New Alzheimer’s Drug ANAVEX 2-73: A Phase 2a Study, Clinical Safety, Tolerability and Maximum Tolerated Dose Finding in mild-to-moderate Alzheimer's Patients

Steve Macfarlane¹, Marco Cecchi², Dennis Moore³, Paul Maruff⁴, Kristina M Capiak⁵, Anastasios Zografidis⁶, Christopher U Missling⁷

¹ Caulfield Hospital, Melbourne, Australia; ² Neuronetrix, KY, USA; ³ Cogstate, Melbourne, Australia, ⁴ Anavex Life Sciences Corp., New York, USA

Background
ANAVEX 2-73 acts by selectively activating the specific stress reducing and survival protein, the Sigma-1 receptor, and muscarinic receptors believed to be responsible for cognitive improvement. The compound may thus combine neuroprotective/disease-modifying properties with benefits to cognition (Villard 2011, Lahmy 2013). Its neuroprotective properties may facilitate prolongation of initial cognitive benefits over a longer period than current therapies.

Sigma-1 Receptor: Upstream Pluripotent Modulator:
- Reducing mitochondrial dysfunction
- Reducing protein misfolding
- Modulating Ca²⁺
- Reducing oxidative stress
- Reducing inflammation
- Enabling neuroprotection

Phase 2a with Adaptive Trial Design
Phase 2a study of 32 patients with mild-moderate Alzheimer’s disease (AD) with PART A: 5 weeks duration, randomized, open-label, adaptive design. Baseline MMSE 16-28. Either on a stable donepezil dose for at least 3 months (n = 25) or donepezil-naïve (n = 7). Primary endpoint: Safety, tolerability and maximum tolerated dose (MTD) finding study. Exploratory secondary endpoints: Pharmacokinetics, MMSE, Cogstate, EEG/ERP, ADCS-ADL. Open-label extension with daily oral dosing (26 weeks, extended by 104 weeks at patient/caregiver request, now further extended by 104 weeks after end of PART B).

Safety and Tolerability (Continued)
No differences in blood pressure or resting heart rate. Clinical laboratory parameters, vital signs, and 12-lead ECG did not show any clinically relevant or dose-dependent changes.

Methodology Maximum Tolerated Dose (MTD)
AEs were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 and were taken into account for maximum tolerated dose (MTD) determination. More precisely, the dose limiting toxicity (DLT) was considered as an overall event, composed of several graded AEs, referred to as joint toxic events (JTEs):

- Frequent
- Important AEs

The dose limiting toxicity (DLT) is defined by the notes presented in the grid, as a set of joint toxic events (JTEs) matching:

- A: Frequent
- B: Important AEs

Mathematical model was fitted to the recorded AEs to establish the dose-risk relationships:

Safety Overview Adverse Events (AEs)

Mathematical model was fitted to the recorded AEs to establish the dose-risk relationships:

Conclusions
- The traditional definition of MTD was updated in the presence of inter-patient variability. For AD patients 50.58 mg of ANAVEX 2-73 is the maximum tolerated dose taking into account most frail patients (5% of total patients). In half of these patients a DLT event will occur.
- In PART A, MMSE-Δ, ERP-Δ scores vs. ANAVEX 2-73 doses displayed a significant positive slope for the ANAVEX 2-73 dose with confidence intervals that excluded the zero value.
- The MTD determination from the present Phase 2a study, allows for a Phase 2b study to be conducted according to a double-blind design including placebo. To complete the design of a future study, population PK data (and the evaluation of inter-patient variability) are necessary in order to compute the patients’ sample size and to achieve conclusions associated with a given statistical power. This is currently in progress.
- ANAVEX 2-73 may have a broader scope in addressing diseases by virtue of both its molecular biology and the favorable safety profile observed thus far. Estimating MTD is a prerequisite for the progression of ANAVEX 2-73 as well as for other clinical trials.

Quantitative Dose-Response Analysis
Phase 2a (PART A) results demonstrate a favorable tolerability/risk profile. Patients were unaware of high-low dose assignment via randomization. Dose-related small sample size dose-response analysis seem to indicate a cognitive benefit associated with ANAVEX 2-73 (Cogstate, MMSE, EEG/ERP improved significantly at 5 weeks of treatment). Low-high dose was statistically significant to affect MMSE-Δ and ERP-Δ scores with MMSE-Δ (p<0.02) and ERP-Δ (p<0.05), respectively.

References
- Lahmy, Neuropsychopharmacology (2013), pp. 1708-1723
- Schindler, CNS Summit Poster (2014)