TECHNICAL SUMMARY OF RESULTS
2006-005161-18 [DEB-ZTSR-201]

Sponsor: Debiopharm International SA	Tabulated Study Report		(For National Authority Use Only)
Name of Finished Product: N/A			
Name of Active Ingredient: ZT-1	Page:	Number:	

Study Title	A randomised, double-blind, double-dummy, oral donepezil ontrolled study on the safety and efficacy of repeated monthly subcutaneous injections of a sustained-release implant of ZT-1 in patients with moderate Alzheimer's Disease 2006-005161-18 [DEB-ZTSR-201]
Study Centres	**Australia**: Chermside, Daw Park, East Gosford, Kogarah, Nedlands, Heidelberg West, Woodville **Canada**: Calgary, Edmonton, Kelowna, Medicine Hat, Montreal (4 sites), North London, Penticton, Toronto (2 sites) **UK**: Belfast, Blackburn, Cardiff, Crowborough, Glasgow, London, Manchester, Newcastle, Southampton
Clinical Phase	IIb
Study Dates	First patient in: 21 February 2007 Last patient out: 15 April 2009
Objectives	• To assess the efficacy of the ZT-1 implant in improving cognitive function, behavioural and overall outcomes compared to oral daily doses of donepezil; • To assess the safety of the ZT-1 implant compared to oral daily doses of donepezil; • To measure plasma concentrations of ZT-1, its active metabolite Hup A, and other potentially related metabolites; • To measure the inhibition of RBC AChE activity.
Methodology	ZT-1 is a pro-drug of huperzine A, a selective inhibitor of acetylcholinesterase (AChE). This 24-week study was comprised of a 4-week titration period with either a daily ZT-1 1 mg capsule (ZT-1 active arm) or a daily donepezil 5mg capsule (comparator arm), followed by two consecutive maintenance periods: • the first maintenance period lasted 4 weeks with one ZT-1 9 mg implant injection (three 3mg implants) and 2 daily donepezil placebo capsules (ZT-1 active arm) or one ZT-1 placebo implant injection (three placebo implants) and 2 daily donepezil 5 mg capsules (comparator arm); • the second maintenance period lasted 16 weeks with a similar treatment except for the implant dose, which was increased to 12 mg ZT-1 (four 3 mg implants or corresponding placebo). In case of AChEI intolerance during a) titration: patients were withdrawn and replaced, b) maintenance period 1: oral treatment could be reduced to 1 capsule daily. In the latter case, patients remained on the same implant and oral dose levels during the second maintenance period.

Methodology (cont.)	Two conditions had to be fulfilled for transition into the second maintenance period: a) the patient had not experienced any moderate AE with a 'reasonable causal relationship' to the study drug having lasted more than 3 days (72 hours) and b) his/her plasma Hup A concentration dosed at Cmax on Day 50 was □□20 nmol/L. If one of these conditions was not met, the patient remained at the dose levels of the first maintenance period. Oral medications were self-administered in the evening 2 hours before or after the evening meal together with 200 mL water. Implants were administered by health professionals at the study centre 2 hours before or after a meal via s.c. injection into the abdominal wall (on each occasion all implants were injected together in one single injection) using the implantation device provided. Injections were rotated between the abdominal quadrants. Patients received an occlusive dressing containing a local anaesthetic approximately 60 minutes prior to implantation.
Number of Patients	Planned: 128; Enrolled: 228; Randomised: 158; Safety: 151; ITT: 147; PP: 125; PK subset: 30; Genotyping population: 141
Diagnosis and Main Inclusion Criteria	Donepezil naïve patients aged > 50 with moderate AD diagnosed according to the DSM-IV and NINCDS-ARDRA criteria and a MMSE score at screening between 14 and 22, inclusive.
Test Product	ZT-1 3 mg injectable implant ZT-1 placebo injectable implant ZT-1 1 mg tablet (over-encapsulated for blinding purposes)
Treatment Duration	Treatment lasted twenty-four weeks including a 4-week titration period and two consecutive maintenance periods (4 and 16 weeks, respectively).
Criteria for Evaluation	**Efficacy** *Primary* • Change from baseline in the MMSE score at end of treatment *Secondary (at end of treatment)* • Responder rate as defined by at least 2 points improvement in the MMSE score • Change on the ADAS-cog 11-items subscale • Change in the NPI-Q and IADL scales • Patient's convenience questionnaire **Pharmacokinetcs and Pharmacodynamics** • Maximum plasma concentration of ZT-1, its active metabolite Hup A, and potentially other related metabolites. • Maximum inhibition of RBC AChE activity. **Safety endpoints** • Incidence of AEs, change in vital signs, ECG, and standard haematology, biochemistry and urinalysis parameters

