New Exploratory Alzheimer's Drug ANAVEX 2-73 Changes in Electrophysiological Markers in Alzheimer's Disease - First Patient Data from an ongoing Phase 2a Study in mild-to-moderate Alzheimer's Patients

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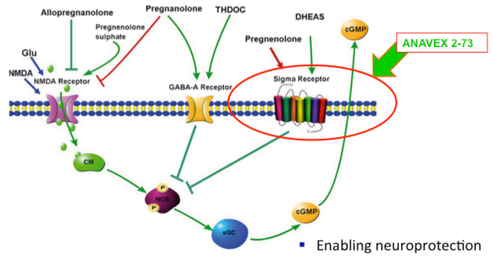
Background

ANAVEX2-73 acts by activating specific stress reducing and survival protein Sigma-1 receptor as well as muscarinic receptors that are believed to be responsible for cognitive effects and can potentially combine symptomatic with neuroprotective and disease modifying properties (Villard 2011, Lahmy 2013). The neuroprotective properties may carry the initial cognitive effect over a longer period of time than current therapies.

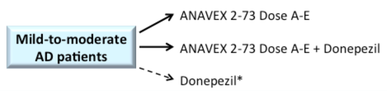
Sigma-1 Receptor is a Multi-Targeted Key Cellular Modulator:



Cauli et al., Neuroscience, Volume 190, 2011, Pages 27-36; Miki et al, Dec 9. doi: 10.1111/neup.12080 Neuropathology 2013 Glembotski et al., Circulation Research. 2007;101:975-984

A previously completed randomized, placebo-controlled single ascending dose Phase 1 study of ANAVEX2-73 in 22 healthy volunteers reported no serious adverse events. At highest doses, observed adverse events included moderate and reversible dizziness and headache, common in drugs that target the central nervous system. Blood pressure and resting heart rate and clinical laboratory parameters, vital signs and 12-lead ECG did not show any clinical relevant or dose-dependent changes. QT interval and QTcB did not reveal any clinically significant changes. PK of ANAVEX2-73 was found suitable for daily oral dosing (Schindler 2014).

Phase 2a with Adaptive Trial Design



No. of Patients:	▪ 32 mild-to-moderate AD patients
No. of Sites:	▪ Up to 7 sites
Allocation:	▪ Randomized
Duration:	▪ PART A: 36-days, PART B: 3-month and 6-month data analyses
Endpoints:	▪ Safety ▪ Bioavailability ▪ Exploratory cognitive efficacy (EEG/ERP, MMSE, Cogstate and ADSC-ADL) ▪ Exploratory add-on therapy to AD standard of care

- **Efficient** design embraces both **adaptive trial features** and **population pharmacokinetics**
  - ***Minimizes both timelines and cost***
- **Captures** all relevant information **for a larger Phase 3** study

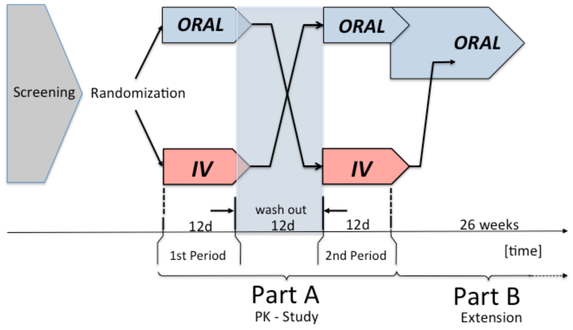
** Comparison to published data*

The Phase 2a trial of ANAVEX2-73 in both male and female mild-to-moderate Alzheimer's disease (AD) patients seeks to enroll 32 patients. The trial started in January 2015 and the first 12 patients have completed Part A.

Part A and Part B Design

PART A is a multicenter simple randomized, open-label, two-period with on-off-on dosing regimen, cross-over between oral (30mg/50mg) and IV (3mg/5mg) dosing, adaptive trial lasting up to 36 days for each patient. Resting EEG and event related potentials (EEG/ERP) are used to assess cognitive effects and optimize dosing of ANAVEX2-73 in subjects with mild-to-moderate AD.

PART B is an open-label extension for an additional 26 weeks, with daily oral dosing so as to establish a longer drug effect.



Objectives and Endpoints

Primary:

Evaluate the maximum tolerated dose of ANAVEX2-73.

Secondary:

Dose response, bioavailability, exploratory cognitive efficacy using electroencephalographic (EEG) activity, including event-related potentials (EEG/ERP), Mini Mental State Examination (MMSE), Cogstate and evaluation of ADSC-ADL and add-on therapy to donepezil, the current standard of care.

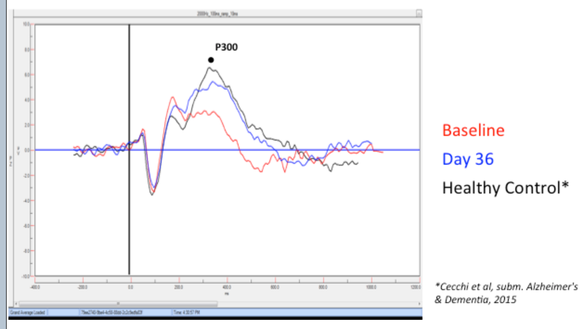
Electrophysiological Markers

EEG/ERP P300 signal is a real-time physiological measure of cognitive processes with demonstrated sensitivity to Alzheimer's disease and more proximal to disease pathology and pharmacological intervention than psychometric measures (Polich 1990, Jeong 2004).

