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 bioconversion into huperzine A, to be a highly potent and selective AChe inhibitor. In vivo, ZT-1 results in a marked dose-dependent inhibition of AChe and increased acetylcholine brain cortical levels in rats and reversal of scopolamine-induced memory defects 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-I. 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 tolerability 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, in active metabolite, for a subsequent population pharmacokinetic (PK) analysis of pooled data to establish standard PK parameters.

**Materials and Methods**

Patients with mild to moderate AD, diagnosed according to the DSM-IV and NINCDS-ADRDA criteria, and with a MMSE score at study entry ≥12 and ≤29, were included into this 12-week double-blind, placebo and active controlled comparator 4-weeks dose titration followed by 8-week maintenance therapy. Patients were randomized into 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-week washout period. Dose reductions during the titration and/or maintenance period were authorized during both treatment phases.

**Results**

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

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 or moderate in intensity. The most clinically important AEs were gastrointestinal in origin, and were markedly lower in the ZT-1 1.5 mg group (30%) than in the donepezil group (40%) (Table 3).

In the double-blind treatment phase, the change from baseline to end of treatment (week 12) was not statistically significantly different between placebo and donepezil 10 mg (p=0.034) arms.

In the double-blind treatment phase, the change from baseline to end of treatment (week 12) was not statistically significantly different between placebo and donepezil 10 mg (p=0.034) arms. In the ZT-1 subgroup, a 35% responder rate on the MMSE (defined as at least 2 points improvement on the scale) was observed (p=0.012) (Figure 3).

**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 in 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 share the QTc interval whereas it remains unaltered 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-I as marketed for the treatment of AD.