Statistical Methods	*Sample size* Sample size was calculated to fulfil the objective of this trial to assess the efficacy of ZT-1 on improving the cognitive function in comparison to donepezil. Assuming between ZT-1 and donepezil an expected difference of at least 1.4 points ± 2.8 (mean ± SD) on the MMSE change from baseline, 64 patients per treatment group were required to demonstrate a statistically significant difference between ZT-1 and donepezil. Sample size calculation was performed by a formula for comparing two independent samples by the t-test, with a nominal two-sided $\alpha = 0.05$ and $\beta = 0.20$. *Randomisation* Randomisation was centralised and stratified by study centre in a ZT-1: donepezil 1:1 balanced ratio. *Statistical analysis* The primary efficacy analysis was conducted in the ITT and the secondary analysis in the PP populations. Safety analysis was run on the Safety population. The change in MMSE rating scale from baseline to end of treatment was compared between treatment groups by Wilcoxon rank sum test. Other rating scales ADAS-cog, NPI-Q and IADL were analysed similarly. Responder rate on MMSE scale was compared between treatment groups by the chi-square. Relationships between RBC AChE inhibition and plasma concentrations of ZT-1 and Hup A and with efficacy were explored by regression analyses. Safety criteria were analysed on the AE incidence by the chi-square test or by Fisher exact test when expected cell frequencies are < 5. Laboratory, vital signs and ECG criteria were evaluated by the analysis of variance for continuous variables, and by chi-square or Fisher test for categorical variables. Scatter plots and shift tables were produced.
Summary and Conclusions	*Efficacy*: On the efficacy profile, an improvement on the MMSE score was observed in both treatment groups between baseline and end of treatment. Mean increase was 1.2 in the ZT-1 group and 2.1 in the Donepezil group. These changes from baseline to end of treatment were statistically significant in both treatment groups. There was no statistically significant difference between the treatment groups in term of change from baseline to end of treatment ($p = 0.087$) A 56.0% responder rate (defined as at least 2 points improvement on the MMSE) was reached in the Donepezil group, which is statistically significantly higher than the one observed in the ZT-1 group (38.9%; $p = 0.038$). A statistically significant change on the ADAS-cog between baseline and end of treatment was achieved in the Donepezil group compared to ZT-1 ($p = 0.003$). The mean decrease (improvement) was of 2.4 in the Donepezil group, while the mean increase was 0.3 in the ZT-1 group. Regarding the 'non-cognitive' ZT-1 efficacy profile, the NPI-Q scale showed a minor change from baseline to end of treatment for 'Severity': 0.2 mean increase in the ZT-1 group and 0.2 mean decrease in the Donepezil group ($p = 0.480$). Regarding the Distress, a slight (0.5) mean increase was observed from baseline to end of treatment in the ZT-1 group while a nearly null mean decrease (0.03) was observed in the Donepezil group ($p = 0.564$). The change from baseline to end of treatment in the IADL scales was not statistically significantly different between treatment groups ($p = 0.824$). A slight mean increase was observed in both treatment groups: 1.3 in the ZT-1 group and 0.8 in the Donepezil group.

Summary and Conclusions (cont.)	*Pharmacokinetics (PK) and Pharmacodynamics (PD):* Regarding the PK/PD relationship AChE inhibition increased with the ZT-1 and Huperzine A levels. However, the correlation between the AChE inhibition and the efficacy profiles was very weak in both treatment groups. Overall, the present data whilst not demonstrating superiority to donepezil on measures of cognition, do give some further support for the efficacy of ZT-1 monthly implants. Indeed, if ZT-1 showed an inferiority when compared to Donepezil in the ADAS-cog assessment, data indicate that ZT-1 was clinically equivalent to donepezil on the other measures (MMSE, NPI-Q, IADL). Moreover, ZT-1 showed to stabilize the mean values in the ADAS-cog set close to the baseline score, indicating it lowered the mean natural cognitive decline of AD. *Safety:* ZT-1 was well tolerated. Adverse events (AE) were quite evenly distributed between treatment groups: 58 (78.4%) patients reported AEs in the ZT-1 group vs. 66 (85.7%) in the Donepezil group. Most AEs were mild to moderate in intensity. The most clinically important AEs (more than 10% of patients in at least one treatment group) were of gastrointestinal origin: • nausea (16.2% of patients in ZT- 1 group and 14.3% of patients in Donepezil group) • diarrhoea (9.5% of patients in ZT-1 group and 15.6% of patients in Donepezil group) • vomiting (16.2% of patients in ZT-1 group and 7.8% of patients in Donepezil group) An interesting finding is the significantly lower number of cardiovascular side effects of ZT-1 when compared to Donepezil. A total of 18 serious adverse events occurred during the study in the two treatment group, and one death was reported in a patient receiving Donepezil. An independent central ECG review was also performed and showed ZT-1 having a better impact on the QT interval when compared to Donepezil.
GCP Compliance	This study, including the archiving of documents, was performed in compliance with ICH E6 Good Clinical Practices (GCP), which has its foundation in the Declaration of Helsinki.
Amendments	None available
Report Date	27 November 2009