.5% and 29.6%, respectively.

A 29% responder rate on the **ADAS-cog** scale was observed amongst patients in the 'ZT-1 subgroup' after 38 weeks of treatment.

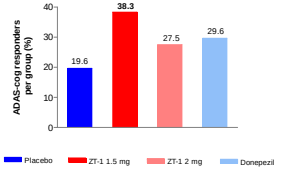

Figure 2 ADAS-cog responders per treatment group in the double-blind phase

Efficacy (cont'd)

MMSE

In the double-blind treatment phase, a statistically significant change on the **MMSE** between baseline and end of treatment (week 12) was achieved by the ZT-1 1.5 mg group compared to donepezil (p=0.022) (Figure 3). In addition, a slight mean increase was observed in all treatment groups between baseline and the end of treatment. The mean increase was 2.0 in the ZT-1 1.5 mg group, 1.5 in the ZT-1 2 mg group, 0.61 in the donepezil group and 0.85 in the placebo group. These increases were of statistical significance in the ZT-1 1.5 mg (p=0.001) and ZT-1 2 mg (p=0.034) arms.

In the 'ZT-1 subgroup', a statistically significant change on the MMSE was also observed between baseline and week 38 (p=0.0205). In addition, the 'ZT-1 subgroup' saw a 55% responder rate on the MMSE (defined as at least 2 points improvement on the scale[1]) by the end of week 38.

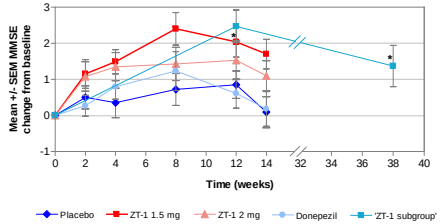

Figure 3 Mean +/- SEM MMSE change from baseline per treatment group during the double-blind treatment phase including the washout period (weeks 1 to 14) and in the ZT-1 subgroup (weeks 1 to 38)

NPI-Q

In the double-blind treatment phase, the **NPI-Q** scale showed a change from baseline to end of treatment (week 12) for both 'Severity' and 'Distress' that was significantly higher in the ZT-1 1.5 mg group compared to donepezil (p=0.018 and p=0.012, respectively) (Figure 4).

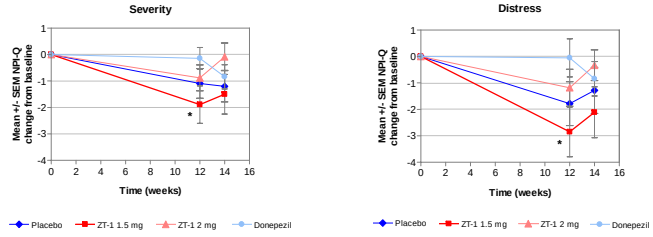

Figure 4 Mean +/- SEM NPI-Q change from baseline for 'Severity' and 'Distress' in the double-blind treatment phase

OTHER

In the double-blind treatment phase, the change from baseline to end of treatment (week 12) was not statistically significantly different between treatment groups either on the **CDR** or **IADL** scales, or in the **time spent on care giving**.

Conclusion

The results of this phase II study show that ZT-1 is safe and efficacious at doses up to 2 mg per day in patients with mild to moderate AD. The double blind phase suggests that the 1.5 mg dose is optimal as it tends to be more effective than the 2 mg dose, and is better tolerated than donepezil, especially by the gastrointestinal system. Furthermore, ZT-1 appears to shorten the $QTc_{(B)}$ interval whereas it remains unchanged with donepezil.

Preliminary results of the open label phase confirm that ZT-1 reduces AD patients' cognitive impairment over time with more than a 50% responder rate on the MMSE after 38 weeks treatment. These findings indicate that ZT-1 could be a valid alternative to current AChE-Is marketed for the treatment of AD.

[1] Doraiswamy P.M., et al. The Alzheimer's disease assessment scale: Patterns and predictors of baseline cognitive performance in multicenter Alzheimer's disease trials. Neurology 1997;48:1511-1517

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