TECHNICAL SUMMARY OF RESULTS
2004-002941-11; DEB-ZT-201

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

Title of study:	A multicentre, 3-month, randomised, double blind, placebo and active controlled study on the tolerability and efficacy of ZT-1 for the symptomatic treatment of mild to moderate Alzheimer's Disease. [2004-002941-11; DEB-ZT-201]
Study centres:	**France:** Bordeaux, Bourg en B, Angers, Rodez, Tours, Saint-Etienne, Dijon, Rennes, Lille, Pessac, Toulouse, Nantes **RSA:** Paarl, Bloemfontein, Pinetown, Port Elizabeth, Cape Town 45, Cape Town 46 **UK:** Southampton, Bradford, Glasgow, Blackpool **Bulgaria:** Sofia 51, Sofia 52 **Switzerland**: Lausanne **Belgium:** Bruxelles
Clinical phase:	II
Study dates	First patient in: 19.01.2004; Last patient out: 29.09.2005
Objectives	• To assess safety and tolerance of two ZT-1 dose levels (1.5 mg, 2 mg 1x/d) compared to placebo and donepezil in patients with mild to moderate AD • To assess the efficacy of two ZT-1 dose levels (1.5 mg, 2 mg 1x/d) to improve cognitive function compared to placebo and donepezil in patients with mild to moderate AD • To assess the efficacy of two ZT-1 dose levels (1.5 mg, 2 mg 1x/d) to improve behavioural, overall and functional outcomes compared to placebo and donepezil in patients with mild to moderate AD • To measure plasma concentrations of ZT-1 and its active metabolite huperzine A for a subsequent population pharmacokinetic analysis • To assess relationships between plasma concentrations of ZT-1, huperzine A vs. RBC AChE activity and ZT-1, huperzine A, RBC AChE activity vs. efficacy and safety endpoints
Methodology	*ZT-1:* One mg/d during the titration period followed by 1.5 mg or 2 mg/d during the maintenance period - If the treatment is not well tolerated during titration or maintenance period, a dose reduction (actual dose reduced by 0.5 mg) can be considered according to the Investigator's clinical evaluation. *Comparators:* Donepezil (active comparator) 5 mg/d titration period, 10 mg/d maintenance period and placebo - Dose reduction for donepezil is possible during maintenance period to 5 mg/d according to the Investigator's clinical evaluation. All study medications were administered orally (p.o.) fasted in the evening (i.e., 2 hours prior to or 2 hours after the evening meal).
Number of Patients	Planned 180; Enrolled 186; Safety 186; ITT 177; PP 148; PD Subset 15; PK subset 81

Test product:	ZT-1 tablets 0.5 mg - ZT-1, prodrug of huperzine A, is a novel cholinesterase inhibitor
Duration of Treatment	Twelve weeks, of which 4 weeks is the titration period and 8 weeks is the maintenance period
Criteria for Evaluation	**Primary** *Efficacy:* • Change in conventional ADAS-cog from pre-treatment to end of treatment **Secondary** *Efficacy:* • Responder rate defined as the proportion of patients with an improvement by at least 4 points on conventional ADAS-Cog from pre- treatment to end of treatment. • Change from pre-treatment to end of treatment in each rating scale: extended ADAS-cog, MMSE, CDR, IADL, NPI-Q and time spent on care given to the patient. *Pharmacokinetics:* • Plasma concentrations of ZT-1 and huperzine A *Pharmacodynamics:* • Inhibition of RBC AChE activity *Safety:* • Adverse events, laboratory parameters, vital signs and ECG
Statistical methods	Statistical analysis was performed on two occasions: one interim analysis during the study and one final analysis on all patients enrolled in the study. Efficacy analysis was conducted in the ITT (primary analysis) and the PP populations. The primary efficacy criteria was the change from pre- treatment to end-of-treatment for the conventional ADAS-cog rating scale. All rating scales change from pre-treatment to end-of treatment or last observation carried forward was analysed by the general linear model. Study treatment and possible predictive factors were considered in the model. Repeated measures over time were analysed by the mixed-effects model. Responder rate on conventional ADAS-cog scales was compared between treatment groups by the Cochran-Maentel-Haenszel test. Pharmacokinetics results will be pooled with phase I and future phase III trials for subsequent analysis using standard population based PK modelling. Relationships between plasma concentrations of ZT-1, huperzine A vs. RBC AChE activity and ZT-1, huperzine A, RBC AChE activity vs. efficacy and safety endpoints were assessed by regression analyses. Safety data were analysed on the adverse events incidence by the chi-square test or by Fisher exact test when expected cell frequencies are < 5. Laboratory parameters, vital signs and ECG were evaluated by the analysis of variance for continuous variables, and by chi-square or Fisher test for categorical variables. Shift tables and scatter plots were produced.
Summary and conclusions	*Efficacy* On the efficacy profile, a trend towards improvement on the conventional ADAS-cog score was seen in all treatment groups between baseline and end of treatment. Mean decrease was of 2.6 in the ZT-1 1.5 mg group, 1.5 in the ZT-1 2 mg group, 2.5 in the donepezil group and 1.1 in the placebo group. These changes from baseline to end of treatment were statistically significant in the ZT-1 1.5 mg (p=0.007) and in the donepezil (p=0.011) arms. No statistically significant difference between baseline and end of treatment was observed for either ZT-1 or donepezil when compared to placebo. This could be partially due to an unexpected and sustained improvement in the placebo group, to a 'study population' effect with a rather 'high' proportion of 'mild AD', and to a 'center effect'. Nevertheless, 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, which is statistically significantly higher than that of the placebo group (19.6%; p=0.047). In the ZT-1 2 mg and donepezil groups responder rates reached 27.5% and 29.6%, respectively.

