ACD856 – a novel positive allosteric modulator of Trk-receptors in clinical development for the treatment of Alzheimer's disease

POSTER

Nordvall, G., Madjid, N., Backlund, M., Halldin, M., Rother., M., Nilsson, B., **Sandin, J.*** and Forsell, P.

KEY TAKEAWAY: The small molecule compound ACD856 increases cellular activity of Trk-receptors by binding to the receptor, thereby increasing the catalytic efficiency of the kinase activity. This unique mechanism of action results in increased levels of neurotransmitters, enhanced synaptic plasticity and potent procognitive effects in preclinical models. The compound is currently in clinical development for the treatment of cognitive dysfunction in Alzheimer's disease.

The neurotrophins nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) mediate their effects by binding to their Trk-receptors; TrkA or TrkB, respectively. NGF and BDNF have in numerous studies been shown to be important for neuronal cell function, communication and cell survival in brain areas vital for cognitive function. The Val66Met-BDNF polymorphism can affect brain anatomy and modulate episodic memory and hippocampal function in patients with Alzheimer's disease (AD). The strong genetic linkage of BDNF and the role of NGF in cholinergic function strongly support the development of stimulators of NGF and BDNF signaling as cognitive enhancers for treatment of AD.

The aim of this study was to explore the mode of action of ACD856, a compound that potently stimulates neurotrophin signalling, and to investigate the effects of such a compound in various preclinical models. Moreover, the aim was also to assess its pharmacokinetic properties, safety and tolerability in both animals and man.

METHODS

Single site biotinylated intracellular domain of TrkA was captured onto a series Biotin CAPture sensor chip. All subsequent binding studies were performed using a BiacoreT200 instrument.

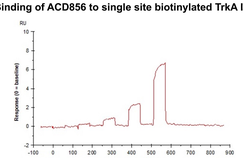
Full length HA-tagged TrkA was used for a LANCE-based kinase assays to determine the apparent maximal velocity ($Vmax_{(app)}$)

The effects of ACD856 was investigated in different *in vivo* behavioural models to assess its effect on cognitive function. Moreover, the effect of subcutaneous administration of ACD856 on neurotransmitter release in the ventral hippocampus was investigated by microdialysis in freely moving rats. Safety and toxicology studies were subsequently conducted in line with regulatory requirements. The PK of ACD856 was examined in preclinical species and a separate microdosing study in humans was also performed to evaluate the pharmacokinetics, safety and tolerability in man.

RESULTS

A binding site on the intracellular domain of TrkA was observed for the compound ACD856 using surface plasmon resonance (Fig. 1). Using an in vitro kinase assay with human full-length TrkA, ACD856 could significantly increase the $Vmax_{(app)}$ of TrkA (Fig. 2A). Furthermore, in a cell-based assay, ACD856 could potentiate signaling of both NGF/TrkA (data not shown) and BDNF/TrkB (Fig 2B) at different concentrations of ligand.

Figure 1: Binding of ACD856 to single site biotinylated TrkA ICD



In vivo experiments demonstrate that ACD856 significantly and dose-dependently reverse scopolamine-induced memory impairments in mice in the passive avoidance (PA) model (Fig. 3A). Interestingly, ACD856 was also able to reverse MK-801 induced memory impairment (Fig. 3B). Moreover, the pro-cognitive effects of ACD856 could be blocked by a TrkB antagonist (Fig. 3C). Moreover, ACD856 showed additive effects to that of an acetylcholine esterase inhibitor (data not shown).

Subcutaneous administration of ACD856 results in increased levels of the neurotransmitters serotonin (5-hydroxytryptamine (5-HT)), noradrenalin (NA) and dopamine (DA) in the ventral part of hippocampus as measured by in vivo microdialysis in freely moving rats. There was a significant increase in the amount of serotonin levels after administration of ACD856 as compared to vehicle (figure 4A and C) and a clear trend of increased levels of both noradrenalin(Fig 4A and B) and dopamine (Fig. 4A).

The compound was shown to be safe and well tolerated in the preclinical toxicological studies up to 1 g/kg (data not shown).

Pharmacokinetic studies in rat showed a favourable profile (Fig. 5A). Micodosing results in man showed that ACD856 was well tolerated and exhibited a mean terminal half-life of 19.4 hours with a mean $AUC_{0\text{-}inf}$ of 160.9 h*ng/mL (Fig 5B).

FIGURES

Figure 2: Mechanism of action of ACD855 and ACD856 on TrkA

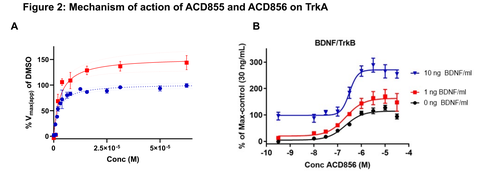


Figure 3: Effect of ACD856 on associative memory in the PA task

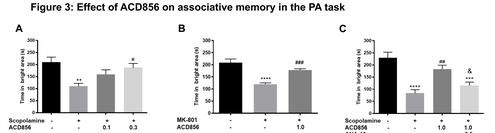


Figure 4: Effects of ACD856 on release of neurotransmitters in the ventral hippocampus

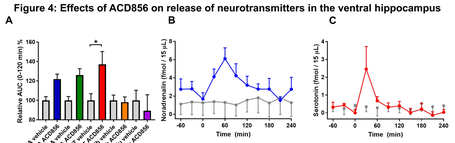
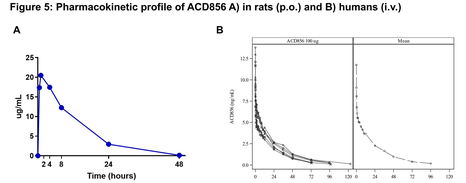


Figure 5: Pharmacokinetic profile of ACD856 A) in rats (p.o.) and B) humans (i.v.)



CONCLUSIONS

In summary, we have developed ACD856, a compound with a novel mechanism of action, that binds to Trk-receptors, acts as a positive modulator and increases Trk-mediated signalling. We have also demonstrated that ACD856 acts as a potent cognitive enhancer in various animal models.

The results from the preclinical studies together with the existing safety and toxicology data, demonstrate a clear potential of ACD856 to improve cognition. Considering the broad role of neurotrophins, including supportive and neuroprotective activity, positive allosteric modulators of Trk receptors may also have an additional upside of achieving disease-modifying effects in neurodegenerative disorders like Alzheimer's or Parkinson's disease.

ACD856 is currently in a clinical phase 1 study

E-mail: Johan.sandin@alzecurepharma.com

Web: www.alzecurepharma.com

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