Initial Results from the Ongoing Phase 2a Study

Initial cognitive EEG/ERP P300 ANAVEX2-73 data of 12 mild-to-moderate Alzheimer's patients (MMSE 16-28) mostly on donepezil, the current standard of care at end of Part A (day 36).

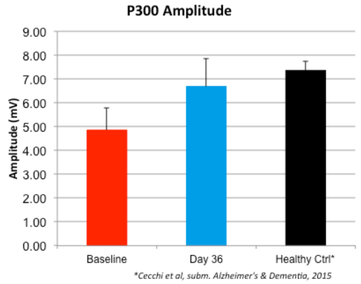
ANAVEX2-73 changes the ERP Wave to Resemble more Closely the Shape of Healthy Controls



**Cecchi et al, subm. Alzheimer's & Dementia, 2015*

ANAVEX2-73 data is from 12 patients at baseline and day 36 with on-off-on dosing regimen without dose optimization.

ANAVEX2-73 Increases P300 Amplitude by 38% from Baseline



**Cecchi et al, subm. Alzheimer's & Dementia, 2015*

ANAVEX2-73 improves P300 signal in 10 out of 12 (83%) patients.
ANAVEX2-73 data is from 12 patients at baseline and day 36 with on-off-on dosing regimen without dose optimization.

ANAVEX2-73 Improves Accuracy and Reaction Time in the Target Detection Task of the ERP Test

Effects of ANAVEX2-73 on the Target Detection Task of the ERP Test

	Baseline	Day 36	Healthy Control*
Button press accuracy (%)	86.2 ± 4.47	87.5 ± 4.01	94.1 ± 1.10
False alarms (%)	2.67 ± 1.12	0.64 ± 0.26	1.10 ± 0.20
Median reaction time (ms)	593 ± 33.0	534 ± 42.0#	458 ± 11.4

Data are mean ± SEM #$p<0.05$

**Cecchi et al, subm. Alzheimer's & Dementia, 2015*

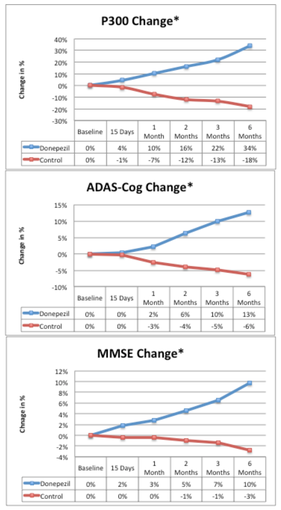
Reference Study

Clinical Neuropharmacology Vol. 25, No. 4, pp. 207–215 (2002)

Study parameters:

- 15 patients with mild AD (MMSE 19-26) on donepezil
- 15 patients with mild AD (MMSE 19-26) on control (Vitamin E)
- Double blind 6 month study with regular measure points from baseline to 6 months

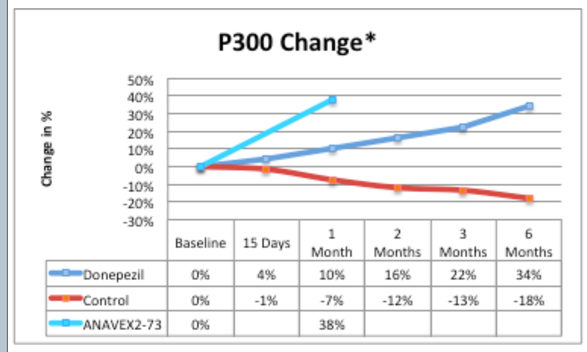
P300 Amplitude change Correlates with ADAS-Cog and MMSE



**Clinical Neuropharmacology Vol. 25, No. 4, pp. 207–215 (2002); ±SE omitted since not statistical significant*

Comparison to Reference Study

ANAVEX2-73 Increases P300 Amplitude Earlier and Higher than Donepezil



** Historical control: Donepezil and Control (15 AD patients each) from Clinical Neuropharmacology Vol. 25, No. 4, pp. 207–215 (2002); ±SE omitted since not statistical significant*

ANAVEX2-73 data is from 12 patients at baseline and day 36 with on-off-on dosing regimen without dose optimization.
The cognitive EEG/ERP P300 amplitude of ANAVEX2-73 increased by 38% from baseline. A published data comparison shows that this is about 4 times higher than donepezil at the same time point and already higher than what donepezil reaches after 6 months of continuous administration.

Conclusions

- This poster reports positive cognitive EEG/ERP P300 data of the first initial 12 out of 32 mild-to-moderate Alzheimer's patients (MMSE 16-28) mostly on donepezil, the current standard of care at end of Part A (day 36).
- ANAVEX2-73 data is from 12 patients at baseline and day 36 with on-off-on dosing regimen without dose optimization. Further data will show if dose optimization leads to further increased P300 signal.
- Cognitive EEG/ERP P300 amplitude increased by 38% from baseline. A published data comparison shows that this is about 4 times higher than donepezil at the same time point and already higher than what donepezil reaches after 6 months of continuous administration.
- ANAVEX2-73 improves the P300 signal in 10 out of 12 (83%) patients.
- ANAVEX2-73 improves accuracy and reaction time in the target detection task of the ERP test.
- ANAVEX2-73 appears to show early measurable strong cognitive EEG/ERP effects.
- The study is continuing on schedule with finishing Part A for the remaining patients and progressing into longitudinal Part B.

References

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- Jeong, Clinical Neurophysiology, Volume 115, Issue 7 (2004), pp. 1490–1505