Summary and conclusions (cont.)	*Efficacy (cont.)* A statistically significant change on the MMSE between baseline and end of treatment was also achieved by the ZT-1 1.5 mg group compared to donepezil (p=0.022) and placebo (p=0.056). In addition, a slight mean increase was observed in all treatment groups between baseline and the end of treatment. The mean increase was of 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. Regarding the 'non-cognitive' ZT-1 efficacy profile, the NPI-Q scale showed a change from baseline to end of treatment 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). The change from baseline to end of treatment in the CDR, IADL scales, or in the time spent on care giving was not statistically significantly different between treatment groups. This could be partially explained by the pretty short treatment duration. *Pharmacokinetics and Pharmacodynamics* On the PK and PD profiles, the dispersion of the data makes most analysis irrelevant. Nevertheless, it could be summarized briefly that the higher the ZT-1 dose administered, the higher both ZT-1 and huperzine A plasma levels were. Accordingly, the higher the huperzine A plasma level was, the higher the inhibition of AChE was. However, no statistically significant correlation between the AChE inhibition and both the safety and efficacy profiles was observed. *Safety* Overall, ZT-1 was well tolerated at both dose levels. Adverse events (AE) 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 'time to first' occurrence analysis of all AE put altogether showed a later incidence in the ZT-1 1.5 mg compared to the ZT-1 2 mg and donepezil groups. The most clinically important AEs were of gastrointestinal origin, and were lower in the ZT-1 1.5 mg group (36%) than in the donepezil group (43%). The 'Repeated AEs analysis', showed that the best general safety profile was observed in the placebo group, and the worst in the ZT-1 2 mg group; middle, similar safety profiles were observed in the ZT-1 1.5 mg group and in the donepezil group. The difference between the treatment groups was statistically significant (p=0.024). A total of 13 serious AEs - evenly distributed amongst treatment arms - occurred during the study, 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 not related to the study drug. One patient died in the placebo group of pulmonary embolism post surgery or of fatal cardiac arrhythmia. With respect to the cardiovascular area, an independent central ECG review was performed. ZT-1 shortened the QTc(B) interval in both the 1.5 mg (-5.1 bpm) and 2 mg (-4.2 bpm) groups. This positive effect on QTc(B) seemed to be ZT-1 specific as on donepezil the QTc(B) remained unchanged. Finally, no relevant elements were observed in vital signs and/or safety laboratory tests.
GCP Compliance:	This study was performed in compliance with the Declaration of Helsinki and with the ICH Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), including the archiving of essential documents.

Amendments	Four successive protocol amendments were written respectively on 12 November 2003, 5 December 2003, 10 March 2004 and 6 October 2004 for the following reasons : • Amendment 1: To open new centres in France • Amendment 2: To replace the CIBIC scale by the IADL scale; to introduce an additional assessment of the time spent on care given to the patient; to modify the procedures for study drug box number allocation; to change the time period for reporting of medication administered prior to study; to introduce a single patient diary card for the study; to allow the Data Management Safety Committee (DMSC) to be aware of the study treatment groups identification, if necessary, to issue a recommendation about the continuation of the study and to modify and correct some details in the presentation of assessments and to add references • Amendment 3: To open new centres in France • Amendment 4: To extend the treatment by an optional open-label ZT-1 therapy according to the following regimen: 1mg/d from week 15 to week 18 followed by 2 mg/d from week 19 to week 38; to add 3 additional study visits at week 18, 24 and 38 to assess safety, cognitive and global clinical evaluation; to extend the study recruitment period to June 30, 2005; to change the sponsor address - in addition, new study centres were opened in Bulgaria, RSA, UK and Belgium.
Report Date:	12.09.2006