Quantitative EEG results from a multiple ascending dose study in healthy volunteers with NeuroRestore® ACD856, a positive modulator of Neurotrophin Trk-receptors

Kristin Önnestam[1] MSc, Boel Nilsson[1] MSc, Matthias Rother[1] MD, PhD, Erik Rein-Hedin[2] MD, Peter Anderer[3] PhD, Manuel Kemethofer[3] MSc, Magnus M. Halldin[1] PhD, Pontus Forsell[1] PhD, Gunnar Nordvall[1] PhD, Johan Sandin[1] PhD, Märta Segerdahl[1] MD, PhD

1. AlzeCure Pharma AB, Hälsovägen 7, Huddinge, Sweden 2. CTC Clinical Trial Consultants AB, Dag Hammarskjölds väg 10B, Uppsala, Sweden 3. The Siesta Group Schlafanalyse GmbH, Schlosshofer Strasse 11-3rd Floor, A-1210 Vienna, Austria

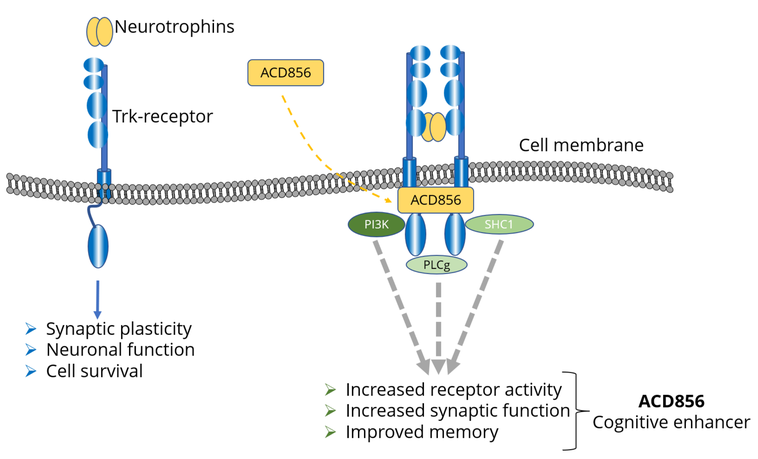
Background

NeuroRestore® ACD856 is a novel positive allosteric modulator of Trk-receptors in clinical development for the treatment of Alzheimer's disease (AD) and other disorders where cognition is impaired.

Neurotrophin signaling pathways, such as those mediated by NGF (nerve growth factor) and BDNF (brain derived neurotrophic factor), have in numerous studies been shown to be important for neuronal cell function, communication, and cell survival in brain areas vital for cognitive function, such as the hippocampus and basal forebrain. BDNF and NGF mediate their effects by binding to their Trk- receptors; TrkA or TrkB, respectively.

A large body of pathological and mechanistic evidence suggests that loss of NGF signaling contributes significantly to the dysfunction of basal forebrain cholinergic neurons during the course of AD. Several studies have also shown a decrease of BDNF in the hippocampus and in cerebrospinal fluid (CSF) in disease states with cognitive decline, including AD. This suggests that decreased BDNF signaling may contribute to the progression of hippocampal dysfunction. Increased NGF and BDNF signaling could potentially enhance cholinergic function, synaptic plasticity and improve cognition. This supports the development of stimulators of NGF and BDNF signaling, such as ACD856, as cognitive enhancers for the treatment of Alzheimer's disease.

Fig 1. Illustration of ACD856 binding to the Trk-receptor



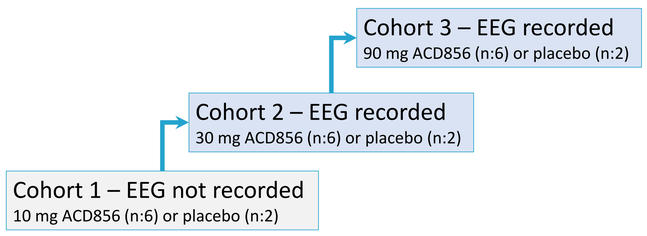
Objectives

The aim of the multiple ascending dose study was to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of ACD856. As part of the same study, quantitative electroencephalography (qEEG) was included to allow for an exploratory analysis of pharmacodynamic effects of ACD856 on CNS activity and target engagement.

