

# THE PROLONGED ACTION OF THE ACETHYLCHOLINESTERASE INHIBITOR ZT-1 AFTER SUBCUTANEOUS INJECTIONS OF SUSTAINED RELEASE IMPLANTS IN HEALTHY VOLUNTEERS

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Introduction

The huperzine A (Hup A) derivative ZT-1 is a very potent and selective acetylcholinesterase inhibitor (AChE-I) producing a marked increase in cerebral acetylcholine (ACh) levels and demonstrating a neuroprotective effect *in vitro* and *in vivo*<sup>1,2,3</sup>. ZT-1 has hence been selected as a promising candidate for the treatment of symptomatic Alzheimer's disease (AD) and is currently undergoing clinical trials in this indication. Treatments by the oral route in AD patients suffer from serious drawbacks: lack of compliance resulting in variable drug exposure and potentially reduced treatment effect. Therefore, a sustained-release ZT-1 implant (Figure 1) has been developed to overcome these difficulties.



Figure 1: ZT-1 implant

Objectives

The objectives of the present pilot study were the following:

- To assess the plasma concentration-time profiles of ZT-1 and Hup A (its active metabolite) after s.c. administration of the sustained-release ZT-1 implant in healthy young male volunteers;
- To assess AChE inhibition after s.c. administration of the sustained-release ZT-1 implant in healthy young male volunteers (results not presented in this poster);
- To assess the tolerance and safety of s.c. administration of the sustained-release ZT-1 implant in healthy young male volunteers.

Healthy and body mass index (BMI) matched male volunteers aged 18 to 40 years were selected into this open-label, single- and multiple-dose pilot study. After a 7-day run-in period of orally administered ZT-1 (1 mg/day) followed by 7 days of wash-out, volunteers were administered 3 mg ZT-1 implants by the s.c. route in cohorts of 3 volunteers as outlined in Table 1.

Table 1: Treatment schedule

COHORT	DOSE LEVEL	Day 1	Day 29
1	3 mg	1 x 3 mg implant	-
2	6 mg	2 x 3 mg implants	-
3	6 mg	2 x 3 mg implants	2 x 3 mg implants
4	9 mg	3 x 3 mg implants	3 x 3 mg implants

Materials and Methods

ZT-1 and Hup A were quantified in plasma up to 85 days after the first implantation. As direct determination of ZT-1 in biological matrices is hampered by its rapid degradation into Hup A, NaBH<sub>4</sub> was used during blood collection to transform ZT-1 into the stable reduced form ZT-1R. A validated bioanalytical method enabled the simultaneous quantification of both ZT-1R and Hup A using solid phase extraction followed by reversed phase chromatography hyphenated with mass spectrometric detection (LC-MS/MS). Concentration-time profiles were established and pharmacokinetic (PK) metrics were computed according to non-compartmental analysis.

Tolerance and safety were assessed on standard parameters including incidence of adverse events (AEs), changes in vital signs and ECG, and laboratory parameters.

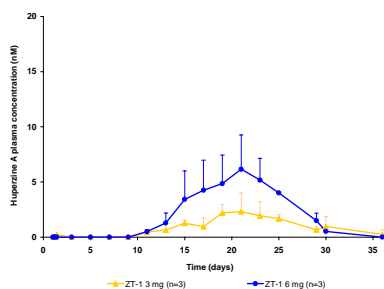


Figure 2: Huperzine A mean (±SD) plasma concentration after one administration of s.c. ZT-1 implants

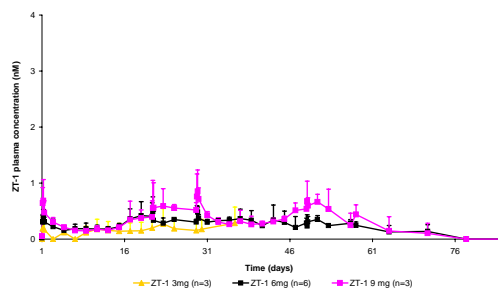


Figure 3: ZT-1 mean (±SD) plasma concentration after single and repeated administration of s.c. ZT-1 implants

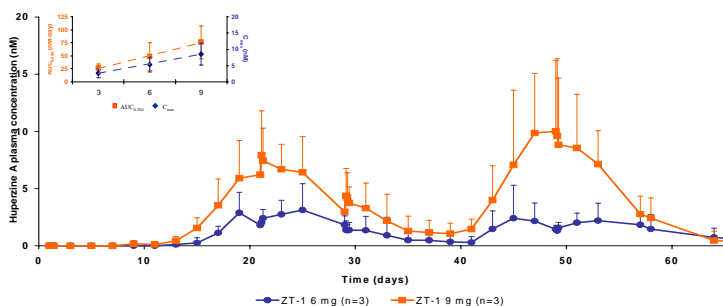


Figure 4: Huperzine A mean (±SD) plasma concentration after two administrations of s.c. ZT-1 implants at 4-week intervals  
Inset: Mean (±SD) plasma C<sub>max</sub> and AUC<sub>0-29 days</sub> of huperzine A in function of the ZT-1 dose after administration of s.c. ZT-1 implants

Results

- Prolonged release of Hup A (the active metabolite) for up to four weeks was observed after single or repeated administration of ZT-1 implants. Plasma Hup A C<sub>max</sub> was progressively reached between Days 19-25 after a delay of around 10 days, and was followed by a gradual decrease leading to levels above the limit of quantification (LOQ) but below 2 nM by Day 35 for most individuals whatever the dose (Figures 2 and 4).
- No significant accumulation after repeated monthly s.c. implants was observed. In the group dosed with 9 mg ZT-1 twice at an interval of four weeks, the highest Hup A C<sub>max</sub> reached 17 nM. The mean Hup A C<sub>max</sub> was 10 nM (Figure 4).
- As ZT-1 progressively hydrolyses itself into Hup A, ZT-1 plasma levels were very low and often below the limit of quantification (LOQ=0.2 nM) as illustrated in Figure 3.
- These data revealed linear PK between dose and exposure as assessed by AUC and C<sub>max</sub> after the first administration, as depicted in the inset of Figure 4.
- No tolerance or safety concerns were observed. The only relevant observed AEs were mild headache (n=4) and severe migraine (n=1). All cases were rated as unlikely related to the study drug, except two cases of mild headache that were rated as possibly related to the study drug.

The preliminary results of this pilot study demonstrate that sustained levels of Hup A can be achieved over several weeks after administration of ZT-1 implants every four weeks. Given the excellent tolerance of this new route of administration, ZT-1 implants offer an alternative treatment of AD patients with improved compliance and therefore a probable increase in efficacy.

In view of these positive results, the study has been extended to include additional dosage arms, and a phase II b trial is already planned to assess the safety and efficacy of ZT-1 implants in patients with AD.

Conclusion

<sup>1</sup> E. Ezan. Measurement of *in vitro* acetylcholinesterase inhibition induced by ZT-1 and huperzine A in human red blood cells. Final report. Gif Sur Yvette, (France): Laboratoire d'Etude du Métabolisme des Médicaments (LEMM); 2003 Jan. Study DEB-02-PRECL-ZT-07 / LEMM no 238143.  
<sup>2</sup> X. C. Tang. The studies of ZT-1 on cortical acetylcholine level in rats: comparison with huperzine A and donepezil. Final report. Shanghai (China): State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences; 2002 Apr.  
<sup>3</sup> Debiopharm internal data.