Methods

ACD856 was administered once daily over a treatment period of 7 days in 3 ascending dose cohorts (Fig 2). Subjects in each cohort were randomized to receive either ACD856 (n=6) or placebo (n=2). qEEG was recorded for the two last study cohorts. This resulted in 6 subjects treated with 30 mg ACD856, 6 subjects with 90 mg ACD856, and 4 placebo subjects included in the qEEG analysis.

Fig 2. Study design and dose escalation steps



EEG recordings were performed at baseline, 1.5, 6 and 24 hours following the first dose of ACD856 or placebo, and at 1.5 hours following the last dose. At each timepoint, the 4 min EEG segments were recorded during the following conditions; 1. Vigilance-controlled EEG with eyes closed; 2. Resting EEG with eyes closed; 3. Resting EEG with eyes open. The EEG was recorded in accordance with the international 10/20 system. The absolute power EEG variables were determined by spectral analysis for the total band, delta, theta, alpha1, alpha2, beta1, beta2, beta3, gamma as well as combined delta&theta, alpha and beta bands. Post-pre treatment changes were calculated for all timepoints, and paired samples t-tests have been applied for post-pre changes within each treatment group. Independent samples t-tests have been used to compare post-pre changes between the treatment groups.

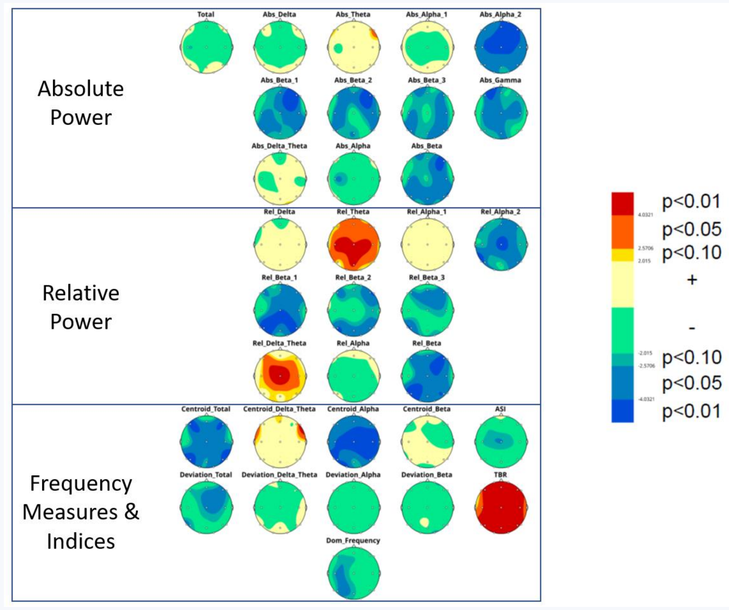
The following derived EEG variables were determined, per subject, day, time point, recording condition and electrode:

- Alpha slow-wave index
- Theta/Beta ratio
- Delta activity
- Theta activity
- Alpha activity
- Beta activity
- Gamma activity
- Dominant frequency
- Alpha reactivity (only resting EEG with eyes open)

Results

The qEEG results show that treatment with ACD856 significantly increases the relative theta power and decreases fast alpha and beta power which leads to an acceleration of the delta+theta centroid and an increase in the theta/beta ratio (TBR). These effects are seen both in comparison to placebo (TBR: $p<0.05$) and when analyzing intraindividual treatment induced EEG changes (TBR: $p<0.01$) (Fig 3). These effects are most evident in the vigilance-controlled EEG recordings with eyes closed as opposed to resting EEG recordings with eyes closed or open and are most pronounced at 24 hours post 1st dose and 1.5 hours after dose on day 7.

Fig 3. Statistical Probability Maps based on paired samples t-values between 24 hours post-dose and pre-dose for ACD856 90 mg, vigilance-controlled condition with eyes closed (n=6). Warm colors indicate treatment induced increases compared to pre-dose; cold colors indicate decreases



Conclusion

NeuroRestore® ACD856 has a pharmacodynamic effect on EEG activity in healthy volunteers. The qEEG results are in line with previously reported exposure of ACD856 in the cerebrospinal fluid, with relevant concentrations reaching the CNS compartment. The new data show that ACD856 not only passes the blood brain barrier but also has an effect suggestive of target engagement. In the next step, ACD856 will be evaluated in a patient population to better understand the clinical relevance of these results.

Martin.jonsson@alzecurepharma.com
www.alzecurepharma.com